Vancomycin-Resistant *Staphylococcus aureus* in the Absence of Vancomycin Exposure

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We report findings from our investigation of the world’s second clinical isolate of vancomycin-resistant *Staphylococcus aureus* (VRSA). An elderly man was hospitalized with an infected chronic heel ulcer and osteomyelitis. Before hospital admission, he received multiple courses of antibiotic therapy but, notably, no vancomycin. Numerous cultures of ulcer specimens (performed on an outpatient basis) grew methicillin-resistant, vancomycin-susceptible *S. aureus* and vancomycin-resistant *Enterococcus* species. At admission, an additional culture of a specimen from the heel ulcer grew *S. aureus* that was identified as VRSA (minimal inhibitory concentration for vancomycin [by broth-microdilution], 32 μg/mL). Further evaluation confirmed the presence of the *vanA* gene mediating vancomycin resistance. To assess VRSA transmission, we performed a carriage study of 283 identified contacts and an environmental survey of the patient’s home; no VRSA isolates were recovered. This case illustrates that recent exposure by patients to vancomycin is not necessary for development of *vanA*-containing VRSA. For clinical and public health reasons, it is essential that microbiology laboratories adequately test for vancomycin-resistance in *S. aureus*.

*Staphylococcus aureus* is one of the most common causes of serious infection in community and hospital settings [1, 2]. Methicillin-resistant *S. aureus* (MRSA) is now endemic in health care facilities, with rates of >50% in some health care settings [3]. Also, recent reports describe MRSA carriage in persons in the community who do not have health care–associated risks [4]. The increased incidence of MRSA has led to more frequent use of vancomycin, the drug commonly relied on for treating MRSA infections.

In 1988, vancomycin-resistant enterococci (VRE) were first reported [5, 6]. These organisms quickly became endemic in hospital intensive care units. In vitro conjugative transfer of the *vanA* gene from enterococci to *S. aureus* was demonstrated in 1992 [7]. However, it was not until 1996, when the first case of vancomycin-intermediate *S. aureus* (VISA; MIC, 8–16 μg/mL) was detected, that decreased susceptibility to vancomycin became a clinical reality [8]. None of the VISA strains identified contained the *vanA* gene or any of the other vancomycin-resistant genes found in VRE [9–16]. In vitro studies suggest that, with prolonged vancomycin exposure, VISA organisms produce a thickened cell wall matrix, limiting drug penetration [17–21].

In June 2002, the first clinical *S. aureus* isolate with high-level vancomycin-resistance (VRSA; MIC, ≥32 μg/mL [22]) was detected in a patient from Michigan who had extensive exposure to vancomycin [23]. That organism contained the *vanA* gene, suggesting transfer of genetic material from a *vanA* containing vancomycin-
cin-resistant Enterococcus faecalis. We describe, to our knowledge, the world’s second clinical isolate of VRSA and report the findings of our associated epidemiologic investigation [24].

CASE REPORT

In September 2002, a 70-year-old, obese white man presented to The Penn State Milton S. Hershey Medical Center (HMC; Hershey, PA) emergency department with nausea, vomiting, fever, somnolence, and purulent drainage from a right heel ulcer. Samples of blood and the wound were obtained for culture, and the patient was admitted to a private room.

The patient developed this right heel ulcer in 1999. He was treated as an outpatient by his primary care physician (PCP) with intermittent ulcer debridements, topical antimicrobial agents, routine dressing changes, and 63 courses of oral antimicrobial agents (including tetracycline, fluoroquinolones, and cephalosporins) in response to the results of 21 heel swab cultures. In the year preceding the VRSA infection, MRSA and ampicillin-susceptible VRE, which was not identified to species level, were isolated frequently. At the referral laboratory, all MRSA isolates demonstrated susceptibility to vancomycin (MIC, ≤2 μg/mL) by MicroScan (Dade Behring).

In 1995, the patient underwent a left below-the-knee amputation (BKA) for calcaneal osteomyelitis. The BKA was complicated by a polymicrobial (ampicillin-susceptible VRE, methicillin-susceptible S. aureus, and P. aeruginosa) stump abscess and osteomyelitis, which was cured in 1997.

The patient received intermittent courses of parenteral vancomycin from 1990 until December 1996, when he reportedly developed a vancomycin allergy manifested by urticaria, dyspnea, and possible nephrotoxicity. In the 5 years before his hospital admission with VRSA, the patient had not been hospitalized and had not received vancomycin, apart from receipt of vancomycin-impregnated beads for 5 days in September 1997.

