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***Staphylococcus aureus*,**  
**Vancomycin-intermediate (VISA)**  
**Vancomycin-resistant (VRSA)**

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VISA/VRSA are types of *Staphylococcus aureus* that have developed resistance to vancomycin, an antibiotic to which most *S. aureus* bacteria are susceptible. VISA/VRSA infections are only different from other *S. aureus* infections in that they cannot be treated with vancomycin. Vancomycin continues to be a critical antimicrobial agent for treating infections caused by *S. aureus* strains that are resistant to oxacillin (MRSA), and other antimicrobial agents. The decreased susceptibility of VISA and VRSA strains to vancomycin leaves clinicians with few therapeutic options for treating these infections.

### **History**

The first case of vancomycin resistance involved a four-month-old boy treated unsuccessfully in Japan for twenty-nine days for an MRSA infection after heart surgery; the organism isolated from the incision site during therapy had a minimal inhibitory concentration of 8 µg of vancomycin per milliliter. According to the National Committee for Clinical Laboratory Standards, this strain is certainly not susceptible (defined as having a minimal inhibitory concentration of less than 4 µg per milliliter), but it is also not yet resistant (defined as having a minimal inhibitory concentration of greater than or equal to 32 µg per milliliter). This type of *S. aureus* was therefore described as *S. aureus* with intermediate resistance to vancomycin (or glycopeptides).

In 1997, two infections due to *S. aureus* with reduced susceptibility to vancomycin were identified in the United States. Both patients had other underlying conditions (including renal failure), indwelling medical devices and infections with MRSA strains that were treated with vancomycin intravenously for eighteen weeks each. In both cases, organisms with intermediate resistance to vancomycin were isolated during therapy. In both isolates the minimal inhibitory concentration of vancomycin remained 8 µg per milliliter even after passage through twenty subcultures, attesting to the strains' newly acquired genetic stability. Comparison of antibiotic-susceptibility patterns and pulsed-field gel electrophoresis of the isolates with intermediate resistance and those of the organisms initially recovered from the same patients showed enough similarity to suggest that prolonged treatment with vancomycin was responsible for the emergence of glycopeptide resistance in these strains.

In these cases, the stage was set in the same way for the emergence of resistance: a patient with chronic renal failure and other conditions, an indwelling catheter and infection with MRSA. Vancomycin was administered for six weeks. Isolates were recovered on days one and eleven and then five weeks after the end of therapy. The isolates were genetically identical, but the last isolate had acquired intermediate resistance to glycopeptides.

From 1996 to 2001 there were 48 identified VISA isolates in adults. Each case had received multiple courses of vancomycin for MRSA (methicillin-resistant *S. aureus*) infection. Resistance to vancomycin seems to develop from pre-existing strains of MRSA in the presence of vancomycin. Extensive vancomycin uses allows the vancomycin-intermediately susceptible *S. aureus* strains (VISA) to grow. VRSA strains are characterized by expression the of *vanA* gene residing on Tn1546-like element which was acquired from an *Enterococcus* spp. As

of September 2006, six VRSA infections have been reported in patients from the United States. To date all VRSA isolates have been susceptible to other FDA approved drugs.

### **Glycopeptide-intermediate *S. aureus* (GISA)**

The term glycopeptide refers to a group of antimicrobial agents that includes vancomycin and teicoplanin. Since the first two VISA isolates in the United States were also resistant to teicoplanin, the term glycopeptide-intermediate *S. aureus* (GISA) was used to indicate this broader resistance profile. While GISA may be a more specific term for strains intermediate to both vancomycin and teicoplanin, not all VISA strains are intermediate to teicoplanin; therefore, VISA is a more accurate and more widely used term.

### **Epidemiology**

To date, VISA strains [vancomycin MIC = 4-8 µg/ml] are characterized by a resistance mechanism that is not transferable to susceptible strains and is usually associated with vancomycin exposure. Therefore, both the likelihood of transmission to contacts and the maintenance of the VISA phenotype in the absence of vancomycin pressure are presumed to be low. Contact investigations for VISA cases are not routinely recommended unless there is suspicion that transmission has occurred.

