Letters to the Editor

Trends in Antimicrobial Susceptibility Patterns Among Inpatient Enterococcal Isolates (1990 to 1999): Implications for Therapeutic Options

To the Editor:

Enterococci are among the most common causes of hospital-acquired infection and are associated with significant morbidity and mortality.[1,2] The impact of enterococcal infections has been intensified by the emergence of vancomycin-resistant enterococci (VRE), which are associated with increases in mortality, length of hospital stay, and hospital costs when compared with their vancomycin-susceptible counterparts.[3] Although the incidence of infections due to VRE has risen dramatically in the past decade,[4] the potential implications of this trend can be fully appreciated only if taken in the context of trends in enterococcal susceptibilities to other agents.

We investigated antimicrobial susceptibility trends for all enterococci isolated during a 10-year period (1990 to 1999) at the Hospital of the University of Pennsylvania. All clinical specimens for this institution are processed and undergo culture in a central clinical microbiology laboratory. Enterococci were identified to the genus level by conventional methods.[5] Antimicrobial susceptibilities were determined according to established criteria.[6] Prior to May 1995, the VITEK system (bioMérieux, Inc., St. Louis, MO) was the primary method of susceptibility testing. After this time, the laboratory changed to MicroScan conventional panels that were read on the MicroScan WalkAway (Dade Behring, Deerfield, IL). In addition to the semiautomated susceptibility systems, vancomycin resistance was detected using BBL Vancomycin Screen Agar (6 µg/mL) and high-level aminoglycoside susceptibility was determined using the BBL Enterococcus Screen Agar Quad Plates (Becton Dickinson, Cockeysville, MD). Although enterococci are not routinely identified to the species level at our institution, approximately 98% of VRE isolates in a 1997 survey were *Enterococcus faecium* demonstrating *van*A resistance (personal communication, Paul H. Edelstein, MD, July 7, 1998).

All clinical enterococcal isolates identified during the study were categorized by year of isolation and anatomic site of infection (ie, blood, non-urine, or urine). If multiple isolates from the same anatomic site were collected during a single patient admission, only the first isolate was included. For blood and non-urine isolates, susceptibilities to the following agents were tested: ampicillin, vancomycin, high-level gentamicin (minimum inhibitory concentration ≥ 500 µg/mL), and high-level streptomycin (minimum inhibitory concentration ≥ 2,000 µg/mL). Urine isolates were tested for susceptibility to ampicillin, vancomycin, nitrofurantoin, and tetracycline. Testing for nitrofurantoin and tetracycline commenced in 1995.

Proportions were compared using a chi-square test of binomial proportions. To evaluate the trend in the proportion of positive test results over time, the Cochran–Armitage trend test was performed. A significance level of .05 (two-sided) was used for all tests. Statistical analyses were performed using standard programs in Stata 6.0 (Stata Corp., College Station, TX) and StatXact 4.0 (Cytel Software Corp., Cambridge, MA).

During the 10-year study, 8,106 inpatient enterococcal isolates underwent susceptibility testing. For bloodstream isolates, there were three agents (ampicillin, vancomycin, and gentamicin) for which the percentage of enterococci susceptible was significantly lower in the second half of the study than in the first half of the study (1990 to 1994). Also noted were significant declining trends in susceptibilities for these three agents (Table; Figure, top). In the latter 1990s, the percentage of enterococci susceptible to vancomycin and ampicillin was 52% and 49%, respectively.

For non-urine isolates, there were significant differences in susceptibility to gentamicin and strepto-

TABLE
ANTIMICROBIAL SUSCEPTIBILITY RATES FOR BLOOD, NON-URINE, AND URINE ENTEROCOCCAL ISOLATES

Agent	1990 to 1994 Susceptible/ Tested (%)	1995 to 1999 Susceptible/ Tested (%)	Chi-square*	Trend†
Blood isolates				
Ampicillin	264/348 (75.9)	591/926 (63.8)	< .001	< .001
Vancomycin	297/348 (85.3)	637/926 (68.8)	< .001	< .001
Gentamicin (HL)‡	160/250 (64.0)	426/926 (46.0)	< .001	< .001
Streptomycin (HL)‡	102/175 (58.3)	509/926 (55.0)	.42	.59
Non-urine isolates				
Ampicillin	639/935 (68.3)	1,506/2,113 (71.3)	.10	< .001
Vancomycin	679/935 (72.6)	1,482/2,113 (70.1)	.16	< .001
Gentamicin (HL)‡	441/750 (58.8)	580/2,113 (27.4)	< .001	< .001
Streptomycin (HL)‡	399/700 (57.0)	787/2,113 (37.2)	< .001	< .001
Urine isolates				
Ampicillin	1,140/1,455 (78.4)	1,754/2,329 (75.3)	.04	.03
Vancomycin	1,242/1,455 (85.4)	1,777/2,329 (76.3)	< .001	< .001
Tetracycline	Not tested	2,287/2,329 (98.2)	—	.14
Nitrofurantoin	Not tested	877/2,329 (37.7)	—	.52

HL = high-level.
*Chi-square test comparing susceptibility rates for 1990 to 1994 and 1995 to 1999.
†Chi-square test for trend for the 10-year period using annual rates.
‡Gentamicin susceptibility testing was not performed from 1990 to 1991. Streptomycin susceptibility testing was not performed from 1990 to 1992.

