

## BRIEF REPORT

## Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the *vanA* Resistance Gene

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UNTIL RECENTLY, VANCOMYCIN WAS THE ONLY UNIFORMLY EFFECTIVE treatment for staphylococcal infections. In 1997, the first clinical isolate of *Staphylococcus aureus* with reduced susceptibility to vancomycin was reported,<sup>1</sup> and as of June 2002, eight confirmed infections with such strains had been reported in patients in the United States.<sup>2-6</sup> The minimal inhibitory concentrations (MICs) of vancomycin reported for these isolates are in the intermediate range (8 to 16  $\mu\text{g}$  per milliliter) according to interpretive criteria defined by the National Committee for Clinical Laboratory Standards.<sup>7</sup>

In June 2002, a clinical isolate of vancomycin-resistant *S. aureus* (VRSA) (MIC, >32  $\mu\text{g}$  per milliliter) was identified.<sup>8</sup> In this report, we describe our investigation of this infection, describe the mechanism of resistance, and discuss the clinical significance and public health implications of this finding.

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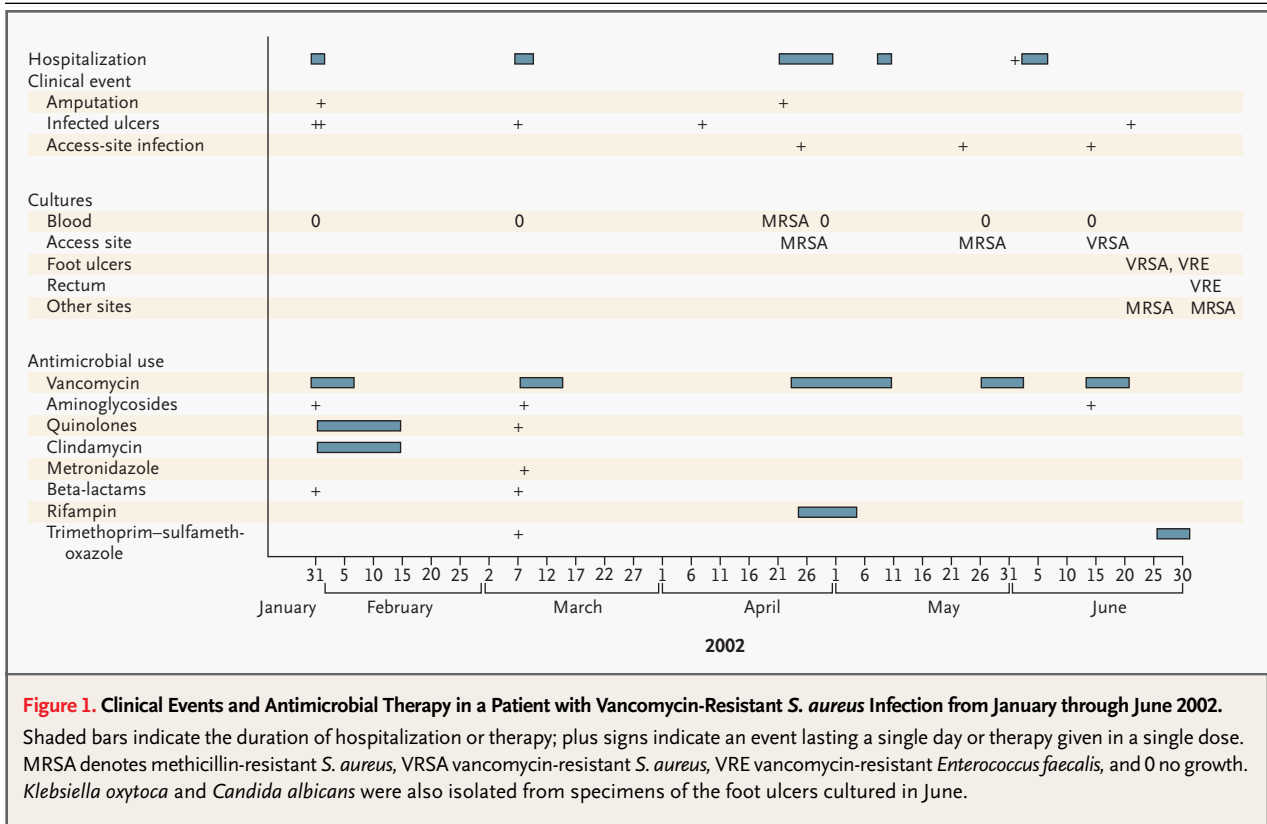
### CASE REPORT