At the time of presentation, the patient was afebrile. Physical examination findings included morbid obesity, with a weight of ~215 kg, pulmonary wheezes, and venous stasis changes, with edema of the right leg. The right lateral foot and heel regions demonstrated callous formation and mild cellulitis. Copious, bloody, purulent drainage was noted from the right heel ulcer, which measured 6 × 5 × 1 cm. A probe passed through the ulcer base reached bone.

Laboratory studies demonstrated a WBC count of 15,800 cells/μL, a hemoglobin level of 11.3 g/dL, a platelet count of 262,000 platelets/μL, a blood urea nitrogen level of 27 mg/dL, a creatinine level of 1.5 mg/dL, and an erythrocyte sedimentation rate of 68 mm/h. Plain radiographs of the right foot revealed no definite evidence of osteomyelitis. An MRI of the foot visualized changes consistent with osteomyelitis of the plantar aspect of the calcaneous and cellulitis along the plantar fascia.

Within 24 h after hospital admission, blood cultures grew group B Streptococcus (GBS), and therapy with piperacillin-tazobactam was started. Transthoracic echocardiographic examination revealed a 40% ejection fraction, tricuspid regurgitation with pulmonary hypertension, and a dilated right heart. No valvular vegetations were seen. The results of follow-up blood cultures were negative. Two bedside debridements of the heel ulcer were performed. Bone biopsy was deferred because of clinical improvement and perceived high operative risk.

By the fifth day of hospitalization, the microbiology laboratory reported that the culture of the sample obtained from the patient’s heel yielded GBS, P. aeruginosa, Stenotrophomonas maltophilia, and MRSA. Before the laboratory completed vancomycin susceptibility testing for the MRSA isolate, the patient was discharged from the hospital with home health care services and a regimen of antimicrobial agents (i.e., linezolid, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole [TMP-SMX]). The hospital microbiology laboratory preliminarily reported that the MRSA isolate was VRSA on the afternoon of the patient’s discharge, and the Pennsylvania Department of Health (PA-DOH; Harrisburg) and the Centers for Disease Control and Prevention (CDC; Atlanta, GA) were notified. The PA-DOH invited the CDC to assist HMC personnel in the investigation to determine the extent of VRSA transmission and to develop a strategy to prevent and control transmission of VRSA.

METHODS

Review of the case. We reviewed medical records of the case patient from the PCP’s office (starting from July 1999), HMC, 2 hospitals from which he received care during 1990–1996, and 2 pharmacies that provided all of the case patient’s antimicrobial agents in the preceding 7 years.

Assessment of VRSA cross-transmission. Health care and household contacts were defined as persons who had physically touched the case patient, either through social interactions or through direct patient care. This group included all household members, family, and friends who visited the case patient, as well as health care workers from the PCP’s office, HMC, and the home health care agencies (HHA).

Patients considered to be contacts were those inpatients who resided in rooms in the same wing as the case patient and patients who were cared for by health care contacts. The latter group included patients who received care from an HHA nurse who had visited the case patient previously on that same day and HMC patients who had received direct care by a physician who had cared for the case patient within the previous 24 h and who were considered at high risk for VRSA carriage. High
risk for carriage was defined as disruption of skin integrity (e.g., open wounds, major inpatient surgical wounds, psoriasis, eczema, cellulitis, and burns). Patients from the PCP’s office were not evaluated.

Carriage in contacts was assessed by placing a dry, sterile culturette swab (Becton Dickinson Culturette Systems) 1.5–2.0 cm into the anterior nares and rotating the swab. Both nares were sampled with the same swab. In addition, any skin lesions or wounds were swabbed separately for culture.

Surveillance swabs of the case patient’s heel ulcer, nares, minor ulcers, groin, axillae, and perirectum were performed 2 weeks after the patient’s hospital discharge for detection of VRE and S. aureus. Additional surveillance specimens were obtained for culture on 5 occasions during the subsequent 6 weeks.

Environmental sampling of the case patient’s home was performed with the use of swabs and replicate organism detection and counting (RODAC) plates. Samples were obtained from several rooms, including the bedroom, office, and bathroom. Air samples were obtained using an MSA 100 air sampler (EMD Chemicals) during a period of no activity and then during a wound-dressing change.

