Vancomycin-Intermediate and -Resistant *Staphylococcus aureus*: What the Infectious Disease Specialist Needs to Know

Scott K. Fridkin
Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta

Ever since the first strain of *Staphylococcus aureus* with reduced susceptibility to vancomycin and teicoplanin was reported from Japan, there has been a lot of confusion regarding the laboratory and clinical approach to patients with infections due to *S. aureus* with reduced susceptibility to vancomycin. To date, 6 clinical infections with vancomycin-intermediate *S. aureus* (VISA) have been reported in the United States. Intermediate resistance appears to develop from preexisting strains of methicillin-resistant *S. aureus* in the presence of vancomycin, and all but 1 infection occurred in patients with exposure to dialysis for renal insufficiency. Detection of VISA is difficult in the laboratory, and special inquiries about susceptibility testing methods may be needed. These VISA-infected patients had underlying illnesses, and their infections did not appear to respond well to conventional treatment. Prevention strategies have been outlined. Without continued vigilance in enforcing infection-control measures, improved use of antimicrobials, and coordination of efforts among public health authorities, increasing levels of vancomycin resistance in *S. aureus* are likely to be encountered.

Clinicians are continually being challenged by infections caused by *Staphylococcus aureus*. Not only is *S. aureus* a major cause of both community-acquired and health care–associated infections, but the treatment of suspected *S. aureus* infections is becoming increasingly more complicated [1]. Among patients in the intensive care unit reported to the Centers for Disease Control and Prevention’s (CDC) National Nosocomial Infections Surveillance (NNIS) system, the proportion of *S. aureus* nosocomial infections that were oxacillin (methicillin) resistant (i.e., methicillin-resistant *S. aureus* [MRSA]) surpassed 50% in 1999 (http://www.cdc.gov/ncidod/hip/Aresist/aresist.htm). Of great concern are reports of community-acquired infections associated with MRSA, such as those that contributed to the deaths of 4 children in 1999 [2]. Most alarming, however, are reports of *S. aureus* that exhibits intermediate levels of resistance to glycopeptides, particularly vancomycin.

In 1997, the first strain of *S. aureus* with reduced susceptibility to vancomycin and teicoplanin was reported from Japan [3]. Soon thereafter, a report of 2 additional cases from the United States was published [4]. There have been considerable research and an array of published reports focusing on this topic during the past 3 years. These reports have shed some light on the microbiological characteristics of these organisms, but they have also created a lot of confusion regarding the laboratory and clinical approach to patients with infections caused by *S. aureus* with reduced susceptibility to vancomycin. Central to this confusion are the inconsistent use of definitions, an evolving understanding of proper laboratory methods for susceptibility testing of this organism, and a lack of sufficient clinical and epidemiologic data on patient management. Although infection with *S. aureus* that demonstrates decreased susceptibility to vancomycin is rare, there is a need to clarify these confusing issues and to bring their relevance to light for the physician dealing with infectious disease.
DEFINITIONS

Vancomycin-intermediate S. aureus (VISA). The National Committee for Clinical Laboratory Standards (NCCLS) defines staphylococci requiring concentrations of vancomycin of ≤4 µg/mL for growth inhibition as “susceptible,” those requiring concentrations of 8–16 µg/mL for inhibition as “intermediate,” and those requiring concentrations of >32 µg/mL as “resistant” [5]. Thus the acronyms VISA and GISA (glycopeptide-intermediate S. aureus) are derived from these criteria. Although the term “GISA” may be more accurate, since early reports indicated that most of these strains also were intermediate to the glycopeptide teicoplanin, the term “VISA” is more commonly used. The latter term emphasizes how the change in vancomycin susceptibility is similar to that of vancomycin-resistant enterococci, a term with which most clinicians are familiar.

Vancomycin-resistant S. aureus (VRSA). In the United States, the term “VRSA” is reserved for isolates of S. aureus for which the MICs of vancomycin are ≥32 µg/mL. However, outside of the United States, the term “resistant” may be used to refer to S. aureus isolates for which the MICs of vancomycin are ≥8 µg/mL. For instance, in Japan, strains that have MICs of 8 µg/mL and that grow on brain-heart infusion (BHI) screening agar containing vancomycin (typically, vancomycin, 4 µg/mL) within 24 h may be considered resistant [6]. Review of the MICs included in a VRSA definition must be a part of the evaluation of published reports of VRSA.