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The patient, a 40-year-old woman who lived in Michigan, had hypertension, diabetes mellitus, peripheral vascular disease, and chronic renal failure, which had necessitated hemodialysis since August 1999. The patient had recurrent foot ulcers due to diabetic neuropathy and localized infections of the right lower leg. In March 2001, she underwent amputation of the right fifth metatarsal, which was gangrenous. Cultures of the amputation wound site revealed heavy growth of oxacillin-susceptible *S. aureus* (MIC,  $\leq 0.25$   $\mu\text{g}$  per milliliter). Two months later, she was successfully treated for an infected fissure and associated foot cellulitis; cultures of the fissure showed minimal growth of vancomycin-susceptible methicillin-resistant *S. aureus* and vancomycin-susceptible *Enterococcus faecalis*.

From January to March 2002, recurrent infections of the foot ulcers were treated empirically with systemic antimicrobial agents, including vancomycin, gentamicin, ampicillin-sulbactam, piperacillin-tazobactam, levofloxacin, clindamycin, cefazolin, trimethoprim-sulfamethoxazole, tobramycin, and metronidazole (Fig. 1). The patient's condition required amputation of the right first metatarsal in February 2002 and the right fourth metatarsal in April 2002. During this time, the patient was changing her own dressings daily and using a loose-fitting foot covering. As of July 2002, the foot ulcerations had persisted.

During the hospitalization for the amputation in April 2002, methicillin-resistant



**Figure 1. Clinical Events and Antimicrobial Therapy in a Patient with Vancomycin-Resistant *S. aureus* Infection from January through June 2002.**

Shaded bars indicate the duration of hospitalization or therapy; plus signs indicate an event lasting a single day or therapy given in a single dose. MRSA denotes methicillin-resistant *S. aureus*, VRSA vancomycin-resistant *S. aureus*, VRE vancomycin-resistant *Enterococcus faecalis*, and 0 no growth. *Klebsiella oxytoca* and *Candida albicans* were also isolated from specimens of the foot ulcers in June.

*S. aureus* bacteremia developed, as did an abscess associated with an arteriovenous graft for dialysis access (Gore-Tex). The patient received vancomycin for 3 weeks and rifampin for 10 days. After removal of the graft, access for hemodialysis was maintained with the use of three sequentially placed, temporary, nontunneled dialysis catheters until June 14, at which time a newly placed graft became functional. The first temporary catheter was removed on May 23 because of a suspected exit-site infection (growth on the catheter tip of >15 colonies of methicillin-resistant *S. aureus*, with sterile blood cultures). The patient was treated with one dose of vancomycin. The second catheter was placed on May 23 and then removed electively on June 6, and a third temporary catheter was placed. In sum, during the six months before the identification of VRSA, the patient had received vancomycin for a total of six and a half weeks.

On June 14, the third temporary catheter was removed because of a suspected exit-site infection, and one dose of vancomycin and one dose of gentamicin were given. Cultures of exudates from the catheter exit site and from the catheter tip subse-

quently grew VRSA (MIC,  $\geq 32$   $\mu\text{g}$  per milliliter), identified simultaneously by two local clinical microbiology laboratories that processed two separate specimens. The catheter-tip specimen also grew vancomycin-resistant *E. faecalis* (MIC,  $\geq 32$   $\mu\text{g}$  per milliliter). The identification and susceptibility of the *S. aureus* isolates were confirmed by the Michigan Department of Community Health and by the Centers for Disease Control and Prevention (CDC). One week after the catheter was removed, the exit site appeared to have healed. However, a culture of specimens from two plantar ulcers, obtained to evaluate a possible soft-tissue infection, also contained VRSA and vancomycin-resistant *E. faecalis*, as well as *Klebsiella oxytoca* and *Candida albicans*.

Cultures of swab specimens obtained from other sites (the nares, axilla, and umbilicus and the catheter exit site) on June 21 and June 28 were negative for VRSA. However, cultures of swabs from the nares and umbilicus grew vancomycin-susceptible, methicillin-resistant *S. aureus*. In addition, a culture of a perirectal-swab specimen grew vancomycin-resistant *E. faecalis* but no *S. aureus*.

