

Recommendations for Preventing the Spread of Vancomycin Resistance

Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC)

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Recommendations for Preventing the Spread of Vancomycin Resistance

Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC)

Summary

Since 1989, a rapid increase in the incidence of infection and colonization with vancomycin-resistant enterococci (VRE) has been reported by U.S. hospitals. This increase poses important problems, including a) the lack of available antimicrobial therapy for VRE infections, because most VRE are also resistant to drugs previously used to treat such infections (e.g., aminoglycosides and ampicillin), and b) the possibility that the vancomycin-resistant genes present in VRE can be transferred to other gram-positive microorganisms (e.g., *Staphylococcus aureus*).

An increased risk for VRE infection and colonization has been associated with previous vancomycin and/or multiantimicrobial therapy, severe underlying disease or immunosuppression, and intraabdominal surgery. Because enterococci can be found in the normal gastrointestinal and female genital tracts, most enterococcal infections have been attributed to endogenous sources within the individual patient. However, recent reports of outbreaks and endemic infections caused by enterococci, including VRE, have indicated that patient-to-patient transmission of the microorganisms can occur either through direct contact or through indirect contact via a) the hands of personnel or b) contaminated patient-care equipment or environmental surfaces.

This report presents recommendations of the Hospital Infection Control Practices Advisory Committee for preventing and controlling the spread of vancomycin resistance, with a special focus on VRE. Preventing and controlling the spread of vancomycin resistance will require coordinated, concerted efforts from all involved hospital departments and can be achieved only if each of the following elements is addressed: a) prudent vancomycin use by clinicians, b) education of hospital staff regarding the problem of vancomycin resistance, c) early detection and prompt reporting of vancomycin resistance in enterococci and other gram-positive microorganisms by the hospital microbiology laboratory, and d) immediate implementation of appropriate infection-control measures to prevent person-to-person transmission of VRE.

INTRODUCTION

From 1989 through 1993, the percentage of nosocomial enterococcal infections reported to CDC's National Nosocomial Infections Surveillance (NNIS) system that were caused by vancomycin-resistant enterococci (VRE) increased from 0.3% to 7.9% (1). This overall increase primarily reflected the 34-fold increase in the percentage of VRE infections in patients in intensive-care units (ICUs) (i.e., from 0.4% to 13.6%), although

a trend toward an increased percentage of VRE infections in non-ICU patients also was noted (1). The occurrence of VRE in NNIS hospitals was associated with larger hospital size (i.e., a hospital with ≥ 200 beds) and university affiliation (1). Other hospitals also have reported increased endemic rates and clusters of VRE infection and colonization (2-8). The actual increase in the incidence of VRE in U.S. hospitals might be greater than reported because the fully automated methods used in many clinical laboratories cannot consistently detect vancomycin resistance, especially moderate vancomycin resistance (as manifested in the VanB phenotype) (9-11).

Vancomycin resistance in enterococci has coincided with the increasing incidence of high-level enterococcal resistance to penicillin and aminoglycosides, thus presenting a challenge for physicians who treat patients who have infections caused by these microorganisms (1,4). Treatment options are often limited to combining antimicrobials or experimental compounds that have unproven efficacy (12-14).

The epidemiology of VRE has not been clarified; however, certain patient populations are at increased risk for VRE infection or colonization. These populations include critically ill patients or those with severe underlying disease or immunosuppression (e.g., patients in ICUs or in oncology or transplant wards); persons who have had an intraabdominal or cardio-thoracic surgical procedure or an indwelling urinary or central venous catheter; and persons who have had a prolonged hospital stay or received multiantimicrobial and/or vancomycin therapy (2-8). Because enterococci are part of the normal flora of the gastrointestinal and female genital tracts, most infections with these microorganisms have been attributed to the patient's endogenous flora (15). However, recent studies have indicated that VRE and other enterococci can be transmitted directly by patient-to-patient contact or indirectly by transient carriage on the hands of personnel (16) or by contaminated environmental surfaces and patient-care equipment (3,8,17).