In contrast, VRSA strains [vancomycin MIC 16 µg/ml] are characterized by expression of vanA residing on Tn1546-like element which was acquired from an Enterococcus spp; therefore, this resistance is potentially transferable to susceptible strains or other organisms. Contact investigations and follow-up for VRSA cases are recommended.

### Risk Factors

Identified risk factors for development of *S. aureus* infections with reduced susceptibility to vancomycin include

- Prior vancomycin use
- Prior methicillin-resistant *S. aureus* infection two or three months before current infection
- Underlying health conditions (renal disease, diabetes)

### VRSA and MRSA

Most VRSA isolates are also oxacillin/methicillin-resistant and contain mecA. However, some VISA isolates became oxacillin-susceptible upon repeat isolation from patients and some tested oxacillin-susceptible but contained mecA.

VRSA isolates contain the vanA vancomycin resistance gene. The vanA gene is usually found in enterococci and typically confers high-level vancomycin resistance (MICs= 512-1024µg/ml) to these organisms. Vancomycin-resistant enterococci containing vanA are often isolated from patients in addition to MRSA. It is likely that the vanA determinant is transferred via plasmids from enterococci to a resident MRSA strain, resulting in the VRSA.

The mechanism of decreased vancomycin susceptibility in VISA strains is not fully understood. VISA cells have thicker cell walls that contain many cell wall monomers capable of binding vancomycin extracellularly. Vancomycin must reach the cell membrane and bind to the growing cell wall complex to inhibit cell growth.

### **Case Definition and Laboratory Detection**

Isolation of VISA/VRSA from any site is reportable to the Louisiana Office of Public Health. Case definitions for classifying isolates of *S. aureus* with reduced susceptibility to vancomycin are based on laboratory breakpoints established by Clinical and Laboratory Standards Institute (CLSI).

- Vancomycin-intermediate *S. aureus* - Vancomycin MIC =4-8µg/mL
- Vancomycin-resistant *S. aureus* – Vancomycin MIC ≥16µg/mL

Routine susceptibility testing methods may not detect VISA/VRSA isolates. Three of six confirmed VRSA isolates were not reliably detected by automated testing systems. The CDC provides guidance to improve laboratory capacity to detect vancomycin resistance in *S. aureus*.

Laboratory Detection of Vancomycin-Intermediate/Resistant *Staph. Aureus*  
[www.cdc.gov/ncidod/dhqp/ar\\_visavrsa\\_labFAQ.html](http://www.cdc.gov/ncidod/dhqp/ar_visavrsa_labFAQ.html)

### Procedure for Culturing Anterior Nares

Anterior nares specimens should be obtained with a commercially prepared sterile swab. Although various methods (e.g., swabbing one nostril vs. both, pre-moistening swabs vs. dry) have been used to obtain nasal swab specimens for *S. aureus* and MRSA, data are lacking to recommend one method. However, if obtaining swabs from multiple individuals, pre-moistening by dipping the swab into a common container of sterile saline might increase the chance of cross contamination if an appropriate aseptic technique is not followed. Below is an example of a method that could be used.

1. Label swab container with either the patient name or patient code.
2. Obtain informed consent from participants. Explain to the participants that you will only be touching the inside of the nostril (1-2 cm or the length of fingernail from cuticle to tip of finger). Inform them that it may make their nose itch, eyes water, or sneeze, but it should not hurt.
3. Have participant tilt head back.
4. Carefully remove swab from plastic packaging making sure not to touch any object with the swab.
5. Insert swab into one nostril (about 2 cm on an adult) without touching anything but the inside or anterior part of the nostril.
6. Lightly rotate swab on all surfaces of the anterior, or forward, internal part of the nasal mucosa for about three seconds and remove.
7. Immediately return swab into its plastic transport container, taking care not to touch anything else with it; tighten the cap of the swab container and ensure that the swab is firmly secured in the transport container and properly labeled; invert the swab and then activate the ampule of transport medium if present (e.g., squeeze bottom bulb until you feel the bulb with transport medium break).
8. Package swabs according to testing laboratory's instructions (e.g., sealed in biohazard plastic bags, properly labeled, in a suitable container with or without ice packs) and send swabs to the laboratory for processing.

