CME CREDIT

PATRICIA A. FLORES, PharmD
Infectious diseases pharmacy specialist,
Cleveland Clinic.

STEVEN M. GORDON, MD
Hospital epidemiologist and staff physician,
Department of Infectious Diseases,
Cleveland Clinic.

Vancomycin-resistant *Staphylococcus aureus*: An emerging public health threat

ABSTRACT

Three reported cases of infection with strains of *Staphylococcus aureus* that had only intermediate susceptibility to vancomycin raise fears that high-level vancomycin resistance may soon be seen. To forestall this occurrence, physicians need to limit their use of vancomycin, and hospitals need to intensify their infection-control efforts. We review treatment options and the recommendations from the Centers for Disease Control and Prevention to identify and slow the spread of resistant strains.

KEY POINTS

The virulent nature of *Staphylococcus aureus*, coupled with the limited treatment options for methicillin-resistant *S aureus* infections, make the emergence of vancomycin-resistant *S aureus* a significant public health threat.

Organisms are deemed susceptible to vancomycin if the minimum inhibitory concentration (MIC) is ≤ 4 μg/mL, intermediately susceptible at 8 to 16 μg/mL, and resistant at ≥ 32 μg/mL.

In both coagulase-negative staphylococci and *S aureus*, most cases of vancomycin resistance occurred after prolonged vancomycin use.

If a strain of *S aureus* that has intermediate susceptibility to vancomycin ("vancomycin-intermediate *S aureus*"—VISA) is isolated in clinical practice, the physician should notify the Centers for Disease Control and Prevention and place the patient in strict isolation.

THE RAPID EMERGENCE OF RESISTANCE to antimicrobial drugs among infectious pathogens is quickly diminishing the treatment options for several common infections. One of the most recent problems to arise is resistance to vancomycin in *Staphylococcus aureus*. Although *S aureus* remains susceptible to vancomycin, the emergence of strains with only intermediate susceptibility to the antibiotic is raising fears that the emergence of a fully resistant strain is not too far off.

The first report of an infection with an *S aureus* strain that had only intermediate susceptibility to vancomycin came from Japan in June 1996.[1] This report raised concern among infectious-disease experts and led the Centers for Disease Control and Prevention (CDC) to issue interim recommendations about how to control such "vancomycin-intermediate *S aureus*" (VISA) infections.[2] More recently, two reports of VISA infections in the United States brought the issue closer to home.[3,4]

These cases may be a prelude to the development of high-level resistance to this frequently used antibiotic. Such a development could be serious, since vancomycin-resistant *S aureus* would be a virulent pathogen for which we have no proven therapy.

To prevent the spread of vancomycin resistance, physicians must use vancomycin appropriately (ie, more sparingly),[5] and hospitals need to focus on reducing the use of antimicrobial agents in general and reinforcing infection-control policies (eg, strict handwashing) to slow the evolution of resistant

TABLE

HOW TO MEASURE VANCOMYCIN RESISTANCE*

Category	Minimum inhibitory concentration μg/mL†
Susceptible	≤ 4
Intermediate	8–16
Resistant	≥ 32

*According to the National Committee for Clinical Laboratory Standards (NCCLS)
†By the broth microdilution method

organisms and reduce the risk of nosocomial transmission. Since most VISA strains are also resistant to most other antimicrobial agents, therapeutic options for this virulent organism may be limited to investigational or less-proven drugs.

Approximately 35% of *S aureus* strains are resistant to methicillin

In this article, we briefly review the cases of vancomycin resistance that have been identified to date, discuss possible mechanisms of the resistance, and, most important, review strategies for slowing the development of full-blown resistance.

DESCRIPTION OF THE THREE CASES

June 1996. A 4-month-old boy in Japan with a surgical wound infected with methicillin-resistant *S aureus* was treated unsuccessfully with vancomycin for 29 days.[1] The patient improved after an aminoglycoside (arbekacin) was added to the regimen; unfortunately, 12 days after the antibiotics were stopped, the infection recurred and subcutaneous abscesses were detected. The patient improved after debridement of the abscesses and antimicrobial therapy with arbekacin and ampicillin-sulbactam for 23 days. The organism isolated from the purulent surgical wound had a vancomycin minimum inhibitory concentration (MIC) of 8 μg/mL, which is in the intermediate range (TABLE 1). (The MIC is defined as the lowest concentration of a drug that inhibits visible bacterial growth.)