The potential emergence of vancomycin resistance in clinical isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* also is a public health concern. The *vanA* gene, which is frequently plasmid-borne and confers high-level resistance to vancomycin, can be transferred in vitro from enterococci to a variety of gram-positive microorganisms (18,19), including *S. aureus* (20). Although vancomycin resistance in clinical strains of *S. epidermidis* or *S. aureus* has not been reported, vancomycin-resistant strains of *Staphylococcus haemolyticus* have been isolated (21,22).

In November 1993 and February 1994, the Subcommittee on the Prevention and Control of Antimicrobial-Resistant Microorganisms in Hospitals of CDC's Hospital Infection Control Practices Advisory Committee (HICPAC) responded to the increase in vancomycin resistance in enterococci by meeting with representatives from the American Hospital Association, the American Society for Microbiology, the Association for Professionals in Infection Control and Epidemiology, the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Surgical Infection Society. Meeting participants agreed with the need for prompt implementation of control measures; thus, recommendations to prevent the spread of VRE were developed. Public comments were solicited and incorporated into the draft recommendations. In November 1994, HICPAC ratified the following recommendations for preventing and controlling the spread of vancomycin resistance, with special focus on VRE.

HICPAC recognizes that a) data are limited and additional research will be required to clarify the epidemiology of VRE and determine cost-effective control strategies, and b) many U.S. hospitals have concurrent problems with other antimicrobial-resistant organisms (e.g., methicillin-resistant *S. aureus* [MRSA] and beta-lactam and aminoglycoside-resistant gram-negative bacilli) that might have different epidemiologic features and require different control measures.

RECOMMENDATIONS

Each hospital—through collaboration of its quality-improvement and infection-control programs; pharmacy and therapeutics committee; microbiology laboratory; clinical departments; and nursing, administrative, and housekeeping services—should develop a comprehensive, institution-specific, strategic plan to detect, prevent, and control infection and colonization with VRE. The following elements should be addressed in the plan.

Prudent Vancomycin Use

Vancomycin use has been reported consistently as a risk factor for infection and colonization with VRE (2,4,7,8,17) and may increase the possibility of the emergence of vancomycin-resistant *S. aureus* (VRSA) and/or vancomycin-resistant *S. epidermidis* (VRSE). Therefore, all hospitals and other health-care delivery services, even those at which VRE have never been detected, should a) develop a comprehensive, antimicrobial-utilization plan to provide education for their medical staff (including medical students who rotate their training in different departments of the health-care facility), b) oversee surgical prophylaxis, and c) develop guidelines for the proper use of vancomycin (as applicable to the institution).

Guideline development should be part of the hospital's quality-improvement program and should involve participation from the hospital's pharmacy and therapeutics committee; hospital epidemiologist; and infection-control, infectious-disease, medical, and surgical staffs. The guidelines should include the following considerations:

- Situations in which the use of vancomycin is appropriate or acceptable:
 - For treatment of serious infections caused by beta-lactam-resistant gram-positive microorganisms. Vancomycin may be less rapidly bactericidal than are beta-lactam agents for beta-lactam-susceptible staphylococci (23,24).
 - For treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials.
 - When antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening.
 - Prophylaxis, as recommended by the American Heart Association, for endocarditis following certain procedures in patients at high risk for endocarditis (25).
 - Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices (e.g., cardiac and vascular procedures [26] and total hip replacement) at institutions that have a high rate of infections caused by MRSA or methicillin-resistant *S. epidermidis*. A single dose of vancomycin administered immediately before surgery is sufficient unless the procedure lasts

>6 hours, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses (27–30).