### **Case Investigation**

Contact investigations to identify potential transmission may be warranted on a case-by-case basis after consultation with OPH. **Contact investigations for VISA cases are not routinely recommended unless there is suspicion that transmission has occurred.**

In contrast, VRSA strains [vancomycin MIC 16 µg/ml] are characterized by expression of vanA residing on Tn1546-like element which was acquired from an Enterococcus spp; therefore, this resistance is potentially transferable to susceptible strains or other organisms. Contact investigations and follow-up for VRSA cases are recommended.

This section discusses how and where to obtain specimens from healthcare workers, patient roommates and others having had contact with a patient infected or colonized with VISA or VRSA.

#### Step 1: Develop a written plan for VRSA colonized individuals

Before any culturing is performed, a plan should be developed outlining how VRSA colonized individuals will be handled. OPH recommendations are:

Decolonization of carriers is only indicated if they are implicated in transmission of infection.

For colonized/infected individuals screening cultures should be collected at weekly intervals. Collection sites

- Anterior nares
- Armpit(axilla)
- Wounds, drains, other clinically relevant sites
- Consider rectal, perirectal specimens for VRSA-infected patients to determine vancomycin-resistant enterococci (VRE) carriage status.

Obtain follow-up cultures once weekly and consider individual free of colonization after three negative cultures over three weeks post therapy.

Infected/colonized individuals should be placed under contact precautions. Contact precautions can be removed following three negative screening cultures over three weeks post therapy.

The application of Contact Precautions for patients infected or colonized with multi-drug resistant organisms (MDROs) is described in the HICPAC/CDC MDRO guideline

- A single patient room is preferred for patients who require contact precautions
- Minimize the number of persons caring for the patient (assign dedicated staff to care for VRSA patient)
- Educate and inform appropriate personnel about the presence of patient with VRSA and the need for contact precautions

Nasal decolonization treatment: Regimens to eliminate *S. aureus* colonization have been used in healthcare settings in an effort to prevent autoinfection among colonized patients and control MRSA. However, a limited number of antimicrobial agents are available for the eradication of *S. aureus* colonization. These regimens have included various combinations of topical and systemic antimicrobial agents and antiseptic body washes and have typically been used as part of multi-faceted infection control interventions, making it difficult to evaluate the effectiveness of any individual component. Mupirocin, a topical antimicrobial with anti-staphylococcal activity, is usually the agent of choice for eradication of staphylococcal nasal colonization in patients and healthcare workers during localized MRSA outbreaks. Data from healthcare settings indicate that intranasal mupirocin can be effective at eliminating *S. aureus* colonization in the short term; however, recolonization is common.

Before the decision is made to use mupirocin, several limitations of the agent must be considered. First, elimination of colonization may be transient. In settings where MRSA is endemic, persons may be recolonized from external sources. Second, *S. aureus* can develop resistance to mupirocin during therapy and resistance has been attributed to widespread application of intranasal mupirocin ointment for hospitalized patients. Finally, in most studies of its use to eliminate MRSA carriage in outbreak situations, mupirocin was administered in conjunction with multiple infection control measures. Therefore, it is difficult in these studies to attribute eradication of MRSA colonization to the use of mupirocin alone.

#### Step 2: Identify and categorize contacts

Contacts should be categorized based on their level of interaction (i.e., extensive, moderate, or minimal) with the colonized or infected patient. Priority should be given to identifying contacts that have had extensive interaction with the VRSA patient during a defined period before the VRSA culture date. The length of this period depends on recent culture results, the setting where the patient is receiving healthcare and the clinical assessment.