On July 2, the patient underwent surgical dé-

bridement of the foot ulcers on an outpatient basis. She completed a 14-day postoperative course of trimethoprim-sulfamethoxazole and metronidazole. The ulcers were evaluated twice per week, with débridement if necessary, application of gentian violet, and application of contact casts. Each of the three foot ulcers was cultured weekly for VRSA, which was recovered on July 16 and August 20. By December 2002, the patient's ulcers had healed.

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#### METHODS

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To document any cross-transmission of VRSA to other persons, we performed a carriage survey of the patient's known contacts during the period from April 25 through July 2, 2002 — that is, the last date before the isolation of VRSA that vancomycin-susceptible *S. aureus* was isolated from multiple sites until the first date that all cultured specimens grew no VRSA. To assess the possibility of previous transmission, we identified social and health care-associated contacts, including all family members, close friends, concurrent health care providers, and patients cared for on the same hospital ward or in the same clinic office on the days when the patient infected with VRSA was present. Specimens from as many contacts as possible were collected from the anterior nares, any catheter sites, and any open wounds or skin lesions.

To identify any ongoing transmission during the investigation, we prospectively monitored all health care personnel involved in the care of the VRSA-infected patient by culturing specimens from their anterior nares weekly and examining the cultures for VRSA. We also reviewed infection-control policies, interviewed health care personnel, and observed infection-control practices at the facilities where the patient was receiving care.

VRSA isolates recovered from the patient's catheter tip and catheter exit site were initially identified at two local hospital laboratories with the use of MIC testing methods (Dade MicroScan). Species identification was carried out by standard biochemical methods.<sup>9</sup>

Genomic staphylococcal and enterococcal DNA, isolated by the silica-gel-membrane method (Qiagen DNeasy), was used as a template for the polymerase chain reaction to detect the presence of *mecA*,<sup>10</sup> *vanA*, *vanB*, *vanC*,<sup>11</sup> and *vanD*.<sup>12</sup> DNA sequences were determined with an automated sequencer (ABI377, Applied Biosystems).<sup>13</sup> Antimicrobial-susceptibility testing was performed by the broth-microdilution method.<sup>7</sup>

Pulsed-field gel electrophoresis was performed on *Sma*I macrorestriction fragments of DNA from the isolates of VRSA and methicillin-resistant *S. aureus* from the patient, her family members, and other dialysis-center patients.<sup>14,15</sup> The Dice coefficients (representing the percent similarities) of gel-electrophoresis restriction profiles were then compared (BioNumerics analysis software, Applied Maths).

During the carriage survey, specimens from the patient's contacts were collected with dry, sterile swabs (Culturette, Becton Dickinson). The swabs were inoculated onto mannitol salt agar. After a 48-hour incubation at 35°C, all presumptive *S. aureus* colonies were isolated on blood-agar plates containing 5 percent sheep's blood for further analysis. Identification of *S. aureus* was confirmed by Gram's staining, catalase testing, latex-agglutination testing (Staphaurex, Murex), and tube coagulase testing, if indicated. Finally, to screen for vancomycin resistance, all *S. aureus* isolates were inoculated onto brain-heart infusion agar containing 6 µg of vancomycin per milliliter and incubated at 35°C for 24 hours.

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#### RESULTS

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##### EPIDEMIOLOGIC STUDIES

During the period of potential transmissibility, the patient had received care at one free-standing dialysis center (dialysis center A) and at one physician's outpatient office and had been admitted to a single hospital on three occasions. The patient lived alone but frequently received nine family members and one close friend into her home. During this period, she was not employed.

Contacts were identified at each of these three health care facilities. Two of the contacts at dialysis center A had switched to another center, dialysis center B. One business establishment, a nail salon, was identified as having been frequently visited by the patient and thus as carrying the potential for transmission of VRSA to its employees. All contacts from these facilities who were available for interview agreed to have specimens taken from the anterior nares for culture. We obtained specimens from 371 of the 547 identified contacts. Of the 371 cultured specimens, 110 (30 percent) were positive for *S. aureus*, including 28 (8 percent of the 371 cultures) that were positive for methicillin-resistant *S. aureus* (Table 1). No carriage of VRSA was identified. In the prospective evaluations of staff from di-

alysis center A and staff from the podiatry center caring for the patient, no carriage of VRSA was identified.

