Vancomycin-Intermediate Staphylococcus aureus (VISA) and Vancomycin-Resistant Staphylococcus aureus (VRSA)

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Overview

Staphylococcus aureus (*S. aureus*), often referred to simply as "staph", are bacteria that are commonly carried on the skin or in the nose of healthy people. Staph is one of the most common causes of skin infections in the United States. Most of these infections are minor such as pimples and boils and most can be treated with antibiotics. However, staph can also cause serious infections such as blood stream infections, surgical wound infections, and pneumonia. They can produce a toxin, which can cause gastrointestinal symptoms when ingested. Strains that are oxacillin and methicillin resistant, while more accurately might be named "ORSA", are historically termed methicillin-resistant S. *aureus* (MRSA).

MRSA infections are now common in the United States and as a result there has been increased reliance on vancomycin for the treatment of MRSA infections. In the mid-1990's, reports indicated that the susceptibility of S. aureus to vancomycin was changing. Fortunately, VISA and VRSA infections have been rare in the United States and although they have been resistant or intermediately resistant to vancomycin, they have been susceptible to several other Food and Drug Administration (FDA) approved drugs.[6] However, the fear is that should they ever become common we would not have the appropriate antibiotics available to treat them effectively and they could cause severe morbidity and mortality. Currently, both VISA and VRSA are reportable diseases/conditions in Missouri.

For a complete description of diseases associated with S. aureus, refer to the following resources:

- *Control of Communicable Diseases Manual*. (CCDM), American Public Health Association. 19th ed. 2008.
- American Academy of Pediatrics. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. 2009.

Case Definition [6]

CDC definitions for classifying isolates of S. aureus with reduced susceptibility to vancomycin are based on the laboratory breakpoints published by the Clinical and Laboratory Standards Institute (formerly NCCLS), M100-S16; Jan 2006.

Vancomycin-susceptible S. aureus (VSSA): Vancomycin MIC*: $\leq$ 2 µg/ml.
Vancomycin-intermediate S. aureus (VISA): Vancomycin MIC: = 4-8 µg/ml.
Vancomycin-resistant S. aureus (VRSA): Vancomycin MIC: $\geq$16 µg/ml.

*Minimum Inhibitory Concentration

Clinical case definition [6, 7]
Staphylococcus aureus can produce a variety of syndromes with clinical manifestations including skin and soft tissue lesions, empyema, pyarthrosis, bloodstream infection, pneumonia, osteomyelitis, septic arthritis, endocarditis, sepsis, and meningitis.

Laboratory Criteria
1. Isolation of *Staphylococcus aureus* from any body site. **AND**
2. Intermediate or high-level resistance of the *Staphylococcus aureus* isolate to vancomycin, detected and defined according to CLSI approved standards and recommendations (MIC: 4-8µg/ml for VISA and MIC: ≥16 µg/ml for VRSA).

Case Classification
Confirmed: A clinically compatible case of vancomycin-intermediate or vancomycin-resistant *Staphylococcus aureus* that is laboratory-confirmed (MIC4-8 µg/ml for VISA and MIC: ≥16 µg/ml for VRSA).

Information Needed for Investigation

Verify the diagnosis. Confirm the diagnosis by assuring that the testing was done according to the guidelines outlined above and found in the most current references from CDC.
Establish the extent of illness. When a patient has a laboratory-confirmed VISA or VRSA infection/colonization, it is essential that the extent of transmission of the organism be assessed rapidly.

Notification [6]

Immediately contact the District Communicable Disease Coordinator, or the Senior Epidemiology Specialist for the District or the DHSS Situation Room (DSR) at 800-392-0272 (24/7) if an outbreak* of Staph aureus is suspected. If the case is in a high-risk setting or job such as food handling, childcare or health care contact the District Communicable Disease Coordinator and the appropriate Bureau(s) as listed below.