#### Extensive Interaction

- A. Patients who: Share the VRSA patient's room
- B. Nursing or patient-care providers involved in direct patient care who: clean/bathe/rotate/ambulate the patient change dressings make frequent visits (>3 visits per day including nurses assigned to the patient) handle secretions and body fluids, including respiratory secretions manipulate intravenous lines
- C. Physicians who: care for wound dressings or perform debridement conduct physical exams on the VRSA patient

- D. Ancillary staff who: have documented prolonged patient contact, including physical therapy or rehabilitation personnel and dialysis or respiratory technicians.
- E. Family members or household contacts who: provide primary care had/have close contact with patient (e.g., sleep in the same bed or same room)

#### Moderate interaction

- A. Nursing or patient-care providers who: deliver medications cross-cover patient only
- B. Physicians who: see patient on daily rounds, without conducting extensive exams perform surgical or invasive procedures where sterile barriers or aseptic techniques are used
- C. Ancillary staff who: monitor patient-care equipment without handling secretions have limited interactions (e.g., radiology technicians)

#### Minimal interaction

- A. Nursing or patient-care providers who: work on the same floor without formal cross-coverage of patient performing predominately administrative duties
- B. Physicians who: consult without extensive exam visit during teaching rounds only
- C. Ancillary staff who: provide dietary or maintenance services that do not interact directly with the patient

#### Step 3: Specimen Collection

Clinical laboratories that routinely use rapid polymerase-chain reaction (PCR) assays for detection of MRSA from surveillance swabs, will need to utilize culture-based methods so that vancomycin susceptibilities can be determined.

From patients colonized or infected with VRSA: Culture anterior nares, wounds, drains, other clinically relevant sites (e.g., catheter exit site). Also, consider collecting specimens (e.g., rectal, perirectal) to determine vancomycin-resistant enterococci (VRE) carriage status.

From persons having extensive interaction with colonized/infected patient: Culture anterior nares and skin lesions (e.g., abscess or dermatitis, open wounds). If no contacts among this group are identified as being VRSA positive, no additional groups should be cultured. Ultimately, the decision to culture those with less interaction should be made in consultation with public health authorities.

From persons with moderate or minimal interaction: Only culture if “Extensive Interaction” contacts have positive results. Culture anterior nares and skin lesions (e.g., abscess or dermatitis, open wounds)

If contacts are identified as MRSA carriers but not VRSA carriers, the MRSA isolates may still be of laboratory interest and should be saved for further testing.

#### Step 4: Evaluate Efficacy of Infection Control Precautions

If VRSA colonization of contacts is identified or until the case-patient is no longer colonized or infected, culturing the anterior nares of contacts with extensive interaction could be performed on a regular (e.g., weekly) basis to assess the efficacy of infection control precautions. Placing a log book at the entrance of the patient’s room would help identify and track these VISA/VRSA patient contacts during the evaluation period. The duration of evaluation and the decision to prospectively culture those with less interaction should be made in consultation with public health authorities.

### **Infection Control Issues**

The Centers for Disease Control and Prevention (CDC) has issued specific recommendations intended to reduce the development and transmission of VRSA. Below is a checklist of important infection control recommendations. However, these may need to be customized to special healthcare-settings (e.g., dialysis, home healthcare).

Infection control precautions should remain in place until a defined endpoint (e.g., patient has been culture-negative three times over three weeks or the patient's infection has healed).