Of note, this *S aureus* organism lacked the *vanA* and *vanB* genes responsible for vancomycin resistance in enterococci, indicating that the mechanism of resistance is different in the two organisms.

July 1997. A Michigan patient undergoing chronic ambulatory peritoneal dialysis contracted peritonitis due to a VISA strain.[3] He had received multiple courses of vancomycin intraperitoneally and intravenously for recurrent peritonitis due to methicillin-resistant *S aureus*. One of six *S aureus* isolates from one specimen demonstrated a vancomycin MIC of 8 μg/mL. The isolate was susceptible to rifampin, chloramphenicol, trimethoprim-sulfamethoxazole, tetracycline, and mupirocin. In addition, investigational agents tested which had activity against the isolate included quinupristin-dalfopristin (Synercid), clinafloxacin, the oxazlidinones, arbekacin, eperezolid (U-100592), linezolid (U-100766), and LY333328.[6] Surveillance cultures obtained from the hands and nares of close contacts were negative for VISA. The patient improved following removal of the peritoneal catheter and treatment with trimethoprim-sulfamethoxazole plus rifampin.[7]

August 1997. A New Jersey resident was diagnosed with a VISA-associated bloodstream infection.[4] He had a history of colonization and repeated bloodstream infections with methicillin-resistant *S aureus*, and had received multiple courses of vancomycin over approximately 6 months. The patient was also colonized with vancomycin-resistant enterococcus. All methicillin-resistant *S aureus* isolates were susceptible to vancomycin until a blood culture grew a methicillin-resistant *S aureus* strain with an MIC of 8 μg/mL for vancomycin. The isolate was sensitive to gentamicin, trimethoprim-sulfamethoxazole, tetracycline, and imipenem. The patient was stable after treatment with a combination of vancomycin, gentamicin, and rifampin.[7]

HOW DID THIS BUG OUTSMART US?

Staphylococcus aureus, a frequent cause of community-acquired infections, has also become the most common cause of infections acquired in the hospital.[1] Before penicillin was devel-

oped, *S aureus* infections frequently resulted in death. Penicillin was initially successful in eradicating staphylococcal infections, but by the late 1950s *S aureus* had developed marked resistance to this antibiotic by producing beta-lactamases that inactivate penicillins.

Methicillin was developed in 1960 to combat strains that produce penicillinases. However, by the 1970s some strains had become resistant to methicillin by altering the penicillin-binding proteins to which the antibiotic binds. The reported rate of methicillin resistance among *S aureus* strains in the United States was approximately 35% in 1996.[1] Vancomycin, a glycopeptide antibiotic that has been available since 1958, is the drug of choice for methicillin-resistant staphylococcal infections.

Vancomycin-resistant enterococci are increasing

In recent years gram-positive cocci have developed resistance to vancomycin at an alarming rate. The most notable of these are enterococci with high-level plasma-mediated resistance. Between 1989 and 1995, the number of nosocomial infections with vancomycin-resistant enterococci reported to the CDC increased more than 30-fold, from 0.3% to more than 10%.[8]

Vancomycin resistance also reported in coagulase-negative staphylococci

A few cases of vancomycin-resistant coagulase-negative staphylococci have also been reported.[9–12] In most of these cases, the organisms isolated had MICs in the intermediate range of vancomycin susceptibility.

Enterococci and coagulase-negative staphylococci are generally not highly virulent, although they do cause serious infections such as endocarditis and infections of prosthetic material. Coagulase-negative staphylococci are often contaminants when isolated in the absence of clinical findings suggestive of infection. The story is different with *S aureus*, however, since this organism is usually associated with a significantly more aggressive course of illness. Thus, the virulent nature of *S aureus*, coupled with the limited treatment options for methicillin-resistant *S aureus* infections, make the emergence of vancomycin-resistant *S aureus* a significant public health threat.

Mechanism of resistance not yet clear

The mechanism by which staphylococci become resistant to vancomycin is not clearly understood. Sieradzki and Tomasz[13] isolated a vancomycin-resistant *S aureus* mutant in vitro that appeared to have structural cell-wall alterations that increased its ability to bind vancomycin. The researchers theorized that this alteration may prevent the antibiotic from reaching crucial sites of cell-wall synthesis, thus impeding its bactericidal effect.