Heteroresistant VRSA (hetero-VRSA). The description of heteroresistance to vancomycin in S. aureus may be a source of great confusion for those in the field of infectious diseases. Hetero-VRSA strains may be defined as strains of S. aureus that contain sub-populations of vancomycin-resistant daughter cells but for which the MICs of vancomycin for the parent strain are only 1–4 µg/mL. The prototype strain (Ma3) was described by Hiramatsu et al. [7]. Hetero-VRSA can be identified from staphylococcal isolates that grow on BHI screening agar containing vancomycin (typically, vancomycin, 4–6 µg/mL) and are subsequently selected, propagated, and tested for vancomycin susceptibility. These subpopulations typically have MICs 2–8-fold higher than the original clinical isolate. Often, the vancomycin MICs reported for hetero-VRSA in published reports are those for the daughter colonies, not for the original clinical isolate (i.e., the parent strain).

MECHANISM OF RESISTANCE

The mechanisms by which S. aureus isolates become more resistant to vancomycin are being studied intensively; however, there is no evidence to suggest presence of the enterococcal vanA, vanB, vanC, vanD, and vanE genes in the VISA isolates, or any naturally occurring S. aureus isolate, to date. However, there has been in vitro transfer of the vanA determinant from Enterococcus faecium to S. aureus [8]. Potential mechanisms of resistance in VISA include increases in cell wall turnover that lead to an increase of non-cross-linked d-alanyl-d-alanine side chains; these chains are capable of binding vancomycin outside of the cell wall, making less vancomycin available for intracellular target molecules [9]. Sieradzki and Tomasz [9] demonstrated, when placed into the culture medium of VISA/VRSA laboratory mutant strains, vancomycin virtually disappears, to be recovered only from the cell wall fraction of the bacteria in a biologically active unaltered form. Much research still needs to be done to better understand the mechanisms of resistance. To foster further research on staphylococci with reduced susceptibility to vancomycin, the National Institute for Allergy and Infectious Diseases has funded the Network on Antimicrobial Resistance in Staphylococcus aureus (NARSA). NARSA has established and will maintain a repository of characterized strains to be accessed and used by interested scientists. Information on how to donate strains to this repository or how to access them for further research is available at http://www.narsa.net.

LABORATORY ISSUES

Vancomycin susceptibility testing in S. aureus. Soon after the detection and confirmation of the first 3 VISA isolates in the world, it became evident that disk diffusion was not a sufficiently sensitive means of detecting decreased susceptibility to vancomycin in S. aureus [5, 10]. In addition, the use of rapid automated methods, such as MicroScan rapid panels (Dade Behring), did not reliably identify these organisms either. Also, some automated systems may contain outdated algorithms that will not report an MIC of 8 µg/mL. However, recent changes in Vitek software (version 7.01; bioMérieux) have improved this system’s ability to detect VISA (CDC, unpublished observations). Because of these observations, the CDC published recommended strategies for additional testing of S. aureus for decreased vancomycin susceptibility (table 1) [11, 12]. In summary, all clinical microbiology laboratories should have an algorithm by which their routine testing methods can identify strains of S. aureus that may need additional (i.e., confirmatory) testing, and they should use acceptable confirmatory testing methods (i.e., 24 h of incubation time and an MIC susceptibility testing method). The bottom line is that confirmatory testing should be done on any S. aureus for which the MIC of vancomycin MIC is ≥4 µg/mL.

Any algorithm should consider the patient population served by the laboratory, the routine methods of testing, the resources available, and the requirements from the state health department (many state health departments have made VISA reportable). For example, a hospital in which 400 S. aureus isolates are processed each month by use of MicroScan, and in which 45% of the isolates are determined to be MRSA, will approach confirmatory testing differently than would a laboratory in which MRSA are only infrequently processed by means of disk diffusion. The former hospital may use the initial MIC determination as a screen, and it
A high inoculum of an isolate on screening agars for heteroresistance. Such screening (e.g., plating and there currently is no clinical utility in routine screening of MRSA isolates or may plate all MRSA isolates on screening agar. Several screening methods have been successfully employed to detect VISA/VRSA. The most convenient method may be to plate all clinical MRSA isolates (inoculum of 1–10 McFarland suspension) onto BHI agar containing vancomycin, 6 μg/mL, and to incubate it for 24 h (i.e., vancomycin-resistant enterococci screening agar). If isolates are growing on screening agar, the MIC of the parent isolate should be determined and reported to the clinician. In addition, laboratories and clinicians should notify infection control departments for confirmatory testing immediately after a VISA/VRSA or candidate strain is recognized. The CDC offers expedited confirmatory testing (e-mail, SEARCH@cdc.gov) for any candidate S. aureus strain with reduced susceptibility to vancomycin (i.e., with a MIC ≥4 μg/mL).