To assess infection-control practices, the infection-control supervisor for each facility was interviewed regarding their infection-control policies. The infection-control practices of the hospital personnel and the private duty nurse were directly observed.

**Laboratory methods for detection of VRSA, MRSA, and VRE isolates.** The S. aureus strain isolated from the case patient’s admission wound culture was screened for vancomycin resistance by the HMC laboratory with standard disk diffusion methodology and by inoculation of a vancomycin-agar screening plate (brain heart infusion agar containing vancomycin, 6 \( \mu \text{g/mL} \)) [22]. At the CDC, broth microdilution susceptibility testing was performed to determine the MIC of vancomycin and of several other antimicrobial agents [22].

The surveillance samples obtained from the contacts, the case patient, and the case patient’s home were inoculated onto manitol salt agar and incubated for 48 h at 35°C. All presumptive S. aureus colonies were isolated on 5% sheep blood agar plates, and identification was confirmed by morphology on Gram stains and by tube coagulase testing [25]. Vancomycin-resistance screening of S. aureus was done by inoculation of a vancomycin-agar screening plate incubated for 24 h at 35°C. Skin and wound swabs and environmental samples also were evaluated for the presence of VRE using standard plating and biochemical methods [22].

Genomic staphylococcal DNA, which was isolated by the silica-gel-membrane method (QIAGEN DNeasy), was used as template for the PCR to detect the presence of \( \text{mecA} \) [26], \( \text{vanA} \), \( \text{vanB} \), \( \text{vanC} \) [27], and \( \text{vanD} \) [28]. PFGE was performed on \( \text{Eagl} \) and \( \text{Smal} \) restriction fragments of genomic DNA from the VRSA and MRSA isolates recovered from the case patient and persons in the carriage survey and were interpreted using criteria published elsewhere [29, 30].

**RESULTS**

Species identification of the VRSA isolate recovered from the case patient’s wound was confirmed by the CDC. During disk diffusion testing, the isolate grew up to the vancomycin disk, although a 19-mm zone of reduced growth was perceptible around the disk. The MIC of vancomycin was 32 \( \mu \text{g/mL} \), as determined by broth microdilution. The isolate was susceptible to several antimicrobial agents (table 1). PCR detected the \( \text{mecA} \) and \( \text{vanA} \) genes mediating oxacillin and vancomycin resistance, respectively.

Two hundred eighty-three contacts were identified. Ninety-six percent of health care personnel contacts, 100% of household contacts, and 85% of patient contacts underwent evalu-

**Table 1. Antibacterial susceptibilities of an isolate of vancomycin-resistant Staphylococcus aureus.**

<table>
<thead>
<tr>
<th>Antibacterial group, agent</th>
<th>MIC, ( \mu \text{g/mL}^a )</th>
<th>Resistance profile$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.12</td>
<td>S</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>8</td>
<td>I</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Oxazolidinones: linezolid</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Streptogramins: quinupristin-dalfopristin</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.5</td>
<td>S</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt;0.06</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>2/38</td>
<td>S</td>
</tr>
</tbody>
</table>

*NOTE.* I, intermediate; R, resistant; S, susceptible.

$^a$ Determined by broth microdilution.

$^b$ Determined using NCCLS criteria.
Table 2. Results of an investigation of contacts with a patient infected with vancomycin-resistant Staphylococcus aureus (VRSA).

<table>
<thead>
<tr>
<th>Contact category</th>
<th>No. of persons identified</th>
<th>No. (%) of persons who provided samples for culture</th>
<th>No. (%) of colonized persons (% of those with cultures who were colonized), by isolate type</th>
<th>No. of persons colonized with VRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSSA</td>
<td>MRSA</td>
</tr>
<tr>
<td>Health care workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>185</td>
<td>178 (96)</td>
<td>56 (32)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Physicians</td>
<td>23</td>
<td>23 (100)</td>
<td>10 (43)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hospital nurses</td>
<td>62</td>
<td>61 (98)</td>
<td>16 (26)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Outpatient nurses</td>
<td>8</td>
<td>8 (100)</td>
<td>3 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Othera</td>
<td>92</td>
<td>86 (93)</td>
<td>27 (29)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Household contacts</td>
<td>6</td>
<td>6 (100)</td>
<td>4 (67)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Patientsb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>92</td>
<td>78 (85)</td>
<td>14 (18)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Same wing</td>
<td>29</td>
<td>21 (72)</td>
<td>2 (10)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Same provider</td>
<td>63</td>
<td>57 (90)</td>
<td>12 (21)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>All contacts</td>
<td>283</td>
<td>262 (93)</td>
<td>74 (28)</td>
<td>21 (8)</td>
</tr>
</tbody>
</table>

NOTE. MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus.

