Reduced Susceptibility of *Staphylococcus aureus* to Vancomycin — Japan, 1996

Staphylococcus aureus is a virulent microorganism responsible for many serious infections among the general population. Since recognition of vancomycin-resistant enterococci (VRE), the emergence of vancomycin resistance in *S. aureus* has been anticipated. This report describes the first documented case of infection caused by *S. aureus* with reduced susceptibility to vancomycin and includes the initial characterization of this isolate (*1*); the case occurred in a pediatric patient in Japan. The emergence of reduced vancomycin susceptibility in *S. aureus* increases the possibility that some strains will become fully resistant and that currently available antimicrobial agents will become ineffective for treating infections caused by such strains.

In May 1996, a 4-month-old boy developed a nosocomial surgical-site infection with methicillin-resistant *S. aureus* (MRSA). He received treatment with vancomycin (45 mg per kg body weight per day) for 29 days, but fever and surgical-site purulent discharge continued, and the C-reactive protein (CRP) remained elevated (4 mg/dL; normal: <1 mg/dL). Treatment was changed to a combination of vancomycin and arbekacin (an aminoglycoside approved for MRSA infection in Japan but not in the United States). After 12 days of this regimen, the purulent discharge subsided, the wound site began to heal, and the CRP declined to 0.9 mg/dL; antimicrobial therapy was discontinued. However, 12 days after antimicrobial therapy was discontinued, fever and surgical-site inflammation recurred, subcutaneous abscesses were detected, and the CRP increased to 3.5 mg/dL. Arbekacin was resumed in combination with ampicillin/sulbactam. After 6 days of this regimen, his fever subsided, and the CRP declined below detectable levels (<0.3 mg/dL). However, during the next several days, the CRP fluctuated between <0.3 mg/dL and 1.0 mg/dL, consistent with persistent infection. After debridement of the subcutaneous abscesses and therapy with arbekacin and ampicillin/sulbactam for an additional 17 days, the patient improved, and his CRP remained below detectable levels; his antimicrobial therapy was discontinued, and he was discharged from the hospital.

The MRSA strain that was isolated from the purulent discharge at the surgical site and from the debridement sample demonstrated a vancomycin minimum inhibitory concentration (MIC) of 8 μg/mL (National Committee for Clinical Laboratory Standards breakpoints: susceptible, ≤4 μg/mL; intermediate, 8–16 μg/mL; and resistant, ≥32 μg/mL) by the broth microdilution method performed in Japan and at CDC (*2*). The organism was negative when tested by polymerase chain reaction for *vanA* and *vanB,* the principal genes responsible for vancomycin resistance in enterococci. The mechanism of decreased susceptibility is still under investigation.

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Editorial Note: *S. aureus* is a gram-positive, coccoid bacteria that causes pneumonia and infections of the bloodstream, skin, soft tissues, and bone; this pathogen frequently causes community-acquired infections and is the most common cause of nosocomial infections. In the pre-antibiotic era, *S. aureus* infections were a common cause of death. Although the availability of penicillin in the 1940s offered an important advance in the treatment of infection, susceptibility of *S. aureus* was short-lived.

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Resistance was first recognized in 1944 and was caused by production of a penicillinase enzyme capable of deactivating penicillin; by the late 1950s, approximately 50% of strains were resistant to penicillin. These strains were associated with widespread outbreaks before the development of semisynthetic penicillinase-resistant agents, such as methicillin, in 1960; however, resistance to methicillin was reported as early as 1961 in England. In the United States, the proportion of MRSA isolates reported to the National Nosocomial Infections Surveillance system increased from 2% in 1975 to 35% in 1996. In Japan, analysis of approximately 7000 strains isolated from patients in various geographic areas during 1992–1993 (*3*) indicated that 60% of *S. aureus* isolates were resistant to methicillin.