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mycin when comparing the first half with the second half of the decade, whereas there were significant declining trends for all agents (Table; Figure, middle). Declines in ampicillin and vancomycin susceptibility were greatest from 1990 to 1992. By 1999, the percentage of enterococci susceptible to ampicillin closely approximated the percentage susceptible to vancomycin.

Finally, when the first half of the decade was compared with the second half of the decade, there were significant decreases in susceptibility for ampicillin and vancomycin for urine isolates (Table). Significant declining trends in susceptibility to these agents were also noted (Table; Figure, bottom). Susceptibility to nitrofurantoin and tetracycline remained essentially constant through the 1995 to 1999 time period.

These results demonstrate that not only has vancomycin resistance increased markedly, but resistance to the few remaining agents traditionally available as treatment for enterococcal infections has also risen significantly. Our data suggest that as enterococcal susceptibilities to traditional agents continue to decline, decisions regarding empiric antimicrobial therapy will become increasingly difficult and will likely result in more frequent delays in the time required for a patient to receive an agent to which an infecting organism is susceptible.[7] Interestingly, we noted that enterococcal susceptibilities for vancomycin and ampicillin were roughly equivalent, suggesting that either agent could be used when enterococcal infection is suspected.

The difficulties in selection of empiric antimicrobial therapy may provide a strong argument for routine identification of enterococcal isolates to the species level. Similar to our institution, many microbiology laboratories also do not identify enterococci to the species level.[8] Because resistance to both ampicillin and vancomycin is much less common in *E. faecalis* than in *E. faecium*,[1] identification to the species level may be important in more effectively selecting empiric antimicrobial therapy.

Appropriate antibiotic therapy for enterococcal infection has been demonstrated to reduce mortality even when adjusting for prior surgery, nosocomial acquisition, and polymicrobial infection.[9] However, our results suggest that even when

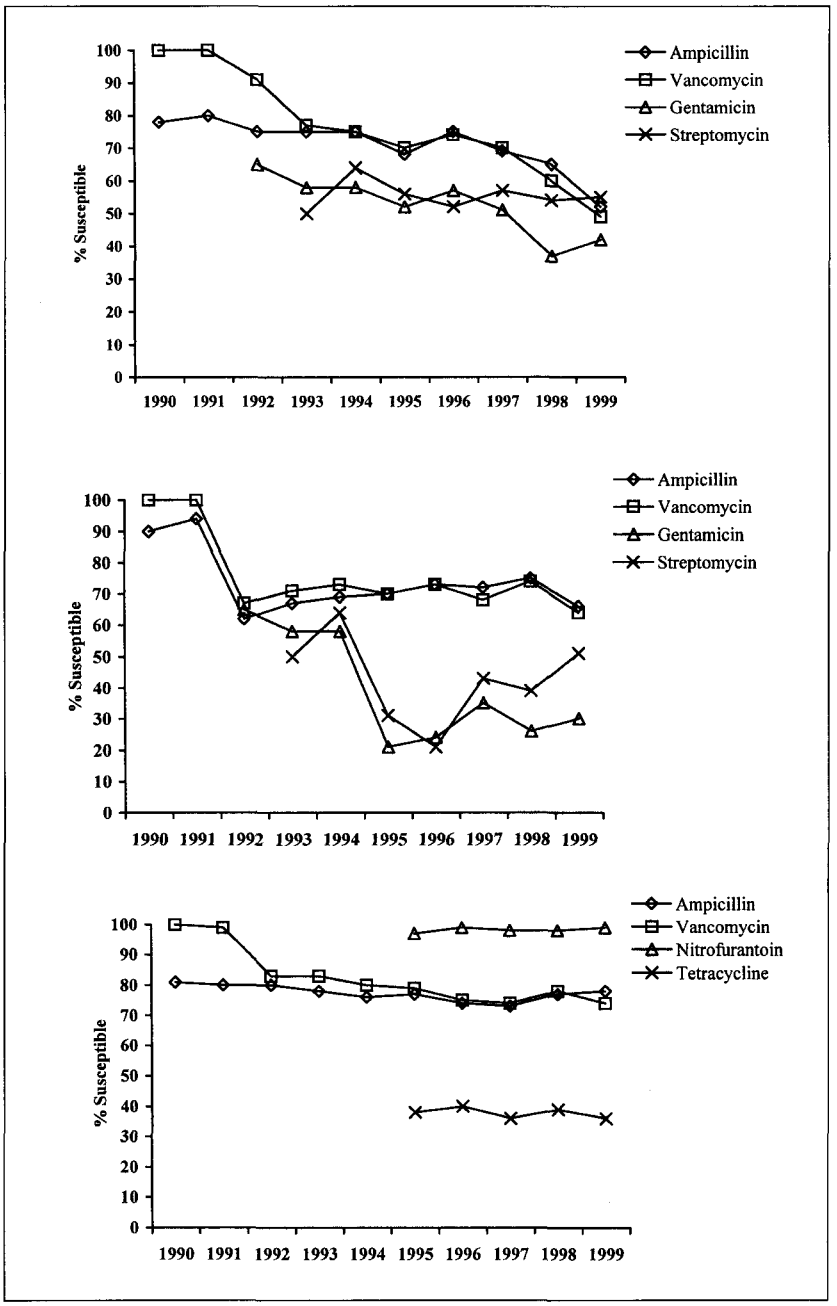

FIGURE. Susceptibilities of enterococcal isolates (1990 to 1999). (Top) Blood isolates. (Middle) Non-urine isolates. (Bottom) Urine isolates.