Like the VISA strain from Japan and that from the Michigan patient, this strain lacked the *vanA* and *vanB* genes responsible for vancomycin resistance in enterococci. A one-band digestion fragment difference was seen between vancomycin-susceptible and intermediate isolates by pulse field electrophoresis, suggesting a chromosomal mutation.[6] Further studies to determine the mechanism of resistance in the three clinical VISA isolates are ongoing.

Gram-positive cocci have developed resistance to vancomycin at an alarming rate

Characterization of vancomycin-resistant strains of coagulase-negative staphylococci has also been attempted. An increased ability to bind vancomycin was also demonstrated in three clinical isolates of *Staphylococcus epidermidis* that had low-level resistance to this antibiotic.[9] Resistance among these isolates was found to be constitutive (ie, inherent) rather than inducible. The National Cancer Center in the Slovak Republic reported four cases of catheter-associated bacteremia due to vancomycin-resistant *S epidermidis* in febrile neutropenic patients who had previously received vancomycin. The isolates differed in their susceptibility patterns, suggesting that different strains were present and making environmental or contact transmission unlikely.[12]

A separate case of stool and throat colonization and bloodstream infection with *Staphylococcus haemolyticus* appeared to involve a single strain with increasing resistance to vancomycin, according to restriction endonuclease analysis of DNA patterns.[11] Schwalbe et al[14] found an association between *S haemolyticus* isolates containing stable vancomycin-resistant subpopulations

and the appearance of a double growth zone around imipenem agar diffusion discs. The significance of this finding is unclear.

Most cases of vancomycin-resistant staphylococcal infections have one feature in common: the organism was initially sensitive to the antibiotic, but a moderately resistant strain was subsequently isolated after prolonged vancomycin use.[1,3,4,10,11] Further research into the mechanism of vancomycin resistance in staphylococci is needed.

TREATMENT OPTIONS ARE LIMITED FOR VANCOMYCIN-RESISTANT STAPHYLOCOCCI

Experience with treating VISA infections is minimal at this point. The first case of a VISA surgical infection was successfully treated by debriding the subcutaneous abscesses and giving a combination of an aminoglycoside (arbekacin) and ampicillin/sulbactam.[1] The other two cases had strains of VISA that were susceptible in vitro to trimethoprim-sulfamethoxazole and tetracycline.[3,4] In addition, one of the two isolates was susceptible to rifampin and chloramphenicol and the other to gentamicin and imipenem. The patient in Michigan was successfully treated by removing the peritoneal catheter and giving trimethoprim-sulfamethoxazole plus rifampin. The VISA bacteremia case improved with a combination of vancomycin, gentamicin, and rifampin.[7]

In most cases, resistance developed after prolonged use of vancomycin

Lessons from treating methicillin-resistant *Staphylococcus aureus*

Some of the clinical experience with treating methicillin-resistant *S aureus* infections with antimicrobials other than vancomycin may prove applicable to vancomycin-resistant staphylococcal infections.

Trimethoprim-sulfamethoxazole. Limited information exists on the clinical efficacy of trimethoprim-sulfamethoxazole for treating methicillin-resistant *S aureus* infections. This agent was reported beneficial in cases of endocarditis and meningitis.[15] It has also been used successfully for eradicating methicillin-resistant *S aureus* colonization.[16]

Minocycline also appeared effective in a few cases of endocarditis due to methicillin-resistant *S aureus*.[17,18]

Rifampin is highly active against methicillin-resistant *S aureus* in vitro; however, resistance develops quickly when the agent is used alone. The combination of rifampin with vancomycin has yielded beneficial results despite apparent antagonism in vitro.[19,20,21]

Aminoglycosides may also provide a synergistic effect when used with vancomycin, although this effect is unlikely to be seen against strains with high-level resistance to gentamicin.[22] Clinical data about treating methicillin-resistant *S aureus* infections with aminoglycosides alone or in combination are lacking.

Chloramphenicol is often active in vitro against methicillin-resistant *S aureus* strains; however, rapid emergence of resistance and clinical failures have been reported.[23]

Additional antimicrobials with potential activity against methicillin-resistant *S aureus* include novobiocin, fusidic acid, clindamycin, erythromycin, fosfomycin, and teicoplanin.[16,23] Use of some of these agents is limited by toxicity or the unavailability of the product in the United States.