- Contact the Bureau of Environmental Health Services (BEHS) at (573) 751-6111 and the Section for Child Care Regulation (573) 751-2450 if a case is associated with a child care facility.
- Contact BEHS at (573) 751-6111 when a case is a food handler.
- Contact the Section for Long Term Care Regulation (573) 526-8505, if a case is associated with a long-term care facility.
- Contact the Bureau of Health Services Regulation (573) 751-6303, if a case is associated with a hospital or hospital-based long-term care facility.

*Outbreak is defined as the occurrence in a community or region, illness(es) similar in nature, clearly in excess of normal expectancy and derived from a common or a propagated source.

Control Measures

Contact investigation may be warranted on a case-by case basis after consultation between healthcare providers, local and state health departments, and CDC. To date VISA strains (vancomycin MIC = 4-8µg/ml) are characterized by a resistance mechanism that is not transferable to susceptible strains and is usually associated with vancomycin exposure. Therefore, the likelihood of transmission to contacts is low and case investigations for VISA cases are **not routinely recommended** unless there is suspicion that transmission has occurred. *If there is suspicion that transmission has occurred follow same infection control procedures as for VRSA outlined below.*

In contrast, VRSA strains (vancomycin MIC≥16µg/ml) have properties that allow them to transfer resistance to susceptible strains or other organisms, therefore contact investigations and follow-up for VRSA cases are recommended.

1. For VRSA, identify and categorize contacts based on their level of interaction (i.e., extensive, moderate, or minimal) with the colonized or infected patients. Prioritize identification of contacts that have had extensive interaction with the VRSA patient during a period before the VRSA culture date. The length of this period depends on recent culture results, the location where the patient is receiving health care and the clinical assessment, and should be determined in consultation with DHSS.
   a. Extensive interaction:
      i. Share the VRSA patient's room.
      ii. Change dressings/clean/bathe/rotate/ambulate the patient.
      iii. Make frequent visits (>3 visits per day including nurses assigned to the patient).
      iv. Physicians who care for wound dressings, debridement or conduct physical exams.
      v. Handle secretions and body fluids (including respiratory secretions).
      vi. Rehabilitation personnel and dialysis or respiratory technicians who have had/have prolonged and unprotected close contact with the patient.
      vii. Family members or household contacts who provide primary care (e.g., sleep in same bed, or same room).
   b. Moderate interaction:
      i. Nursing or patient care providers who deliver medications or manipulate IV lines (≤ 3 visits/day) or cross-cover the patient only.
      ii. Physicians who only see the patient on daily rounds without conducting extensive exams or who perform surgical or invasive procedures where sterile barriers or aseptic techniques are used.
      iii. Ancillary staff that monitor patient care equipment without handling secretions or who have limited interactions such as radiology technicians.
   c. Minimal interaction:
      i. Nursing or patient care providers who work on the same floor without formal cross-covering of the patient who only assist patient with eating or perform predominantly administrative duties.

ii. Physicians who consult without performing an extensive exam and visit during teaching rounds only.
iii. Ancillary staff that provide dietary or maintenance services.

2. Culture anterior nares[6, 8], wounds, drains, or other clinically relevant sites (e.g., catheter exit sites) of index patients and VRSA contacts according to the following guidelines:
   a. Extensive interaction:
      i. Culture nares and skin lesions colonized/infected with VRSA
      ii. Culture hands only if concerned about transient colonization after recent contact (previous 48 hours).
      iii. If no contacts among this group are positive for VRSA, the decision to culture those with less interaction should be made with DHSS consultation.
   b. Moderate or Minimal interaction:
      i. Culture only if "extensive interaction" contacts have positive results.
3. Evaluate Efficacy of Infection Control Precautions:
   a. In order to assess the efficacy of infection control precautions one recommended approach is to culture the anterior nares of contacts with extensive interaction on a regular basis.