Detection of hetero-VRSA. Identification of subpopulations that demonstrate heterogeneous resistance to vancomycin is difficult, and there currently is no clinical utility in routine screening of S. aureus isolates for heteroresistance. Such screening (e.g., plating a high inoculum [10⁸ cfu/mL] of an isolate on screening agars with low concentrations of vancomycin incubated for prolonged periods) may be undertaken as part of research protocols, but it should not be reported on a patient’s medical record. Several methods have been described and are outlined elsewhere [7, 14].

Laboratory capacity in the United States. A 1998 survey of 416 clinical microbiology laboratories from 8 states participating in the CDC’s Emerging Infections Program indicated that most US laboratories have the capacity to detect VISA but are unaware of the need to perform supplemental (i.e., confirmatory) testing on selected strains. Although most (84%) had the capacity to identify a VISA strain (i.e., they did not rely solely on the use of disk diffusion without supplemental testing), only 60% recognized the need to perform supplemental testing on selected isolates [11]. To have confidence in the susceptibility results of clinical specimens of S. aureus, infectious disease clinicians need to be aware of how susceptibility testing to vancomycin is done in their affiliated laboratories. These types of inquiries, in addition to education of the clinical microbiology community, should fill this gap in capacity and awareness.

### Table 1. Recommendations for testing for *Staphylococcus aureus* with reduced susceptibility to vancomycin.

<table>
<thead>
<tr>
<th>Strategies to select strains for additional testing</th>
<th>Select isolates for which the vancomycin MICs are ≥4 μg/mL. This is based on the apparent heterogeneity of strains containing subpopulations with higher MICs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Select isolates for which the vancomycin MICs are ≥8 μg/mL (on the basis of NCCLS breakpoints*)</td>
</tr>
<tr>
<td></td>
<td>Select all MRSA. Most isolates of <em>S. aureus</em> with reduced susceptibility to vancomycin have been MRSA.</td>
</tr>
<tr>
<td></td>
<td>Select all <em>S. aureus</em> isolates. Since little is known about the extent of this resistance, any <em>S. aureus</em> could potentially have reduced susceptibility to vancomycin.</td>
</tr>
<tr>
<td></td>
<td>Select all isolates that grow on screening agar. Commercially available plates containing brain-heart infusion agar and vancomycin, 6 μg/mL, can be used to identify clinical isolates needing additional testing. The CDC recommends using an inoculum of 10⁸ cfu/mL when screening to identify these strains. All staphylococci that grow on the vancomycin screen plates should be inspected for pure culture and the parent strain tested as described below.</td>
</tr>
<tr>
<td>Appropriate testing and confirmation</td>
<td>Primary testing of <em>S. aureus</em> with vancomycin requires 24 h of incubation.</td>
</tr>
<tr>
<td></td>
<td>Disk diffusion is not an acceptable method for vancomycin susceptibility testing of <em>S. aureus</em>. None of the known strains of <em>S. aureus</em> with reduced susceptibility to vancomycin have been detected by this method.</td>
</tr>
<tr>
<td></td>
<td>Laboratories should ensure that the strain is in pure culture and should reconfirm the genus and species of the organism.</td>
</tr>
<tr>
<td></td>
<td>An MIC susceptibility testing method (e.g., broth microdilution, agar dilution, or agar-gradient diffusion) should be used to confirm the vancomycin test.</td>
</tr>
</tbody>
</table>

**NOTE.** CDC, Centers for Disease Control and Prevention; MRSA, methicillin-resistant *S. aureus*; adapted from the CDC [11, 12].

* NCCLS MIC breakpoints for vancomycin are as follows: susceptible, <4 μg/mL; intermediate, 8–16 μg/mL; and resistant, >32 μg/mL [5].