Regimens used against other vancomycin-resistant staphylococci

Antimicrobial drugs for vancomycin-resistant staphylococci must be chosen on the basis of susceptibility testing. Antimicrobial regimens used in managing infections due to the aforementioned coagulase-negative staphylococci with intermediate susceptibility to vancomycin include:

- Vancomycin and rifampin;
- Vancomycin and tobramycin;
- Teicoplanin;
- Vancomycin, trimethoprim-sulfamethoxazole, and amikacin; and
- Gentamicin, trimethoprim-sulfamethoxazole, and imipenem.[10,12]

Several investigational agents may provide alternatives for managing *S aureus* infections with intermediate (and high-level) resistance to vancomycin. One of the most promising of these is quinupristin-dalfopristin (Synercid), a streptogramin antibacterial with good in vitro activity against methicillin-resistant *S aureus* strains.[24] Although not yet approved for use in the United States, preliminary data from an emergency-use Synercid

program suggest a favorable response in 11 patients with bacteremia caused primarily by methicillin-resistant *S aureus*.[25] New and investigational fluoroquinolones have variable in vitro activity against methicillin-resistant *S aureus*; however, rapid emergence of resistance and failure of pathogen eradication have been seen with this class of antibiotics for staphylococcal isolates.[26,27] Potentially useful glycopeptides, oxazolidinone antimicrobials, and lantibiotics are currently under investigation for treating vancomycin-resistant gram-positive bacteria.

GUIDELINES FOR PREVENTING AND CONTROLLING VANCOMYCIN-RESISTANT STAPHYLOCOCCAL INFECTIONS

In response to the clinical isolation of a strain of *Staphylococcus aureus* with intermediate susceptibility to vancomycin, the CDC has issued guidelines for preventing and controlling infections with such organisms.[2] Included are how to detect these staphylococci, how to decrease their spread through infection-control precautions, and how to get information on investigational therapies. Edmund et al[28] have issued similar guidelines.

Both sets of guidelines are more stringent than those previously published for controlling methicillin-resistant *S aureus* or vancomycin-resistant enterococcal infections.

If a VISA strain is isolated, the physician and staff should:

- Notify the state health department and the CDC's Hospital Infections Program (404-639-6400).
- Inform all personnel involved in the care of the patient and educate them on infection control precautions.
- Isolate the patient in a private room and institute appropriate contact precautions for all staff, including gowning, gloving, and hand-washing with antibacterial soap.
- Assign specific workers to provide one-on-one care for the patient.
- Minimize the number of persons with access to the patient.
- Avoid transferring the patient, if this is possible.
- Monitor compliance with contact precautions closely.
- Initiate an epidemiologic and microbiologic investigation.
- Obtain baseline cultures for VISA from the anterior nares and hands of roommates and all persons in direct contact with the patient.
- Obtain additional information. State health departments and the CDC can provide information about what surveillance cultures are needed and how to manage the patient's discharge. The US Food and Drug Administration (301-827-2120) can provide information on investigational antimicrobial agents.

REFERENCES

1. **Centers for Disease Control and Prevention.** Reduced susceptibility of *Staphylococcus aureus* to vancomycin—Japan, 1996. MMWR 1997; 46:624–626.
2. **Centers for Disease Control and Prevention.** Interim guidelines for prevention and control of staphylococcal infection associated with reduced susceptibility to vancomycin. MMWR 1997; 46:626–628,635.
3. **Centers for Disease Control and Prevention.** *Staphylococcus aureus* with reduced susceptibility to vancomycin—United States, 1997. MMWR 1997; 46:765–766.
4. **Centers for Disease Control and Prevention.** Update: *Staphylococcus aureus* with reduced susceptibility to vancomycin—United States, 1997. MMWR 1997; 46:813–815.
5. **Hospital Infection Control Practices Advisory Committee.** Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR 1995; 44(no. RR-12).
6. **Robinson-Dunn B, Jennings G, Mitchell J, et al.** Characterization of a unique isolate of vancomycin-intermediate *Staphylococcus aureus* (VISA) [abstract LB-14]. Presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 28–October 1, 1997.
7. **Smith TL, Pearson M, Wilcox K, et al.** *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997 [abstract LB-16]. Presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 28–October 1, 1997.
8. **Gaynes R, Edwards J, the National Nosocomial Infection Surveillance (NNIS) System.** Nosocomial vancomycin resistant enterococci (VRE) in the United States, 1989–1995: the first 1000 isolates [abstract]. Infect Control Hosp Epidemiol 1996; 17:P18.
9. **Sanyal D, Johnson AP, George RC, Edwards R, Greenwood D.** In-vitro characteristics of glycopeptide resistant strains of *Staphylococcus epidermidis* isolated from patients on CAPD. J Antimicrob Chemother 1993; 32:267–278.
10. **Schwalbe RS, Stapleton JT, Gilligan PH.** Emergence of vancomycin resistance in coagulase-negative staphylococci. N Engl J Med 1987; 316:927–931.
11. **Veach LA, Pfaller MA, Barrett M, Koontz FP, Wenzel RP.** Vancomycin resistance in *Staphylococcus haemolyticus* causing colonization and bloodstream infection. J Clin Microbiol 1990; 28:2064–2068.