Infection Control

To minimize spread and development of endemic strain:

- Isolate patient in a private room and begin one-on-one care by specified personnel using contact precautions. Wear mask/eye protection or face shield if splashing is likely.
- Monitor and strictly enforce compliance with contact precautions and other measures.
- Perform hand hygiene using appropriate agent (e.g., alcohol-based hand sanitizer or antibacterial soap).
- Dedicate non-disposable items that cannot be cleaned or disinfected between patients.
- Initiate epidemiologic and laboratory investigations with assistance of the Department of Health and Senior Services and the Centers for Disease Control and Prevention. Assess efficacy of precautions by monitoring personnel for acquisition of VRSA.
- Educate health care professionals about the epidemiologic implications and necessary infection control procedures
- Consult with state health departments and CDC before discharging and/or transferring and notify receiving institution or unit of presence of VRSA and appropriate precautions.[6]

Laboratory Surveillance and Diagnosis Testing Recommendations

Acceptable methods[1, 6, 7] for testing vancomycin susceptibility in S. aureus include:

- Non-automated MIC methods (e.g., reference broth micro-dilution, agar dilution, agar gradient diffusion).
- Etest® using a 0.5 McFarland standard to prepare the inoculum suspension (AB Biodisk, Piscatway, NJ)]) using a full 24-hour incubation.
- Etest® using a 0.5 MacFarland standard to prepare the inoculum suspension.

- Microscan overnight and Synergies Plus, BD Phoenix system, disk diffusion and the vancomycin screen agar plate (contains 6mg/ul of vancomycin).

Comment: Some manufacturers have optimized their systems for VRSA detection therefore laboratories should check with manufacturers to determine if their system has FDA clearance for VRSA detection.

Unacceptable methods for testing vancomycin susceptibility in S. aureus include:
- Disk diffusion alone.
- Automated MIC methods.

Disk diffusion does not reliably detect staphylococci with reduced susceptibility to vancomycin (CDC unpublished data). Therefore, laboratories using automated methods to detect vancomycin susceptibility or disk diffusion should add a vancomycin agar screen plate to enhance detection of VISA/VRSA. In addition to knowing the appropriate testing methodologies, all laboratories should develop a step-by-step problem-solving procedure or algorithm for detecting VISA/VRSA that is specific for their laboratory. A sample algorithm is available at: http://www.cdc.gov/HAI/settings/lab/visa_vrsa_algorithm.html (November, 2010)

Choosing Specimens For Further Testing [6]
- Select isolates with vancomycin MIC of ≥4 µg/ml. This is based on the apparent heterogeneity of strains, because organisms with MIC of ≥4µg/ml have subpopulations with higher MICs. Clinical treatment failures have occurred with vancomycin in infections with these isolates.
- Select isolates with vancomycin MIC ≥8µg/ml (based on Clinical and Laboratory Standards Institute breakpoints [2]).
- Select all methicillin-resistant Staphylococcus aureus (MRSA). All identified isolates of S. aureus with reduced susceptibility to vancomycin have been MRSA.
- Select all S. aureus isolates. Because little is known about the extent of this resistance, any S. aureus potentially could have decreased susceptibility to vancomycin.

Testing and Confirmation
- Primary testing of S. aureus against vancomycin requires 24 hours of incubation time.
- Disk diffusion is not an acceptable method for vancomycin susceptibility testing of S. aureus. None of the known VISA strains have been or would be detected by this method.
- An MIC susceptibility testing method should be used to confirm vancomycin test results.

Options for enhancing detection of VISA/VRSA include
- Screening all clinical isolates of MRSA on a vancomycin agar screen plate.
- Screening all clinical isolates of S. aureus on a vancomycin agar screen plate.
- Retesting S. aureus isolated from patients who fail to respond to vancomycin therapy because resistance may have emerged during vancomycin therapy. All S. aureus strains for which the

vancomycin MIC ≥4µg/ml are unusual should not be discarded until confirmation has been made either at the local or state health departments and/or CDC. Before sending for confirmation, laboratories should ensure that the strain is in pure culture and reconfirm the genus and species of the organism; then, repeat the susceptibility test for vancomycin using an acceptable MIC method or screen by using a vancomycin agar screen plate. If retesting confirms a vancomycin MIC ≥4 µg/ml or growth (>1 colony) on a screen plate is observed, laboratories should notify infection control, the local and/or state health department and the Division of Healthcare Quality Promotion, National Center for Infectious Diseases, CDC, by telephone 800-893-0485 or by sending an email to SEARCH@cdc.gov. The isolate should be sent to the health department and/or CDC for confirmatory testing. If the isolate is confirmed to have a vancomycin MIC ≥4 µg/ml, CDC will work with the health department and infection control personnel to address any local infection control issues, and the health department to address broader public health implications.