* For example, medical students and housekeeping, transport, and pharmacy staff.

b Five patient contacts could not provide samples for culture because they died.

Infection-control policy and practice. The PCP treated the case patient weekly in his office from July 1999 until September 2002. The staff used standard precautions [31, 32]. All wound-dressing materials were disposed of as biohazard waste, and instruments were autoclaved after the visits. The examining room underwent terminal cleaning [33] after each visit. In the 6 months before the case patient’s admission, there were no other patients who attended the PCP’s office with known colonization or infection with MRSA or VRE.

At HMC, hospital staff used standard precautions from the first assessment in the emergency department through hospital day 3, unaware of the case patient’s MRSA/VRE colonization status. Contact precautions were instituted on day 4 of hospitalization after identification of MRSA. After the isolate was confirmed to be VRSA, the patient was scheduled as the last patient of the day for follow-up clinic visits. The staff used contact precautions that included the use of masks when administering care for this patient. Housekeeping performed terminal cleaning of the room after each visit.

On discharge home, 3 HHA nurses, engaged to monitor the intravenous line site and perform phlebotomy, practiced standard precautions and also wore masks for central line care. They cleaned reusable equipment with alcohol wipes after each visit. Two nurses from another HHA, assigned to assess and dress the heel wound daily, practiced contact precautions, used masks when changing dressings, and kept dedicated equipment at the patient’s home. After receiving notification of the VRSA by the PA-DOH several days after the patient’s discharge, 1 dedicated HHA nurse made 2 visits to the patient per week. The remaining care was provided by a private duty nurse who had no other patients. All equipment used for his care remained in his home, and all materials were disposed of in his home garbage.

Patient follow-up and outcome. The patient washed daily with chlorhexidine, but he discontinued this practice after 2 weeks because of skin irritation. The steady-state serum trough concentration of linezolid was 17.74 μg/mL (reference range, 2–9 μg/mL). Linezolid therapy was discontinued after 4 weeks as a result of thrombocytopenia (nadir platelet count, 56,000 platelets/μL). The platelet count returned to normal levels.
had been identified in clinical until these 2 VRSA cases, none of these resistance determinants vanB, vanD, vanF, and though the acquired vancomycin-resistance determinants gene also was found in the Michigan VRSA isolate [23]. Al-
organism in the community.

The patient’s postoperative hospital course was complicated by respiratory failure, which twice required ventilatory support. He expressed his desire for no future intubations, and he was discharged with home hospice services. Antimicrobial therapy (imipenem-cilastatin, tobramycin, and fluconazole) and wound care were continued. Despite ulcer improvement, the patient died at home of progressive cardiopulmonary failure 11 weeks after his initial hospital presentation.

DISCUSSION

This report describes the second clinical isolate of VRSA in the world and the associated investigation (table 3). This isolate was recovered from infected tissue overlying a calcaneous os-
shallow –cm area of grossly involved bone. Operative cul-
findings revealed no necrotic or purulent tissue and only a

The case patient had antecedent co-colonization with VRE No recent use or exposure to vancomycin by patient before isolation of VRSA

Numerous courses of oral antimicrobial agents received by patient before isolation of VRSA

Antecedent co-colonization with MRSA and VRE

The patient was readmitted to HMC for operative debridement

Several days after all antimicrobial agents were discontinued, the patient was readmitted to HMC for operative debridement of the calcaneous and surrounding soft tissue. Visual operative

No VRSA, MRSA, or VRE were isolated.

P. aeruginosa, Candida albicans, enterococci. No VRSA, MRSA, or VRE were isolated.

The events that trigger in vivo transfer of the vanA gene from a VRE. Before the patient’s recent hospitalization, the VRSA isolates recovered from the patient’s foot were never identified to the species level. However, we suspect that they were E. faecalis, because they were ampicillin susceptible, as are most vancomycin-resistant E. faecalis.