- Situations in which the use of vancomycin should be discouraged:
 - Routine surgical prophylaxis other than in a patient who has a life-threatening allergy to beta-lactam antibiotics (28).
 - Empiric antimicrobial therapy for a febrile neutropenic patient, unless initial evidence indicates that the patient has an infection caused by gram-positive microorganisms (e.g., at an inflamed exit site of Hickman catheter) and the prevalence of infections caused by MRSA in the hospital is substantial (31–37).
 - Treatment in response to a single blood culture positive for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative (i.e., if contamination of the blood culture is likely). Because contamination of blood cultures with skin flora (e.g., *S. epidermidis*) could result in inappropriate administration of vancomycin, phlebotomists and other personnel who obtain blood cultures should be trained to minimize microbial contamination of specimens (38–40).
 - Continued empiric use for presumed infections in patients whose cultures are negative for beta-lactam-resistant gram-positive microorganisms (41).
 - Systemic or local (e.g., antibiotic lock) prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters (42–48).
 - Selective decontamination of the digestive tract.
 - Eradication of MRSA colonization (49,50).
 - Primary treatment of antibiotic-associated colitis (51).
 - Routine prophylaxis for very low-birthweight infants (i.e., infants who weigh <1,500 g [3 lbs 4 oz]) (52).
 - Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis (48,53).
 - Treatment (chosen for dosing convenience) of infections caused by beta-lactam-sensitive gram-positive microorganisms in patients who have renal failure (54–57).
 - Use of vancomycin solution for topical application or irrigation.
- Enhancing compliance with recommendations:
 - Although several techniques may be useful, further study is required to determine the most effective methods for influencing the prescribing practices of physicians (58–61).
 - Key parameters of vancomycin use can be monitored through the hospital's quality assurance/improvement process or as part of the drug-utilization review of the pharmacy and therapeutics committee and the medical staff.

Education Programs

Continuing education programs for hospital staff (including attending and consulting physicians, medical residents, and students; pharmacy, nursing, and laboratory personnel; and other direct patient-care providers) should include information concerning the epidemiology of VRE and the potential impact of this pathogen on the cost and outcome of patient care. Because detection and containment of VRE require an aggressive approach and high performance standards for hospital personnel, special awareness and educational sessions might be indicated.

Role of the Microbiology Laboratory in the Detection, Reporting, and Control of VRE

The microbiology laboratory is the first line of defense against the spread of VRE in the hospital. The laboratory's ability to promptly and accurately identify enterococci and detect vancomycin resistance is essential for recognizing VRE colonization and infection and avoiding complex, costly containment efforts that are required when recognition of the problem is delayed. In addition, cooperation and communication between the laboratory and the infection-control program will facilitate control efforts.

Identification of Enterococci

Presumptively identify colonies on primary isolation plates as enterococci by using colonial morphology, a Gram stain, and a pyrrolidonyl arylamidase (PYR) test. Although identifying enterococci to the species level can help predict certain resistance patterns (e.g., *Enterococcus faecium* is more resistant to penicillin than is *Enterococcus faecalis*) and may help determine the epidemiologic relatedness of enterococcal isolates, such identification is not routinely necessary if antimicrobial susceptibility testing is performed. However, under special circumstances or as laboratory resources permit, biochemical tests can be used to differentiate between various enterococcal species. Although most commercially available identification systems adequately differentiate *E. faecalis* from other species of enterococci, additional tests for motility and pigment production are required to distinguish *Enterococcus gallinarum* (motile and nonpigmented) and *Enterococcus casseliflavus* (motile and pigmented) from *E. faecium* (nonmotile and nonpigmented).

Tests for Antimicrobial Susceptibility

Determine vancomycin resistance and high-level resistance to penicillin (or ampicillin) and aminoglycosides (62) for enterococci isolated from blood, sterile body sites (with the possible exception of urine), and other sites as clinically indicated. Laboratories routinely may test wound and urine isolates for resistance to vancomycin and penicillin or ampicillin if resources permit (see Screening Procedures for Detecting VRE in Hospitals Where VRE Have Not Been Detected).