**CLINICAL AND EPIDEMIOLOGIC CHARACTERISTICS**

**Risk factors.** Several strains of VISA associated with a clinical infection have been reported. The first report described a 4-month-old infant with a surgical-site infection in Japan in 1996 [3]. Subsequently, the CDC has confirmed the presence of VISA in 6 patients in the United States [4, 15–17] (2 reports are from the CDC [unpublished data] (table 2). However, the first infection with VISA appears to have occurred in France, in November 1995, in a 2-year-old girl with leukemia and a central line–associated bacteremia successfully treated with surgical drainage and quinupristin-dalfopristin [18]. Without a proper epidemiologic study, risk
Table 2. Reports of clinical aspects of vancomycin-intermediate *Staphylococcus aureus* (MIC, 8 µg/mL) in patients in the United States.

<table>
<thead>
<tr>
<th>State and reference</th>
<th>Date</th>
<th>Age, y</th>
<th>Source</th>
<th>Diagnosis and underlying illness</th>
<th>Vm exposure, weeks</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Jersey [4]</td>
<td>August 1997</td>
<td>66</td>
<td>Blood</td>
<td>Bacteremia: diabetes mellitus, acute renal failure, recent peritoneal dialysis, recurrent MRSA bacteremia</td>
<td>18</td>
<td>Gm, Rif</td>
<td>Infection cleared, died (candidemia)</td>
<td>SXT, Gm, Chl, Tet</td>
</tr>
<tr>
<td>New York [15]</td>
<td>April 1998</td>
<td>79</td>
<td>Blood</td>
<td>Bacteremia: chronic renal failure, hemodialysis, recurrent MRSA line-associated bacteremia</td>
<td>6</td>
<td>Vm, Tm (12 h only)</td>
<td>Died 12 h after admission</td>
<td>TMP-SMZ, Gm, Chl, Tet</td>
</tr>
<tr>
<td>Illinois [17]</td>
<td>April 1999</td>
<td>63</td>
<td>Blood</td>
<td>Mitral valve endocarditis: chronic hemodialysis, recurrent MRSA line-associated bacteremia</td>
<td>3.5</td>
<td>Vm, Tob, Rif</td>
<td>Refused surgery; died after 10 days</td>
<td>TMP-SMZ, Gm, Tet</td>
</tr>
<tr>
<td>Minnesota a</td>
<td>April 2000</td>
<td>56</td>
<td>Blood</td>
<td>Vertebral osteomyelitis: chronic hemodialysis, peripheral vascular disease, recurrent MRSA line-associated bacteremia</td>
<td>18</td>
<td>Vm, Naf, Gm</td>
<td>Infection cleared; died</td>
<td>Not available</td>
</tr>
<tr>
<td>Nevada a</td>
<td>June 2000</td>
<td>27</td>
<td>Abscess drainage</td>
<td>Polymicrobial (with MRSA) intrahepatic abscess: biliary stent, after complicated cholecystectomy</td>
<td>10</td>
<td>Linezolid, TMP-SMZ, doxycycline</td>
<td>Surgical drainage; infection cleared</td>
<td>TMP-SMZ, Gm, Tet</td>
</tr>
</tbody>
</table>

**NOTE.** Chl, chloramphenicol; Cm, clindamycin; Gm, gentamicin; MRSA, methicillin-resistant *S. aureus*; Naf, nafcillin; Rif, rifampin; TMP-SMZ, trimethoprim-sulfamethoxazole; Tet, tetracycline; Tm, tobramycin; Vm, vancomycin; Vm exposure, vancomycin exposure immediately preceding vancomycin-intermediate *S. aureus* infection.

a Unpublished data (Centers for Disease Control and Prevention, Clarke County Health Department, Nevada, and Minnesota State Health Department.
factors cannot be determined, but we can identify commonalities and consider them to be potential risk factors (table 2). The spectrum of underlying illnesses is remarkably similar among these patients. Most patients had ongoing or recent dialysis, and most had recurrent MRSA central venous catheter–or prosthetic material–associated bacteremias that were treated with vancomycin. Many had prolonged vancomycin exposure (6–18 weeks) in the 3–6 months preceding the infections. The 4 published reports of VISA infections in the United States suggest that the VISA strains appear to have developed from preexisting MRSA strains that infected the patients in the months before the VISA infection, and these strains have pulsed-field gel electrophoresis patterns that are similar to those of the patients’ previously infecting MRSA strains [4, 15, 17]. This suggests that the strains, although susceptible to vancomycin, were never fully eradicated from the patients, or that they may have reinfeeted the patients from an unrecognized reservoir in the home, workplace, or dialysis center. There have been 17 reports to the CDC regarding patients infected with MRSA strains for which the MICs of vancomycin are 4 μg/mL, and these patients appear to have underlying illness and outcomes similar to those of VISA-infected patients (CDC, unpublished observations). An ongoing laboratory and epidemiologic study is attempting to determine whether these isolates are essentially similar to VISA.