During susceptibility testing of the S. aureus isolate at HMC, an ampicillin-susceptible, vancomycin-resistant E. faecalis was recovered from a vancomycin Etest plate (AB Biodisk). This VRSE isolate may have been a contaminant, because it was not isolated from the primary culture plate, but laboratory inves-
tigation of this VRE isolate was pursued because of the patient’s history of colonization with an ampicillin-susceptible VRE. This VRE isolate contained the vanA gene, but plasmid analysis indicated that the gene was on a plasmid that was unrelated to the vanA-containing plasmid in the VRSA. This suggests that the VRSA acquired the vanA gene from a different VRE (e.g., one with which the patient may have previously been colonized) or that the VRSA may have been acquired from an outside source. The latter circumstance seems less likely, given the pa-
tient’s long history of cocarriage of VRE and MRSA, the absence of other known patients from the physician’s office with VRE or MRSA, and the negative results of our contact investigation. The events that trigger in vivo transfer of the vanA gene from VRE to MRSA need further study.

There are several similarities shared among this case, the Michigan VRSA case, and previously reported VISA infections in the United States. All patients had chronic disease, and all had recurrent colonization or infection with MRSA. Common to both VRSA reports are nonhealing ulcers in the lower ex-

Table 3. Salient features of the world’s second known isolate of vancomycin-resistant Staphy-
lococcus aureus (VRSA).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurred independently of the first isolate</td>
<td>Isolated from a heel wound with underlying osteomyelitis</td>
</tr>
<tr>
<td>Isolated only once from patient</td>
<td>Acquired in the community setting</td>
</tr>
<tr>
<td>No recent use or exposure to vancomycin by patient before isolation of VRSA</td>
<td>Numerous courses of oral antimicrobial agents received by patient before isolation of VRSA</td>
</tr>
<tr>
<td>Antecedent co-colonization with MRSA and VRE</td>
<td>Contained the vanA gene</td>
</tr>
<tr>
<td>Patient’s daughter was colonized with vanA negative MRSA with PFGE pattern similar to that of VRSA</td>
<td>Susceptible to other antimicrobial agents</td>
</tr>
<tr>
<td>No evidence of spread to health care workers or other contacts</td>
<td>Illustrates the need to use susceptibility methods that will detect VISA/VRSA</td>
</tr>
</tbody>
</table>

**NOTE.** MRSA, methicillin-resistant S. aureus; VISA, vancomycin-intermediate S. aureus; VRE, vancomycin-resistant enterococci.

within 1 week. Therapy with piperacillin-tazobactam and TMP-SMX was stopped after 6 weeks of treatment. The heel ulcer persisted.

Several days after all antimicrobial agents were discontinued, the patient was readmitted to HMC for operative debridement of the calcaneous and surrounding soft tissue. Visual operative findings revealed no necrotic or purulent tissue and only a shallow 3 × 3–cm area of grossly involved bone. Operative cultures grew P. aeruginosa, Candida albicans, and coagulase-negative staphylococci. No VRSA, MRSA, or VRE were isolated.

The patient’s postoperative hospital course was complicated by respiratory failure, which twice required ventilatory support. He expressed his desire for no future intubations, and he was discharged with home hospice services. Antimicrobial therapy (imipenem-cilastatin, tobramycin, and fluconazole) and wound care were continued. Despite ulcer improvement, the patient died at home of progressive cardiopulmonary failure 11 weeks after his initial hospital presentation.

DISCUSSION

This report describes the second clinical isolate of VRSA in the world and the associated investigation (table 3). This isolate was recovered from infected tissue overlying a calcaneous osteomyelitis. Because the patient had not been hospitalized in the previous 5 years, we conclude that he acquired this resistant organism in the community.

This VRSA isolate contained the vanA gene. This resistance gene also was found in the Michigan VRSA isolate [23]. Although the acquired vancomycin-resistance determinants vanA, vanB, vanD, vanF, and vanG have been isolated from VRE [34], until these 2 VRSA cases, none of these resistance determinants had been identified in clinical S. aureus isolates.

The case patient had antecedent co-colonization with VRE and MRSA, a common finding among patients with VRE [35]. The persistent presence of both organisms in this patient’s ulcer and the documentation of the vanA gene in this VRSA suggest the possibility that the VRSA acquired vancomycin resistance via horizontal transfer of the vanA gene from a VRE. Before the patient’s recent hospitalization, the VRSA isolates recovered from the patient’s foot were never identified to the species level. However, we suspect that they were E. faecalis, because they were ampicillin susceptible, as are most vancomycin-resistant E. faecalis.