- Laboratories that use disk diffusion should incubate plates for 24 hours and read zones of inhibition by using transmitted light (62,63).
- Minimum inhibitory concentrations can be determined by agar dilution, agar gradient dilution, broth macrodilution, or manual broth microdilution (62–64). These test systems should be incubated for 24 hours.

- The fully automated methods of testing enterococci for resistance to vancomycin currently are unreliable (9–11).

When VRE Are Isolated From a Clinical Specimen

Confirm vancomycin resistance by repeating antimicrobial susceptibility testing using any of the recommended methods (see Tests for Antimicrobial Susceptibility), particularly if VRE isolates are unusual in the hospital, OR streak 1 μL of standard inoculum (0.5 McFarland) from an isolated colony of enterococci onto brain heart infusion agar containing 6 $\mu\text{g}/\text{mL}$ of vancomycin, incubate the inoculated plate for 24 hours at 35 C (95 F), and consider any growth indicative of vancomycin resistance (62,63,65).

Immediately, while performing confirmatory susceptibility tests, notify the patient's primary caregiver, patient-care personnel, and infection-control personnel regarding the presumptive identification of VRE so that appropriate isolation precautions can be initiated promptly (see Preventing and Controlling VRE Transmission in All Hospitals). Follow this preliminary report with the (final) result of the confirmatory test. Additionally, highlight the report regarding the isolate to alert staff that isolation precautions are indicated.

Screening Procedures for Detecting VRE in Hospitals Where VRE Have Not Been Detected

In some hospital microbiology laboratories, antimicrobial susceptibility testing of enterococcal isolates from urine or nonsterile body sites (e.g., wounds) is not performed routinely; thus, identification of nosocomial VRE colonization and infection in hospitalized patients may be delayed. Therefore, in hospitals where VRE have not yet been detected, implementing special measures can promote earlier detection of VRE.

Antimicrobial susceptibility survey. Perform periodic susceptibility testing on an epidemiologic sample of enterococcal isolates recovered from all types of clinical specimens, especially from high-risk patients (e.g., those in an ICU or in an oncology or transplant ward). The optimal frequency of testing and number of isolates to be tested will vary among hospitals, depending on the patient population and number of cultures performed at the hospital. Hospitals that process large numbers of culture specimens need to test only a fraction (e.g., 10%) of enterococcal isolates every 1–2 months, whereas hospitals processing fewer specimens might need to test all enterococcal isolates during the survey period. The hospital epidemiologist can help design a suitable sampling strategy.

Culture survey of stools or rectal swabs. In tertiary medical centers and other hospitals that have many critically ill patients (e.g., ICU, oncology, and transplant patients) at high risk for VRE infection or colonization, periodic culture surveys of stools or rectal swabs of such patients can detect the presence of VRE. Because most patients colonized with VRE have intestinal colonization with this organism, fecal screening of patients is recommended even though VRE infections have not been identified clinically (2,4,16).

The frequency and intensity of surveillance should be based on the size of the population at risk and the specific hospital unit(s) involved. If VRE have been detected in other health-care facilities in a hospital's area and/or if a hospital's staff decides to

determine whether VRE are present in the hospital despite the absence of recognized clinical cases, stool or rectal-swab culture surveys are useful. The cost of screening can be reduced by inoculating specimens onto selective media containing vancomycin (2,17,66) and restricting screening to those patients who have been in the hospital long enough to have a substantial risk for colonization (e.g., 5–7 days) or who have been admitted from a facility (e.g., a tertiary-care hospital or a chronic-care facility) where VRE have been identified.

After colonization with VRE has been detected, all the enterococcal isolates (including those from urine and wounds) from patients in the hospital should be screened routinely for vancomycin resistance, and efforts to contain the spread of VRE should be intensified (i.e., by strict adherence to handwashing and compliance with isolation precautions) (see Preventing and Controlling VRE Transmission in All Hospitals). Intensified fecal screening for VRE might facilitate earlier identification of colonized patients, leading to more efficient containment of the microorganism.