Each of these health care settings had written infection-control policies. The hospital used broad universal precautions similar to the standard precautions recommended by the CDC (i.e., use of gloves if any contact with body fluids is anticipated, use of gowns for contact in which soiling of clothes is anticipated, and use of masks if splashing is anticipated).<sup>16</sup> Similar measures were used in the physician's office. The dialysis centers followed infection-control guidelines consistent with the CDC's recommendations for preventing the transmission of infections among patients undergoing long-term hemodialysis.<sup>17</sup> Observed practices were consistent with the written policies.

#### LABORATORY STUDIES

Species identification of the VRSA isolate from the catheter exit site was confirmed by biochemical tests. Polymerase-chain-reaction assays for vancomycin-resistant loci revealed only *vanA*. The DNA sequence of the *vanA* gene from the VRSA isolate was identical to the *vanA* sequence of transposon Tn1546<sup>18</sup> and to the *vanA* sequence from the patient's *E. faecalis* isolate.

In analyses of the VRSA, the MIC of vancomycin was 1024 µg per milliliter by broth microdilution and greater than 256 µg per milliliter by the agar gradient-diffusion method (Etest, AB Biodisk). On disk-diffusion testing, the VRSA had no zone of inhibition, although an 18-mm zone of reduced growth was perceptible around the disk. The isolate was susceptible to chloramphenicol, linezolid, minocycline, quinupristin-dalfopristin, tetracycline, and trimethoprim-sulfamethoxazole (Table 2). The characteristics and susceptibilities of the initial isolates of VRSA from the patient were identical to those of subsequent isolates.

Pulsed-field gel electrophoresis of *Sma*I macrorestriction fragments revealed that the banding patterns of the initial VRSA isolate were indistinguishable from those of the subsequent VRSA isolated from the patient's foot ulcers; indistinguishable from the vancomycin-susceptible, methicillin-resistant *S. aureus* isolated from the patient's nares; and indistinguishable from a methicillin-resistant *S. aureus* isolated from the patient's close friend. Other methicillin-resistant *S. aureus* strains, isolated from a family member and from 13 patients at dialysis center A, were less than 85 percent similar to the

**Table 1. Survey of *S. aureus* Carriage among Contacts of a Patient Infected with Vancomycin-Resistant *S. aureus*.**

Contacts	Cultures Available  no. of contacts (%)	Culture Results	
		Positive for <i>S. aureus</i>  no. of cultures (%)	Positive for Methicillin-Resistant <i>S. aureus</i>  no. of cultures (%)
<b>Health care facility</b>			
Hospital A			
Concurrent health care providers (n=203)	118 (58)	42 (36)	3 (3)
Concurrent patients (n=57)	57 (100)	19 (33)	7 (12)
Previous patients (n=80)	20 (25)	4 (20)	3 (15)
Dialysis centers A and B			
Concurrent health care providers (n=36)	36 (100)	8 (22)	0
Concurrent patients (n=135)	115 (85)	30 (26)	13 (11)
Outpatient office			
Concurrent health care providers (n=2)	2 (100)	0	0
Previous patients (n=22)	11 (50)	2 (18)	0
<b>Community</b>			
Household or family contacts (n=10)	10 (100)	5 (50)	2 (20)
Social contacts (n=2)	2 (100)	0	0
<b>Total (n=547)</b>	<b>371 (68)</b>	<b>110 (30)</b>	<b>28 (8)</b>

patient's initial VRSA isolate according to Dice coefficient analysis.

#### DISCUSSION

This report describes a patient infected with fully vancomycin-resistant *S. aureus* that contained the *vanA* vancomycin-resistance gene. Although the acquired vancomycin-resistance genes *vanA*, *vanB*, *vanD*, *vanE*, *vanF*, and *vanG* have been reported in vancomycin-resistant enterococci, these genes have not previously been identified in any clinical isolates of *S. aureus*. However, conjugative transfer of the *vanA* gene from enterococci to *S. aureus* has been demonstrated in vitro.<sup>19</sup> We suspect the *vanA* detected in the current patient's VRSA isolate probably originated in vancomycin-resistant *E. faecalis*, which

**Table 2. Antimicrobial-Susceptibility Profile of the Vancomycin-Resistant Strain of *S. aureus*.\***

Antimicrobial Agent	Minimal Inhibitory Concentration† μg per milliliter	Interpretation
Chloramphenicol	8	Susceptible
Daptomycin	1	Not available
Gatifloxacin	4	Intermediate
Linezolid	2	Susceptible
Minocycline	0.25	Susceptible
Mupirocin	32	Not available
Oritavancin	4	Not available
Quinupristin–dalfopristin	≤1	Susceptible
Tetracycline	2	Susceptible
Trimethoprim–sulfamethoxazole	2	Susceptible
Vancomycin	1024	Resistant

\* The vancomycin-resistant strain of *S. aureus* was resistant to clindamycin, erythromycin, gentamicin, levofloxacin, oxacillin, penicillin, rifampin, and teicoplanin.