During susceptibility testing of the S. aureus isolate at HMC, an ampicillin-susceptible, vancomycin-resistant E. faecalis was recovered from a vancomycin Etest plate (AB Biodisk). This VRE isolate may have been a contaminant, because it was not isolated from the primary culture plate, but laboratory inves-
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tient’s long history of cocarriage of VRE and MRSA, the absence of other known patients from the physician’s office with VRE or MRSA, and the negative results of our contact investigation. The events that trigger in vivo transfer of the vanA gene from VRE to MRSA need further study.

There are several similarities shared among this case, the Michigan VRSA case, and previously reported VISA infections in the United States. All patients had chronic disease, and all had recurrent colonization or infection with MRSA. Common to both VRSA reports are nonhealing ulcers in the lower ex-
tremities and cohabitation with MRSA and VRE. Also, a close social or family contact was found to carry the MRSA strain that was the suspected recipient of the vanA gene. The VRSA isolate in this report, like the Michigan VRSA, was susceptible to several alternative antimicrobial agents.

Analysis of the VRSA isolate reported here identified differences from the Michigan VRSA isolate. First, although both VRSA isolates belong to the same lineage of MRSA (USA100) [36], the PFGE profiles of the 2 VRSA isolates are diverse enough to indicate that the emergence of vanA-mediated resistance in each isolate is not the result of a genetic event in the same MRSA strain. The data indicate that the 2 VRSA isolates arose independently and that they are not linked epidemiologically. Second, in contrast to the Michigan VRSA isolate, for which the MIC of vancomycin was 1024 μg/mL, the MIC of vancomycin for this isolate was only 32 μg/mL. Third, the current VRSA isolate is susceptible to teicoplanin. This is an unexpected finding, because the vanA phenotype observed in enterococci confers resistance to both vancomycin and teicoplanin. We hypothesize that the lower MIC of vancomycin and the susceptibility to teicoplanin in our isolate may both be due to reduced expression of the vanA gene. Arthur et al. [37] demonstrated that the MICs of glycopeptides increase with vanA cluster copy number in E. faecalis JH2-2, and low-level MICs of glycopeptide may occur. Alternatively, this genetic determinant may be inducible.

Although all previous reports of patients who were infected or colonized with VISA/VRSA have described a history of prolonged vancomycin exposure [15], the patient in our investigation did not receive vancomycin during the 5 years preceding this infection. Therefore, concurrent or recent vancomycin exposure is not a prerequisite for the development of VRSA. Instead, we conclude that frequent use of other antimicrobial agents provided sufficient selective pressure to promote colonization and/or infection with VRE [38] and MRSA, eventually resulting in the emergence of VRSA.

The lack of detection of VRSA in exposed health care workers and patients using standard precautions implies that existing infection-control precautions may be effective in preventing transmission of VRSA to contacts. Alternatively, it is possible that this strain was poorly transmissible or that VRSA transmission occurred but was not detected by surveillance cultures performed 2 weeks after contact with the case patient because of transient carriage. The efficacy of published guidelines to control the spread of vancomycin-intermediate and -resistant organisms [39, 40] is not known because there have been a limited number of cases to date.

The most accurate form of vancomycin susceptibility testing for staphylococci is an MIC method (broth dilution, agar dilution, or agar-gradient diffusion) with 24-h incubation. Strains of staphylococci for which the MIC of vancomycin is 8 μg/mL (i.e., intermediate, according to NCCLS breakpoints) have been missed by disk diffusion testing [41]. Additionally, data from the CDC show that automated susceptibility tests, such as MicroScan (Dade Behring) and Vitek (bioMérieux), do not reliably detect this VRSA isolate with an MIC of 32 μg/mL [42]. Thus, when performing automated susceptibility testing of S. aureus strains, particularly MRSA, it may be prudent to include a vancomycin-agar screen plate in routine testing or to use periodic nonautomated broth- or agar-based MIC tests. Use of vancomycin-agar screening tests for MRSA may be the most reliable method to screen for VISA and/or VRSA [43].

Our investigation indicates that this VRSA isolate arose independently of the first isolate in Michigan, and it developed in the absence of vancomycin use. The identification of a second case just 3 months after the first suggests that more isolates may exist but have gone undetected. Additional VRSA infections are likely to occur. Therefore, clinical microbiology laboratories should use susceptibility testing methods that will detect VISA and/or VRSA. Systematic surveillance for VRSA will enhance the ability of the public health and health care systems to rapidly recognize and aggressively contain infection and colonization due to this resistant pathogen.

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