Preventing and Controlling Nosocomial Transmission of VRE

Eradicating VRE from hospitals is most likely to succeed when VRE infection or colonization is confined to a few patients on a single ward. After VRE have become endemic on a ward or have spread to multiple wards or to the community, eradication becomes difficult and costly. Aggressive infection-control measures and strict compliance by hospital personnel are required to limit nosocomial spread of VRE.

Control of VRE requires a collaborative, institution-wide, multidisciplinary effort. Therefore, the hospital's quality-assurance/improvement department should be involved at the outset to identify specific problems in hospital operations and patient-care systems and to design, implement, and evaluate appropriate changes in these systems.

Preventing and Controlling VRE Transmission in All Hospitals

The following measures should be implemented by all hospitals, including those in which VRE have been isolated infrequently or not at all, to prevent and control transmission of VRE.

- Notify appropriate hospital staff promptly when VRE are detected (see When VRE Are Isolated From a Clinical Specimen).
- Inform clinical staff of the hospital's policies regarding VRE-infected or colonized patients. Because the slightest delay can lead to further spread of VRE and complicate control efforts, implement the required procedures as soon as VRE are detected. Clinical staff are essential to limiting the spread of VRE in patient-care areas; thus, continuing education regarding the appropriate response to the detection of VRE is critical (see Education Programs).
- Establish system(s) for monitoring appropriate process and outcome measures (e.g., cumulative incidence or incidence density of VRE colonization, rate of compliance with VRE isolation precautions and handwashing, interval between VRE identification in the laboratory and implementation of isolation precautions on the wards, and the percentage of previously colonized patients admitted to the ward who are identified promptly and placed on isolation precautions). Relay these data

to the clinical, administrative, laboratory, and support staff to reinforce ongoing education and control efforts (67).

- Initiate the following isolation precautions to prevent patient-to-patient transmission of VRE:
 - Place VRE-infected or colonized patients in private rooms or in the same room as other patients who have VRE (8).
 - Wear gloves (clean, nonsterile gloves are adequate) when entering the room of a VRE-infected or colonized patient because VRE can extensively contaminate such an environment (3,8,16,17). When caring for a patient, a change of gloves might be necessary after contact with material that could contain high concentrations of VRE (e.g., stool).
 - Wear a gown (a clean, nonsterile gown is adequate) when entering the room of a VRE-infected or colonized patient a) if substantial contact with the patient or with environmental surfaces in the patient's room is anticipated, b) if the patient is incontinent, or c) if the patient has had an ileostomy or colostomy, has diarrhea, or has a wound drainage not contained by a dressing (8).
 - Remove gloves and gown before leaving the patient's room and immediately wash hands with an antiseptic soap or a waterless antiseptic agent (68–71). Hands can be contaminated via glove leaks (72–76) or during glove removal, and bland soap does not always completely remove VRE from the hands (77).
 - Ensure that after glove and gown removal and handwashing, clothing and hands do not contact environmental surfaces in the patient's room that are potentially contaminated with VRE (e.g., a door knob or curtain) (3,8).
- Dedicate the use of noncritical items (e.g., a stethoscope, sphygmomanometer, or rectal thermometer) to a single patient or cohort of patients infected or colonized with VRE (17). If such devices are to be used on other patients, adequately clean and disinfect these devices first (78).
- Obtain a stool culture or rectal swab from roommates of patients newly found to be infected or colonized with VRE to determine their colonization status, and apply isolation precautions as necessary. Perform additional screening of patients on the ward at the discretion of the infection-control staff.
- Adopt a policy for deciding when patients infected or colonized with VRE can be removed from isolation precautions. The optimal requirements remain unknown; however, because VRE colonization can persist indefinitely (4), stringent criteria might be appropriate, such as VRE-negative results on at least three consecutive occasions (≥ 1 week apart) for all cultures from multiple body sites (including stool or rectal swab, perineal area, axilla or umbilicus, and wound, Foley catheter, and/or colostomy sites, if present).
- Because patients with VRE can remain colonized for long periods after discharge from the hospital, establish a system for highlighting the records of infected or colonized patients so they can be promptly identified and placed on isolation precautions upon readmission to the hospital. This information should be computerized so that placement of colonized patients on isolation precautions will not be delayed because the patients' medical records are unavailable.

