Vancomycin-Resistant *Staphylococcus aureus* in the Clinic: Not Quite Armageddon

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(See the article by Whitener et al. on pages 1049–55)

In 1992, Noble et al. [1] reported that they could transfer the vancomycin-resistant genes *vanA*, *vanH*, *vanX*, and *vanY* from vancomycin-resistant enterococci to a strain of *Staphylococcus aureus* both in vitro and on the skin of an obese mouse. The world then waited for vancomycin resistance to be identified in a naturally occurring clinical isolate of methicillin-resistant *S. aureus* (MRSA). Dire warnings about the major clinical implications of multidrug-resistant MRSA and vancomycin-resistant *S. aureus* (VRSA) led to much speculation about untreatable staphylococcal infections. However, after waiting 10 years, some clinicians concluded that this was not going to happen on the basis of the observation that enterococci and staphylococci frequently occupy the same ecological niche and had been given every reasonable opportunity to exchange genes in multiple-patient microenvironments. Unfortunately, as was seen in the summer of 2002, two strains of *vanA*-producing MRSA were identified in the United States within 3 months of each other in unrelated patients in Michigan and Pennsylvania [2, 3].

In this issue of the journal, investigators from the Centers for Disease Control and Prevention (CDC) and The Penn State Milton S. Hershey Medical Center (Hershey, PA) describe the clinical presentation of the second of these 2 cases [4]. The information provided is somewhat reassuring, in spite of the ominous predictions in the popular press about the potential of these organisms to become resistant to virtually all known antibiotics [5].

Key features of this study include that this patient, who had an infected heel ulcer and osteomyelitis, had not been admitted to a hospital in the previous 5 years and had not been treated with vancomycin during that time period. Thus, the staphylococcal strain was assumed to have originated from the community. It is notable that the patient’s heel had been infected with MRSA and vancomycin-resistant enterococci (VRE) before his hospital admission, providing an opportunity for horizontal transfer of vancomycin-resistance determinants from the *Enterococcus* species to the *Staphylococcus* species in a dynamic system. The Michigan VRSA isolate was also recovered from a patient with foot ulcerations. In both cases, the patients had underlying chronic illnesses, which may have made them more vulnerable to serious infections. With the increasing number of MRSA strains being reported in the community [6], concomitant with the ubiquity of commensal enterococci, a high possibility exists for additional patients to be exposed to this kind of gene transfer.

It is notable that the patient from Pennsylvania had been treated with multiple antibiotics before the identification of the VRSA strain, but not with vancomycin. This selection by unrelated antibiotics is consistent with the findings from laboratory studies by Noble et al. [1], in which selection of VRSA occurred orders of magnitude more frequently after exposure to rifampicin, erythromycin, or chloramphenicol, compared with vancomycin. This observation once again argues for judicious use of antibiotics to minimize the threat of VRSA selection in patients at risk.

On a molecular level, the 2 VRSA strains appear to be nonclonal. On the basis of staphylococcal PFGE patterns, CDC investigators recently showed that both VRSA isolates had pulse-field types of the USA100 type—the most common, but also the most diverse, MRSA profile in the United States [7]. Although related at a high level, there was sufficient genetic diversity to conclude that the 2 strains emerged independently [4]. Even though both isolates carried only the *vanA* resistance determinant, the Pennsylvania strain was susceptible to teicoplanin, whereas the Michigan strain was resistant to teicoplanin, as predicted for a VanA phenotype. Gene dosage was thought to play a role and would provide a consistent explanation of why the MICs of vancomycin were 32 and 1024 μg/mL for the Pennsylvania...
and Michigan isolates, respectively. These phenotypic differences emphasize the fact that the observed gene transfer was not a single event resulting in 2 clonal strains. Thus, it is likely that other VRSA strains will arise.

In retrospect, one can view the arrival of clinical VRSA somewhat more optimistically than was anticipated. First, it was not a pan-resistant MRSA. Although resistant to vancomycin and to other agents such as aminoglycosides, tetracycline, and the marketed fluoroquinolones, the Pennsylvania strain responded with low MICs for a number of older antibiotics, as well as investigational antibacterial agents [8]. US Food and Drug Administration-approved agents with MICs in the susceptible range included drugs from ≥8 different antibiotic classes: minocycline (MIC, 0.12 μg/mL), trimethoprim-sulfamethoxazole (TMP-SMX; MIC, 2/38 μg/mL), chloramphenicol (MIC, 8 μg/mL), rifampin (MIC, ≤0.06 μg/mL), mupirocin (MIC, 0.12 μg/mL), linezolid (MIC, 1 μg/mL), quinupristin-dalfopristin (MIC, 1 μg/mL), and daptomycin (MIC, 0.5 μg/mL). Investigational drugs with MICs of ≤1 μg/mL for this VRSA isolate included the glycopeptides dalbavancin and oritavancin, tigecycline, and newer agents in the classes of the anti-MRSA cephalosporins, quinolones, and oxazolidinones [8]. However, one cannot dismiss the probability that other resistances may emerge in future VRSA strains.

On the basis of susceptibility data, therapeutic options include a number of reasonable alternatives that may lead to clinical cures. In an in vitro pharmacodynamic model with simulated endocardial vegetations, daptomycin, quinupristin-dalfopristin, and linezolid all demonstrated bactericidal activity against the Michigan VRSA strain [9]. Indeed, after 6 weeks of treatment with linezolid, piperacillin-tazobactam, and TMP-SMX, the patient in Pennsylvania did not have any culturable VRSA, MRSA, or VRE [4]. Likewise, the Michigan patient responded favorably to systemic therapy with TMP-SMX [10].

It is also notable that neither VRSA strain appeared to be highly virulent. In both cases, the strains were not transmitted to contacts, including family members and health care workers. In Michigan, 375 swab specimens obtained from multiple contacts were shown to be negative for VRSA [10]. In the Pennsylvania case, standard infection-control measures were taken, and no additional VRSA or VRE isolates were identified from 283 contacts [4]. Of note, MRSA was cultured from samples obtained from a number of Pennsylvania contacts, including the patient’s daughter, whose MRSA strain had a very similar PFGE pattern to that of the patient’s VRSA strain. It is probable that the MRSA strain was transmitted between daughter and father, but that the VRSA strain developed independently and possibly required a compromised (previously infected) host in order to survive. This may indicate that the current VRSA strains will not become major pathogens in otherwise healthy populations. The fact that only 2 isolates have been identified worldwide since the summer of 2002 supports this hypothesis.

However, rigorous attempts must be made to screen staphylococcal isolates appropriately so that future cases can be rapidly identified and treated effectively. As discussed by Whitener et al. [4], disk diffusion testing alone might have misidentified the Pennsylvania strain. It is critical for laboratories to test vancomycin susceptibility using vancomycin-agar or non-automated broth dilution assays with 24-h incubation periods to detect emerging VRSA strains. This imposes an additional burden on clinical laboratories, but it is essential that proper testing methodology be used before VRSA strains become entrenched in isolated hospitals.

In conclusion, a clinical isolate of the dreaded VRSA has now appeared. However, it is not as catastrophic as it could be. The 2 strains that were identified almost 18 months ago have not been followed by reports of additional strains. Both strains were susceptible to a number of older drugs and were successfully eradicated with familiar agents, including TMP-SMX. In addition, a number of investigational agents may also be effective for future treatment. We should proceed with caution, but, thus far, VRSA has been manageable when detected. Our major challenge in the future may not be treatment and dissemination of VRSA itself but, rather, the accurate detection of VRSA when it appears.

References