Susceptibility profiles. The isolates reported from the United States were all susceptible to trimethoprim-sulfamethoxazole (TMP-SMZ), and at least 2 other Food and Drug Administration (FDA)–approved agents (table 2). These isolates also remained susceptible to agents not routinely tested in clinical microbiology laboratories. In general, the MICs were in the range of 0.25–2 μg/mL for quinupristin-dalfopristin, linezolid, and everninomycin (CDC, unpublished data). Another study demonstrated that the minimum bactericidal concentration of quinupristin-dalfopristin and daptomycin (0.25–1.0 μg/mL) is also low [19]. As part of the CDC’s surveillance initiative (discussed below), VISA isolates sent to the CDC will be screened for susceptibility to several agents not yet approved by the FDA. If necessary, these results will be shared with the FDA and the clinician to facilitate compassionate use of these agents.

Treatment issues. The American patients each received unique treatment modalities and antimicrobial agents to treat their VISA. After the clinician recognized that the infecting isolate was VISA (this did not occur in the case identified in New York, because the patient died 12 h after admission to the hospital), most patients started receiving treatment with an aminoglycoside or rifampin. Vancomycin therapy was usually continued for some time. It is of note that all isolates were susceptible to TMP-SMZ. Although the 6-month mortality rate associated with VISA infections approaches 100% (the patient who was described in the most recent unpublished report is still alive), only 2 of the 5 deaths may be directly attributed to VISA infection. However, in 1 of these 2 patients (the patient in New York), the patient died just hours after treatment was initiated; therefore, the patient cannot be considered to have experienced treatment failure [20]. A patient in Illinois with VISA mitral valve endocarditis died while bacteremic with VISA; the patient had refused surgical intervention [17]. Also, the failure of vancomycin to sterilize the blood of patients with traditional S. aureus endocarditis has been clearly described [21]. Therefore, the role that VISA played in the deaths of these 2 patients remains uncertain. However, it is clear that the organism is virulent, causes disease that necessitates treatment (e.g., removal of prosthetic material, administration of antimicrobial therapy, and, perhaps, surgery), and can be fatal. It is of note that the most recent report from Nevada involves a patient treated with surgery plus linezolid, TMP-SMZ, and doxycycline therapy with apparent success. Furthermore, reports to the CDC regarding patients who have S. aureus with MICs of 4 μg/mL suggest that some of these patients fail to improve clinically even though they receive appropriate vancomycin therapy. These patients’ failure to respond may have been due to decreased susceptibility to vancomycin or other factors, and it is unclear just how different the strains of S. aureus with MICs of vancomycin of 4 μg/mL are from those with MICs of 8 μg/mL (CDC, unpublished data). Likewise, clinical failures among patients with MRSA surgical-site infections involving orthopedic implants were reported in Spain, with MICs to vancomycin of 1–4 μg/mL [22]. Most of these isolates demonstrated heteroresistance to vancomycin. To ascertain the relevance of hetero-VISA in patients with clinical failure, further studies are needed.

There are some prospects for advancing the therapy of VISA on the basis of laboratory studies. Several studies suggest that β-lactam agents and vancomycin work synergistically against VISA. In vitro studies suggest that VISA isolates may be inhibited at lower vancomycin concentrations when exposed to nafcillin or cefazolin [9, 23]. Climo et al. [24] demonstrated that the higher the MIC of vancomycin, the more susceptible the isolate was to combination therapy. They further demonstrated, in a rabbit endocarditis model, that therapy with either vancomycin or nafcillin as a single agent was ineffective, but combination therapy was associated with lower bacterial burden in the rabbits. However, another study did not document a decrease in the MIC of methicillin, because the MIC of vancomycin increased after serial passage of VISA isolates in the absence of vancomycin [25]. These data are experimental and should not suggest that β-lactam agents be a substitute for treatment with antimicrobials to which the infecting organism is susceptible.