Until the identification of the isolate described in this report, MRSA had been susceptible to vancomycin, a glycopeptide antibiotic introduced clinically in 1958. Initially, vancomycin was used infrequently as an alternative to other agents; however, because of the increase in MRSA and other factors (e.g., increased incidence of prosthetic device-related infections and *Clostridium difficile* colitis), its use has increased since the late 1970s. In the late 1980s, clinically important resistance to vancomycin was identified among enterococci (i.e., VRE) associated with *vanA* or *vanB* genes. Transfer of the *vanA* genes experimentally from enterococci to *S. aureus* (*4*) suggested the potential for *S. aureus* to acquire these genes in vivo, producing clinical resistance. Such resistance could result in serious clinical and public health consequences because no currently licensed alternative to vancomycin is available to treat serious MRSA infections.

Infections caused by less virulent coagulase-negative staphylococci (CNS) with reduced susceptibility to vancomycin have been previously recognized (e.g., *S. haemolyticus* [*5*] and *S. epidermidis* [*6*]). In addition, laboratory studies in which both CNS and *S. aureus* isolates have been exposed to increasing levels of glycopeptides have demonstrated the ability of these agents to select for resistant subpopulations (*7,8*). Given these findings and the spread of VRE, for which the prudent use of vancomycin has been recommended as an important control measure (*9*), the prudent use of all antibiotics, especially vancomycin, is critical for preventing the emergence of resistance among staphylococci in the United States.

The impact of reduced vancomycin susceptibility on clinical outcome may be difficult to assess because serious infections caused by fully susceptible *S. aureus* often require treatment with a combination of aggressive surgical and antimicrobial therapy. Reduced vancomycin susceptibility as described in this report may signal the onset of an increase in the MICs of vancomycin against *S. aureus.* The clinical importance of such reduced susceptibility may become most evident for treatment of infections at sites where achievable drug concentrations are lower than those commonly achieved in the bloodstream (e.g., closed space or central nervous system infections) or in treating infections in the presence of a foreign body. Patients with infections caused by *S. aureus* (i.e., MRSA) with reduced susceptibility to vancomycin and who unequivocally have not responded to appropriate therapy may be candidates for treatment with an investigational drug. CDC and the Food and Drug Administration are collaborating to make such agents available in the United States (*10*).

Because clonal dissemination of *S. aureus* with reduced vancomycin susceptibility can occur, efforts must be intensified to prevent the transmission of such strains within and between facilities and to minimize the potential for these strains to become

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endemic. The recovery of *S. aureus* with presumptive reduced susceptibility to vancomycin should be reported immediately to state health departments and to CDC's Hospital Infections Program, National Center for Infectious Diseases, telephone (404) 639-6400. In addition, special infection-control precautions should be adhered to strictly (*10*), and an epidemiologic investigation should be initiated promptly.

References

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Interim Guidelines for Prevention and Control of Staphylococcal Infection Associated with Reduced Susceptibility to Vancomycin

Staphylococci are one of the most common causes of community- and hospital-acquired infection. In many U.S. hospitals, strains of staphylococci (i.e., *Staphylococcus aureus* or coagulase-negative staphylococci) are resistant to all available antimicrobials except vancomycin. Rare cases of infection in the United States (*1*) have been caused by coagulase-negative staphylococci with reduced susceptibility to vancomycin (minimum inhibitory concentration [MIC] ≥8 μg/mL)* (*2*).

In May 1996, an infection caused by a strain of *S. aureus* with reduced susceptibility to vancomycin (MIC=8 μg/mL) was diagnosed in a patient in a hospital in Japan (*3,4*); no such infections have been reported in the United States. Although the strain from Japan was not fully resistant to vancomycin (i.e., MIC ≥32 μg/mL), its appearance increases the likelihood that fully resistant strains may emerge. Because the

*National Committee for Clinical Laboratory Standards breakpoints: susceptible, ≤4 μg/mL or zone size ≥12 mm; intermediate, 8–16 μg/mL or zone size 10–11 mm; and resistant, ≥32 μg/mL or zone size ≤9 mm.