† The minimal inhibitory concentration was determined by the broth-microdilution method.

was also isolated from the patient. Although the DNA sequence of the *vanA* gene in these two strains was identical, additional studies are needed to confirm this hypothesis.

An extensive search for VRSA in all the patient's contacts was undertaken, and no VRSA was identified. However, a close friend of the patient did carry a vancomycin-susceptible, methicillin-resistant strain of *S. aureus* that was indistinguishable from the VRSA on pulsed-field gel electrophoresis. This finding underscores the importance of extending efforts to prevent and reduce the spread of methicillin-resistant *S. aureus* beyond inpatient facilities.

This VRSA isolate was susceptible in vitro to several antimicrobial agents, including quinupristin–dalfopristin and linezolid, which were recently approved by the Food and Drug Administration and have activity against other glycopeptide-resistant, gram-positive microorganisms. The availability of these agents, developed since the first report of *S. aureus* with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus*),<sup>1</sup> provides several options for treating this patient. However, most of the MICs reported for these agents are just one dilution below the susceptibility break point.

There are several similarities between this VRSA infection and the previously reported infections with vancomycin-intermediate *S. aureus*.<sup>1-6</sup> First, the patient infected with VRSA had been exposed for several weeks to vancomycin and had had recurrent infections with methicillin-resistant *S. aureus* during the preceding months, as did the patients with vancomycin-intermediate *S. aureus*. Second, the patient infected with VRSA had underlying illnesses, including diabetes mellitus and chronic renal failure, similar to those affecting most of the previously described patients.<sup>4</sup> Although the isolates from these patients tended to be susceptible to chloramphenicol, linezolid, quinupristin–dalfopristin, and trimethoprim–sulfamethoxazole, the VRSA isolate was highly resistant to vancomycin (MIC, 1024 μg per milliliter), whereas the vancomycin-intermediate *S. aureus* isolates were only moderately resistant to it (MIC, 8 μg per milliliter).<sup>4</sup>

Although recommended measures to control the spread of methicillin-resistant *S. aureus* and vancomycin-resistant enterococci in hospitals have been promoted for several years,<sup>20,21</sup> surveillance data suggest that the existence of these recommendations has not appreciably slowed the increasing rate of infection or colonization with either of these organisms in the United States. The reasons for this lack of effect are unclear and under debate. In some institutions, the recommended measures may be ineffective or poorly followed or implemented.

Preventing the emergence of multidrug-resistant organisms will require a comprehensive, systematic approach that integrates the health care and public health systems. We need to encourage and facilitate adherence to recommended prevention and control guidelines, conduct active surveillance to detect the emergence of these organisms, and ensure vigorous antibiotic stewardship by health care providers. All isolates of *S. aureus* with presumptive vancomycin resistance should be saved, their resistance (or susceptibility) status confirmed by MIC-testing methods, and the test results reported through state and local health departments to the Division of Healthcare Quality Promotion of the National Center for Infectious Diseases of the CDC (mailstop E-68, Atlanta, GA 30333; telephone number, 800-893-0485; e-mail, search@cdc.gov).

The use of trade names and commercial sources is for identification only and does not imply endorsement by the Public Health Service or the Department of Health and Human Services.

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## APPENDIX

In addition to the authors, the following people participated in the Vancomycin-Resistant *Staphylococcus aureus* Investigative Team: Michigan Department of Community Health, Lansing, Mich. — G. Stoltman and P. Somsel; Detroit Medical Center, Detroit — T. Lundstrom, E. Flanagan, and W. Hafeez; Oakwood Healthcare System, Dearborn, Mich. — J. Mitchell; hemodialysis center A, Detroit — R. Johnson; and Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Centers for Diseases Control and Prevention, Atlanta — S. McAllister, L. McDougal, M. Kellum, H. Holmes, J. Chaitram, P. Raney, G. Fosheim, L. Weigel, N. Clark, and M. Arduino.

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