Reporting Requirements

Infection or colonization with Vancomycin-Intermediate or -Resistant (VISA/VRSA) is a Category 2(A) disease and shall be reported to the local health authority or to the Missouri Department of Health and Senior Services within one (1) calendar day of first knowledge or suspicion by telephone, facsimile, or other rapid communication.

1. For all reported cases, complete a DHSS Disease Case Report form (CD-1).
2. For confirmed cases, complete a "Record of Investigation of Communicable Disease (CD-2)
3. Entry of the completed CD-1 into WebSurv negates the need for the paper CD-1 to be forwarded to the District Health Office.
4. Send the completed secondary investigation form to the District Health Office.
5. All outbreaks or "suspected" outbreaks must be reported as soon as possible by phone, fax, or e-mail to the District Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51). See "Reporting Requirements" in the Outbreak Investigation section of the CDIRM.
6. Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the District Communicable Disease Coordinator.

References

1. Key prevention messages for patients with Skin and Soft Tissue Infections http://www.cdc.gov/ncidod/dhqp/pdf/ar/CAMRSA_ExpMtgStrategies.pdf
2. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting**,** *American Journal of Infection Control, Volume 36, Issue 5, June 2008, Pages 309-332*.
3. Siegel JD et al. CDC-Healthcare Infection Control Practices Advisory Committee. Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006 http://www.cdc.gov/ncidod/dhqp/guidelines

4. Centers for Disease Control and Prevention. Investigation and Control of Vancomycin-Intermediate and -Resistant Staphylococcus aureus (VISA/VRSA). A Guide for Health Departments and Infection Control Personnel. Updated September, 2006.
5. Clinical and Laboratory Standards Institute (formerly NCCLS) Standards for Antimicrobial Susceptibility Testing Performance Sixteenth Informational Supplement. M100-S16, Wayne, Pa. CLSI 2006.
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Other Sources of Information

1. Bacterial Infections of Humans 3rd edition. Evans, Alfred S. and Brachman, Philip S. editors, Kluwer Acedemic/Plenum Publishers 1998, New York.
2. CDC. Laboratory capacity to detect antimicrobial resistance, 1998. MMWR 2000; 48(51): 1167-71
3. J Clinical Microbiology Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. Tenover FC, Lancaster MV, Hill BC, et al. 1998; 36:1020-7. [Erratum, J Clinical Microbiology; 36:2167.]
4. Manual of Clinical Microbiology. Algorithm for identification of aerobic Gram-Positive cocci p 262-282. ASM Press, Washington, D.C. 1999.

Web Sites

1. Centers for Disease Control and Prevention " VRSA/VISA" Web site http://www.cdc.gov/HAI/organisms/visa_vrsa/visa_vrsa.html (November 24, 2010)
2. National Institutes of Health VRSA Database. http://science.education.nih.gov/supplements/nih1/diseases/activities/activity5_vrsa-database.htm (December, 2006)
3. Society of Healthcare Epidemiologists of America "Guidelines for Preventing Antibiotic Resistance in Hospitals" http://www.journals.uchicago.edu/CID/journal/issues/v25n3/se39_584/se39_584.web.pdf (December, 2006)
4. Management of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections August, 2005 (Federal Bureau of Prisons - Clinical Practice Guidelines): http://www.bop.gov/news/PDFs/mrsa.pdf
5. Official Statement from the National Athletic Trainers' Association on Community-Acquired MRSA Infections (CA-MRSA) http://www.nata.org/publicinformation/docs/MRSA_Statement.pdf