susceptibilities for an infecting organism have been determined, few treatment choices may exist. Recently, it was noted that among *E. faecium*, 43.5% of isolates exhibited resistance to both ampicillin and vancomycin.[8] For organisms in which no cell-wall active agent is available, few therapeutic options remain.

It is likely that as resistance to multiple agents increases, greater reliance will be placed on alternative agents such as chloramphenicol, quinupristin/dalfopristin, and linezolid. What impact increased use of these agents will have on susceptibilities to other traditional agents remains to be seen. In addition, increased dependence on, and use of, newer agents will likely provide the selective pressure necessary to foster resistance to these drugs as well. Judicious use of these new agents will be of great importance.

Finally, our results have implications for synergistic therapy for ente-

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rococcal infections. Approximately 50% of bloodstream isolates exhibited high-level gentamicin and streptomycin resistance, suggesting that synergistic therapy with an aminoglycoside and a cell-wall active agent is often not possible. These findings may have important implications for clinical outcomes, particularly in the setting of endovascular infections.

There were several potential limitations to our study. First, because we did not routinely identify enterococci to the species level, it is possible that our results may reflect the particular distribution of enterococcal species at our institution. Nevertheless, the implications of our findings for antimicrobial therapeutic options remain unchanged. Another potential limitation was the unavailability of isolates to permit molecular epidemiologic analysis. As such, we were unable to determine whether our results were due to the presence of multiple unrelated strains or the clonal dissemination of a few strains. Whereas such analysis would be important for understanding possible nosocomial spread of resistance, this study focused on potential therapeutic options for enterococcal infections. Finally, our study was conducted at a large academic medical center and our results may not reflect those at other dissimilar institutions.

We found significant decreases in susceptibilities for nearly all traditional anti-enterococcal agents, particularly among bloodstream and nonurine isolates. These results have important implications for the empiric and directed treatment of enterococcal infections and suggest that these infections will continue to present difficult therapeutic decisions.

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Improving Healthcare Workers' Compliance With Hand Hygiene: Is a Picture Worth a Thousand Words?

To the Editor:

The hands of healthcare workers are a major source for spread of nosocomial pathogens.[1] Several investigators have demonstrated that large numbers of pathogenic bacteria may be acquired on hands during routine patient care activities.[2-4] For example, nurses caring for patients colonized with *Klebsiella* species frequently acquired hundreds of these organisms on their hands.[2] Even seemingly low-risk contacts, such as measuring blood pressure or touching environmental surfaces, have been shown to result in transmission of significant numbers of organisms to hands.[2-6] Healthcare workers may not appreciate the extent of the contamination that occurs because microorganisms cannot be seen on their hands.

As a means to educate healthcare workers in our institution, we have used hand cultures and molecular typing techniques to illustrate the spread of pathogens from patients and environmental surfaces to hands. One such illustration involved a 54-year-old man with vancomycin-resistant *Enterococcus faecium* stool colonization who was incontinent of feces, and quantitative cultures revealed that his stool contained more than 100 million vancomycin-resistant *E. faecium* per gram.[6] Broth enrichment cultures from various surfaces in his hospital room were performed as previously described.[6,7] A gloved hand imprint culture was obtained after briefly examining his abdomen (Fig. 1). The imprint culture was performed by placing the fingertips of the gloved hand onto Enterococcosel agar (Becton Dickinson, Cockeysville, MD) containing 6 μg/mL of vancomycin. A similar culture obtained after contact with his bed rail and bedside table yielded 9 colonies of vancomycin-resistant *E. faecium* (data not shown). Pulsed-field gel electrophoresis was performed as previously described.[7] Multiple stool, environmental, and hand isolates were either genetically identical or closely related (Fig. 2). Cultures of sterile gloves obtained prior to contacting the patient or environmental surfaces were negative.

Convincing healthcare workers of the importance of hand hygiene remains an important challenge for infection control practitioners. Clear demonstrations of the hand contamination that occurs during routine patient care activities may be helpful as one component of an educational program. Healthcare workers from our institution have frequently expressed surprise that contamination of hands could be demonstrated after only minor contact with patients or environmental surfaces. In addition to distributing pictures illustrating hand contamination, we have used cultures of healthcare workers' hands with subsequent feedback regarding contaminating organisms as a means to provide personal examples and direct feedback. Others have recommended such culture exercises as a means to educate medical students and other personnel.[8,9]

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