Antibiotics should be used less and infection-control policies enforced more

12. **Krcmery V, Trupl J, Drgona L, Lacka J, Kukuckova E, Oravcova E.** Nosocomial bacteremia due to vancomycin-resistant *Staphylococcus epidermidis* in four patients with cancer, neutropenia, and previous treatment with vancomycin. Eur J Clin Microbiol Infect Dis 1996; 15:259–261.
13. **Sieradzki K, Tomasz A.** Inhibition of cell wall turnover and autolysis by vancomycin in a highly vancomycin-resistant mutant of *Staphylococcus aureus*. J Bacteriol 1997; 179:2557–2566.
14. **Schwalbe RS, Ritz WJ, Verma PR, Barranco EA, Gilligan PH.** Selection for vancomycin resistance in clinical isolates of *Staphylococcus haemolyticus*. J Infect Dis 1990; 161:45–51.
15. **Tamer MA, Bray JD.** Trimethoprim-sulfamethoxazole treatment of multi-antibiotic-resistant staphylococcal endocarditis and meningitis. Clin Pediatr 1986; 21:125–126.
16. **Mulligan ME, Murray-Leisure KA, Ribner BS, et al.** Methicillin-resistant staphylococcus aureus: A consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. Am J Med 1993; 94:313–328.
17. **Kuwabara K, Shigeoka H, Otonari T, Kodoma T, Takii M.** Successful treatment with minocycline of two cases of endocarditis caused by staphylococcus. Chemotherapy 1985; 3:904–905.
18. **Lawlor M, Sullivan M, Levity R, Aruntilani R, Mightingale C.** Treatment of prosthetic valve endocarditis due to methicillin-resistant staphylococcus aureus with minocycline. J Infect Dis 1990; 161:812–814.
19. **Faville RJ, Zaske DE, Kaplan EL, Crossley K, Sabath LD, Orice PG.** Staphylococcus aureus endocarditis; combined therapy with vancomycin and rifampin. JAMA 1984; 240:1963–1965.
20. **Massanari RM, Donta ST.** The efficacy of rifampin as adjunctive therapy in selected cases of staphylococcal endocarditis. Chest 1978; 73:375–377.
21. **Watanakunakorn C, Guerriero JC.** Interaction between vancomycin and rifampin against staphylococcus aureus. Antimicrob Agents Chemother 1981; 19:1089–1091.
22. **Mulazimoglu L, Drenning SD, Muder RR.** Vancomycin-gentamicin synergism revisited: Effect of gentamicin susceptibility of methicillin-resistant staphylococcus aureus. Antimicrob Agents Chemother 1996; 40(6):1534–1535.
23. **Brumfitt W, Hamilton-Miller J.** Methicillin-resistant staphylococcus aureus. N Engl J Med 1989; 320:1188–1196.
24. **Qadri SM Ueno Y, Abu Mostafa FM, Halim M.** In vitro activity of quinupristin/dalfopristin, RP 59500, against gram-positive clinical isolates. Chemotherapy 1997; 43(2):94–99.
25. **Griswold MW, Lomaestro BM, Briceland LL.** Quinupristin-dalfopristin (RP 59500): An injectable streptogramin combination. Am J Health-Syst Pharm 1996; 53:2045–2053.
26. **Baquero F, Canton R.** In-vitro activity of sparfloxacin in comparison with currently available antimicrobials against respiratory tract pathogens. J Antimicrob Chemother 1996; 37(Suppl A):1–18.
27. **Gentry LO.** Oral antimicrobial therapy for osteomyelitis. Ann Intern Med 1991; 114:986–987.
28. **Edmond MB, Wenzel RP, Pasculle AW.** Vancomycin-resistant *Staphylococcus aureus*: Perspectives on measures needed for control. Ann Intern Med 1996; 124:329–334.

ADDRESS: *Patricia A. Flores, PharmD, Department of Hospital Pharmacy, S107, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*