- Local and state health departments should be consulted when developing a plan regarding the discharge of VRE-infected or colonized patients to nursing homes, other hospitals, or home-health care. This plan should be part of a larger strategy for handling patients who have resolving infections and patients colonized with antimicrobial-resistant microorganisms.

Hospitals With Endemic VRE or Continued VRE Transmission

The following measures should be taken to prevent and control transmission of VRE in hospitals that have endemic VRE or continued VRE transmission despite implementation of measures described in the preceding section (see Preventing and Controlling VRE Transmission in All Hospitals).

- Focus control efforts initially on ICUs and other areas where the VRE transmission rate is highest (4). Such areas can serve as reservoirs for VRE, allowing VRE to spread to other wards when patients are well enough to be transferred.
- Where feasible, cohort the staff who provide regular, ongoing care to patients to minimize the movement/contact of health-care providers between VRE-positive and VRE-negative patients (4,8).
- Hospital staff who are carriers of enterococci have been implicated rarely in the transmission of this organism (8). However, in conjunction with careful epidemiologic studies and upon the direction of the infection-control staff, examine personnel for chronic skin and nail problems and perform hand and rectal swab cultures of these workers. Remove from the care of VRE-negative patients those VRE-positive personnel linked epidemiologically to VRE transmission until their carrier state has been eradicated.
- Because the results of several enterococcal outbreak investigations suggest a potential role for the environment in the transmission of enterococci (3,8,16,17,79,80), institutions experiencing ongoing VRE transmission should verify that the hospital has adequate procedures for the routine care, cleaning, and disinfection of environmental surfaces (e.g., bed rails, bedside commodes, carts, charts, doorknobs, and faucet handles) and that these procedures are being followed by housekeeping personnel. To verify the efficacy of hospital policies and procedures, some hospitals might elect to perform focused environmental cultures before and after cleaning rooms that house patients who have VRE. All environmental culturing should be approved and supervised by the infection-control program in collaboration with the clinical laboratory (3,8,16,17,79,80).
- Consider sending representative VRE isolates to reference laboratories for strain typing by pulsed field gel electrophoresis or other suitable techniques to aid in defining reservoirs and patterns of transmission.

Detecting and Reporting VRSA and VRSE

The microbiology laboratory has the primary responsibility for detecting and reporting the occurrence of VRSA or VRSE in the hospital. All clinical isolates of *S. aureus* and *S. epidermidis* should be tested routinely, using standard methods, for susceptibility to vancomycin (62). If VRSA or VRSE is identified in a clinical specimen, confirm vancomycin resistance by repeating antimicrobial susceptibility testing using

standard methods (62). Restreak the colony to ensure that the culture is pure. The most common causes of false-positive VRSA reports are susceptibility testing on mixed cultures and misidentifying VRE, *Leuconostoc*, *S. haemolyticus*, or *Pediococcus* as VRSA (81,82).

Immediately (i.e., while performing confirmatory testing) notify the hospital's infection-control personnel, the patient's primary caregiver, and patient-care personnel on the ward on which the patient is hospitalized so that the patient can be placed promptly on isolation precautions (depending on the site[s] of infection or colonization) adapted from previous CDC guidelines (83) and those recommended for VRE infection or colonization in this report (see Preventing and Controlling Nosocomial Transmission of VRE). Furthermore, immediately notify the state health department and CDC, and send the isolate through the state health department to CDC (telephone [404] 639-6413) for confirmation of vancomycin resistance.

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