### Acute-Care Settings

1. Isolate the patient in a private room.
2. Minimize the number of persons caring for the patient (e.g., assign dedicated staff to care for VISA/VRSA patient).
3. Implement the appropriate infection control precautions during patient care.
  - a. Use contact precautions (gown and gloves for room entry).
  - b. Wear mask/eye protection or face shield if performing procedures likely to generate splash or splatter (e.g., wound manipulation, suctioning) of VISA/VRSA contaminated material (e.g., blood, body fluids, secretions and excretions).
  - c. Perform hand-hygiene using appropriate agent (e.g., alcohol-based hand sanitizer or hand washing with plain or antimicrobial soap and water).
  - d. Dedicate non-disposable items that cannot be cleaned and disinfected between patients (e.g., adhesive tape, cloth-covered blood pressure cuffs) for use only on the patient with VISA/VRSA.
  - e. Monitor and strictly enforce compliance with contact precautions.
4. Educate and inform the appropriate personnel about the presence of a patient with VRSA and the need for contact precautions:
  - a. Patient's physicians
  - b. Admitting or emergency room personnel
  - c. Personnel admitting patients to unit
  - d. Personnel transporting patients between institutions
5. Consult with the local and/or state health department and CDC before transferring the patient (for emergencies only) or discharging the patient.

Dialysis Settings Infection control precautions recommended for all hemodialysis patients are adequate to prevent transmission from most patients infected/colonized with VRSA.

1. Wear disposable gloves when caring for the patient or touching the patient's equipment at the dialysis station; remove gloves and wash hands between each patient or station.
2. Non-disposable items that cannot be cleaned and disinfected (e.g., adhesive tape, cloth-covered blood pressure cuffs) should be dedicated for use only on a single patient.
3. Unused medications (including multiple dose vials containing diluents) or supplies (e.g., syringes, alcohol swabs) taken to the patient's station should be used only for that patient and should not be returned to a common clean area or used on other patients.
4. When multiple dose medications vials are used (including vials containing diluents), prepare individual patient doses in a clean (centralized) area away from dialysis stations and deliver separately to each patient. Do not carry multiple dose medication vials from station to station.
5. Do not use common medication carts to deliver medications to patients. Do not carry vials, syringes, alcohol swabs, or supplies in pockets. If trays are used to deliver medications to individual patients, they must be cleaned between patients.
6. Clean areas should be clearly designated for the preparation, handling and storage of medications and unused supplies and equipment.

7. Use external venous and arterial pressure transducer filters/protectors for each patient treatment to prevent blood contamination of the dialysis machines pressure monitors. Change filter/protectors between each patient treatment and do not reuse them. Internal transducer filters do not need to be changed routinely between patients.
8. Clean and disinfect the dialysis station (e.g., chairs, beds, tables, machines) between patients.
9. For dialyzers and blood tubing that will be reprocessed, cap dialyzer ports and clamp tubing. Place all used dialyzers and tubing in leakproof containers for transport from station to reprocessing or disposal area.

Additional infection control precautions should be considered for treatment of patients who might be at increased risk for transmitting pathogenic bacteria. For these patients, consider adding the following precautions:

1. Staff members treating the patient should wear a separate gown over their clothing and remove the gown when finished caring for the patient
2. Dialyze the patient at a station with as few adjacent stations as possible (e.g., at the end or corner of the unit).

#### Home Healthcare Settings

1. Home healthcare providers should follow the same VRSA precautions as hospital-based healthcare providers.
  - a. Wear gown and gloves upon entering the area of house where the patient care will be provided.
  - b. Wear mask and eye protection or face shield if performing procedures likely to generate splash or splatter (e.g., wound manipulation, suctioning) of VRSA contaminated material (e.g., blood, body fluids, secretions and excretions).
  - c. Perform hand-hygiene using appropriate agent (e.g., alcohol-based hand sanitizer or hand washing with plain or antibacterial soap and water).
  - d. Develop systems to monitor and strictly enforce compliance with contact precautions in the home by healthcare workers.
2. Minimize the number of persons with access to the VRSA colonized/infected patient (e.g., dedicate a single staff person to care for this patient).
3. Dedicate non-disposable items that cannot be cleaned and disinfected between patients (e.g., cloth-covered blood pressure cuffs) for use only on a single patient.

Conversely, VRSA strains are characterized by resistance that is potentially transferable to susceptible strains or other organisms. Contact investigations and follow-up for VRSA cases are recommended.