Surveillance, scope, and magnitude of VISA/VRSA. There have been no confirmed reports of clinical infections with VRSA. Because of the difficulties with laboratory detection outlined above, and because of the rarity of VISA infections, the incidence of disease (i.e., the number of infections per 1 million persons) cannot be known. However, by reviewing several data sources, some as-
sessions can be made. A single-institution study screened 243 patients and identified 14 (6%) colonized with MRSA, but none had VISA; in addition, none demonstrated heteroresistance [26]. A CDC study used several different screening agars to test 630 clinical isolates of *S. aureus* from 33 US hospitals. No strains of VISA were identified, but 2 isolates of *S. aureus* demonstrated heteroresistance [13]. The CDC’s NNIS system, which receives reports on >7000 *S. aureus* hospital-acquired infections each year from over 300 US hospitals, has reported no confirmed strains of VISA. In summary, as of August 2000, the natural occurrence of VISA appears to be a rare event.

However, there are some data to suggest that VISA infections may become more common in the near future. First, the number of reports to the CDC of *S. aureus* with decreased vancomycin susceptibility have increased in the past year compared with previous years, although this may be the result of improved laboratory capacity. Second, if heteroresistance is a precursor to VISA, then such precursors may already be a condition of many clinical strains of *S. aureus*. Several retrospective studies of clinical isolates of MRSA strains screened on BHI agar with vancomycin, 4–6 μg/mL, have identified heteroresistant isolates. The frequency of heteroresistance has been generally low (0.5%–1.5%) [7, 14, 27, 28], but 1 Japanese university hospital reported frequencies as high as 20% [7]. Although the clinical relevance of these isolates is unknown, their occurrence may foretell more frequent infections with VISA, especially in populations of patients receiving recurrent courses of glycopeptide therapy, such as the patient population undergoing hemodialysis.

To aid in the identification of patients with VISA infections, the CDC began a project of enhanced case finding in 1998 called the “Surveillance for Emerging Antimicrobial Resistance Connected to Health Care (SEARCH).” Through partnerships involving private industry, large reference laboratories, the Infectious Diseases Society of America’s Emerging Infections Network, the American Society for Microbiology’s ClinMicronet, public health services (i.e., state health departments), and infection control communities, SEARCH offers expedited confirmatory susceptibility testing of strains suspected to have decreased susceptibility to vancomycin. In relation to the difficulties with laboratory testing described above, many VISAs may have an initial MIC determination of 4 μg/mL for vancomycin. Therefore, the CDC is asking for any clinical *S. aureus* isolate with an MIC ≥4 μg/mL to be sent for confirmatory testing (contact SEARCH@cdc.gov). SEARCH has received approximately 120 isolates from American patients since the first 3 VISA isolates were reported in the fall of 1998, and it has confirmed 3 additional VISA isolates and 17 isolates of *S. aureus* with an MIC of 4 μg/mL.

**Prevention is a primary infection control issue.** Although infection control experience with VISA is limited, infection control recommendations have been proposed by experts in the field [12, 29]. For any patient suspected of having an infection with VISA or VRSA, contact precautions should be followed, and the infection control and local health departments should be notified immediately. If the isolate is confirmed as VISA or VRSA, special precautions recommended by the Healthcare Infection Control Practices Advisory Committee (HICPAC) should be initiated (table 3) [12]. All of the infection control staff members caring for patients with confirmed VISA infections in the United States adopted the HICPAC guidelines; some instituted supplemental measures. Approximately 400 culture specimens obtained from persons who had contact with the VISA-infected patients (both health care workers and family members) failed to identify any additional persons colonized or infected with VISA [4, 15, 17]. Contact precautions were already followed for most of the patients with MRSA infection or colonization. Because MRSA is known to be highly transmissible in health care settings, it is reasonable to assume that VISA isolates will likewise be highly transmissible. Because of the costs involved with the VISA precautions and epidemiologic and laboratory investigations, consultation with the hospital epidemiologist, local health department, and the CDC should be sought until more experience is obtained regarding patient management and infection control issues. These guidelines will be redressed in upcoming meetings by HICPAC after more data are accumulated.

### Table 3. Hospital Infection Control Practices Advisory Committee interim recommendations for prevention of the spread of staphylococci with reduced susceptibility to vancomycin.

