Vancomycin-Resistant *Staphylococcus aureus*: A Perfect but Geographically Limited Storm?

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In this issue of *Clinical Infectious Diseases*, Sievert et al. [1] provide clinical and epidemiologic details of 7 cases of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection. They present a scenario of the “perfect storm” in Michigan—the right patients, the right organisms, and the right selective pressure—resulting in 5 of the 7 reported cases of VRSA infection emerging in that state.

In many ways, this scenario is a reflection of the broader issue of antimicrobial resistance, in which local evolution of bacterial strains progresses until a particularly fit strain emerges and then has the possibility of spreading broadly. Some evolutionary steps are more successful than others. For example, the first β-lactamase-producing strain of *S. aureus* was reported in 1941 and eventually spread around the world [2]. Now, >90% of all *S. aureus* isolates are penicillin resistant as a result of β-lactamase production. On the other hand, β-lactamase–producing isolates of *Enterococcus faecalis* emerged in several locales in the United States [3] and disappeared within a few years [4]. Predicting which resistant strains will ultimately survive and disseminate is virtually impossible; predicting that at least some strains will disseminate broadly is a certainty. Thus, the data on VRSA presented in Sievert et al. [1], when considered in light of a series of other reports regarding emerging *S. aureus* resistance over the past 6 years, provide us with ample cause for reflection on the continuing saga of bacterial evolution. Taken together, the data suggest some good news and some bad news.

GOOD NEWS

First and foremost, there has been no secondary transmission of any of the VRSA strains to patients, health care workers, family, or other contacts. As Sievert et al. [1] note, this was likely the result of appropriate application of infection-control practices for the patients infected with VRSA who were already either in contact isolation or under enhanced infection-control precautions because of known infection or colonization with methicillin-resistant *S. aureus* (MRSA) or vancomycin-resistant enterococci. I hasten to add that we (i.e., public health, infection-control, and infectious disease practitioners) were fortunate that the patients were cared for in institutions that implement adequate infection-control procedures.

The second piece of good news is that these VRSA infections were not manifest in otherwise healthy people but occurred in patients with underlying illnesses, such as diabetes or end-stage renal disease, that likely predisposed them to infection. Unfortunately, these patients are not a small segment of the population, particularly in Michigan; therefore, this good news must be kept in perspective.

Third, all 7 isolates remained susceptible to multiple antimicrobial agents, permitting adequate antistaphylococcal therapy when needed. Yet, it is disturbing to note that the fifth VRSA isolate had intermediate resistance to quinupristin-dalfopristin and was borderline susceptible to linezolid (MIC, 4 μg/mL) and that the seventh VRSA isolate was no longer susceptible to daptomycin (MIC, 2 μg/mL).

Finally, recent laboratory data suggest that VRSA isolates should be readily identified by most clinical microbiology laboratories, whether automated susceptibility testing methods or disk diffusion are used (in contrast with vancomycin-intermediate *S. aureus* strains, which are not detectable with disk diffusion [5]). Although the first VRSA isolate from Michigan was identified as nonsusceptible to vancomycin (i.e., intermediate or resis-
BADM NEWS

The 7 VRSA isolates described to date have evolved through 3 unique genetic mechanisms. The first VRSA isolate likely was the result of a 2-step genetic process that involved the introduction of a VanA-containing enterococcal plasmid into a recipient MRSA strain, likely by conjugation, followed by the transposition of the VanA operon located on the transposon Tn1546 from the enterococcal plasmid to a resident MRSA plasmid. The new chimeric MRSA plasmid containing Tn1546 continued to replicate, and the original enterococcal plasmid was lost (i.e., it was diluted out of the MRSA population as the cells divided) [9]. Importantly, the new chimeric VRSA plasmid was transmissible to other S. aureus strains and was demonstrated to transfer from the VRSA strain to a recipient MRSA strain at a modest frequency [10]. Thus, the first VRSA strain posed a threat of donating its VanA plasmid not only to other S. aureus strains but also potentially to strains of coagulase-negative staphylococci. The second VRSA strain harbored an unusual VanA plasmid containing both staphylococcal and enterococcal sequences from multiple plasmids. This patchwork plasmid of unclear origin was relatively unstable, resulting in only modest vancomycin MIC levels (16–64 μg/mL) [7, 11]. The third VRSA strain, isolated from a biofilm in a nephrostomy tube in a New York patient [12], and the subsequent Michigan VRSA isolates (from patients 4–7) contained enterococcal plasmids that were able to replicate in S. aureus strains [13]. In other words, the latter VRSA strains represent a more direct pathway from MRSA to VRSA via acquisition of presumably unadulterated plasmid DNA from an enterococcal donor.

Considering the multiple mechanisms of VRSA development and the development and spread of vancomycin-intermediate S. aureus and hetero-vancomycin-intermediate S. aureus strains, which result in clinical failure when vancomycin is used as monotherapy [14], it is clear that S. aureus is continually seeking new pathways to vancomycin resistance. The acquisition of VanA from enterococci is only one of those pathways. Although the majority of VRSA infections have been reported from Michigan, it is unlikely that future VRSA infections will be confined to this geographic locale. Indeed, there has been a report of a VRSA strain from Tehran, Iran [15], although there has not been independent confirmation of the organism’s identification or phenotype. Interestingly, the Tehran VRSA strain remained susceptible to teicoplanin, suggesting that it had acquired a VanB rather than VanA resistance determinant. As the VRSA strains from Pennsylvania, New York, and elsewhere have shown, where there is a (bacterial) will, there is a way.

It is intriguing that all 7 of the VRSA isolates from the United States are from the same genetic lineage, known as multilocus sequence type 5. This includes the well-described PFGE types USA100 and USA800 and several unclassified PFGE patterns, such as the pattern of the sixth VRSA strain [13], USA100, which is also known as the New York–Tokyo clone, is the most widely disseminated multidrug-resistant MRSA type in US hospitals and is a cause of community infections as well [16]. Thus, the population of S. aureus that can serve as enterococcal plasmid recipients is very widespread not only in the United States but also elsewhere around the world. Because co-colonization of patients with MRSA and VRE is common [17, 18], the possibility of further VRSA strains developing is likely.

VRSA IN SOUTHEASTERN MICHIGAN

Sievert et al. [1] provide plausible explanations for why 5 of the 7 cases of VRSA infection in the United States occurred in Michigan. These include a large population of patients with diabetes and end-stage renal disease, both of which predispose to staphylococcal infections; a large population of enterococcal donor strains with a specific transmissible plasmid encoding VanA (Inc 18–like plasmid); and a high rate of use of vancomycin therapy because of a long history of MRSA infections in the state. It remains to be seen whether this “perfect storm” (i.e., high-risk patient population, high-risk enterococcal donor population, and appropriate vancomycin selective pressure) is unique to southeastern Michigan. In the mean time, we should be thankful that the ubiquitous and virulent community-associated strain of MRSA, USA300 [16, 19, 20], has not yet proven to be a recipient of enterococcal VanA plasmids. Otherwise, we might have a very different and, indeed, quite frightening epidemiologic picture of VRSA infections in the United States. Nonetheless, we can be confident that S. aureus isolates in general and MRSA isolates in particular will develop additional ways to overcome the deleterious effects of vancomycin.

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References

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