<table>
<thead>
<tr>
<th>Infection control precaution</th>
<th>Use contract precautions as recommended for multidrug-resistant organisms.</th>
<th>Monitor and enforce compliance with contact precautions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolate the patient in a private room. Minimize the number of people in contact with or caring for the patient. Begin one-on-one care by specified personnel.</td>
<td>Initiate epidemiologic and laboratory investigations with the assistance of state health departments and the CDC.</td>
<td>Determine the extent of transmission within the facility. Assess the efficacy of precautions by monitoring acquisition of VISA/VRSA by personnel.</td>
</tr>
<tr>
<td>Educate all health care personnel about the epidemiology of VISA/VRSA and appropriate infection control precautions.</td>
<td>Consult with state health departments and the CDC before transferring or discharging the patient.</td>
<td>Inform the following appropriate personnel about the presence of a patient with VISA/VRSA: patient’s accepting physician, admitting or emergency department personnel, and personnel admitting the patient.</td>
</tr>
</tbody>
</table>

**NOTE.** CDC, Centers for Disease Control and Prevention, VISA/VRSA: *vancomycin-intermediate Staphylococcus aureus* /vancomycin-resistant *S. aureus*. 

*In addition to following standard precautions, wear gowns and gloves when entering the patient’s room, use masks if anticipating contact with potential infective material, and before and after glove use, wash hands with antimicrobial-containing soap or a waterless hand antiseptic agent. Remove gown and gloves before leaving the patient’s room [32].

**b** CDC has developed a public health packet to guide state health departments and infection control programs in evaluating the spread of VISA/VRSA in a health care facility. For information, contact SEARCH@cdc.gov or visit http://www.cdc.gov/ncidod/dhqp/default.htm.
lated on strains of S. aureus for which the MICs of vancomycin are \( \geq 4 \, \mu g/mL \). Up-to-date information can be received from the Hospital Infections Program (available by phone [800-893-0485] or at http://www.cdc.gov/ncidod/hip/default.htm).

The appropriate use of antimicrobials, especially vancomycin, is paramount to the prevention of the continued emergence of VISA and VRSA. Several studies have shown that vancomycin is frequently used for inappropriate reasons [30]. Improved use of vancomycin, use of proper diagnostic techniques to minimize prolonged empiric therapy, minimal use of temporary venous catheters, removal of prosthetic materials involving S. aureus infections, and encouragement for physicians trained to deal with noninfectious diseases to seek advice from infectious disease specialists for the treatment of serious S. aureus infections will help to prevent the emergence of VISA and VRSA.

**Coagulase-negative staphylococci.** Low-level vancomycin resistance has been reported in clinical isolates of coagulase-negative staphylococci [31]. *Staphylococcus haemolyticus* frequently has high MICs of vancomycin (2–8 \( \mu g/mL \)). The clinical relevance of decreased susceptibility in this species is even less clear than that for *S. aureus*. However, the current HICPAC guidelines recommend similar infection control precautions for patients infected with any staphylococci with MICs \( \geq 8 \, \mu g/mL \). Infection control standards for patients with infections associated with these organisms should be determined in consultation with infection control and public health authorities.

**SUMMARY**

To date, several clinical infections with VISA have been reported. Intermediate resistance appears to develop from preexisting MRSA strains in the presence of vancomycin in patients with a considerable underlying illness—in particular, chronic renal failure. Failure of treatment for MRSA infections with vancomycin should alert the clinician to the possibility of infection with a strain of VISA. VISA detection is problematic in the laboratory, and special susceptibility testing procedures or algorithms may be needed. Although all of the VISA-infected patients who died had serious underlying illnesses that may have contributed to their deaths, the infections did not appear to respond to vancomycin. Newly developed agents, including linezolid and quinupristin-dalfopristin, appear to be effective in vitro. Further strategies are needed to evaluate the best therapeutic options for patients infected with VISA.

The clinical relevance of heteroresistance is not known. Any screening for heteroresistance for the purpose of clinical decision-making is not warranted at this time. Prevention of the emergence of VISA/VRSA must be high on the agenda of the infectious disease community. Without continued vigilance in the enforcement of infection control measures, improved use of antimicrobials, and coordination of efforts among public health authorities, increasing levels of vancomycin resistance in *S. aureus* are likely to be encountered.

**Acknowledgments**

I thank Carrie Jepson, RN, Clarke County Health Department, Las Vegas, Nevada; and Timothy Naimi, MD, MPH, Minnesota Department of Health, for kindly contributing information regarding the most recent reports of VISA. I thank Fred C. Tenover, PhD, for his assistance in the preparation and review of this article. Also, special thanks to Jeff Hagemen, MHS, for his assistance in facilitating the SEARCH program, and to the staffs of the Hospital Infections Program’s Nosocomial Pathogens Laboratory Branch and Hospital Environmental Laboratory Branch at the CDC.

**References**


