

The New England Journal of Medicine

© Copyright, 1999, by the Massachusetts Medical Society

VOLUME 340

FEBRUARY 18, 1999

NUMBER 7



EMERGENCE OF VANCOMYCIN RESISTANCE IN *STAPHYLOCOCCUS AUREUS*

THERESA L. SMITH, M.D., MICHELE L. PEARSON, M.D., KENNETH R. WILCOX, M.D., DR.P.H., COSME CRUZ, M.D.,
MICHAEL V. LANCASTER, PH.D., BARBARA ROBINSON-DUNN, PH.D., FRED C. TENOVER, PH.D., MARCUS J. ZERVOS, M.D.,
JEFFREY D. BAND, M.D., ELIZABETH WHITE, M.S., AND WILLIAM R. JARVIS, M.D.,
FOR THE GLYCOPEPTIDE-INTERMEDIATE *STAPHYLOCOCCUS AUREUS* WORKING GROUP*

ABSTRACT

Background Since the emergence of methicillin-resistant *Staphylococcus aureus*, the glycopeptide vancomycin has been the only uniformly effective treatment for staphylococcal infections. In 1997, two infections due to *S. aureus* with reduced susceptibility to vancomycin were identified in the United States.

Methods We investigated the two patients with infections due to *S. aureus* with intermediate resistance to glycopeptides, as defined by a minimal inhibitory concentration of vancomycin of 8 to 16 μg per milliliter. To assess the carriage and transmission of these strains of *S. aureus*, we cultured samples from the patients and their contacts and evaluated the isolates.

Results The first patient was a 59-year-old man in Michigan with diabetes mellitus and chronic renal failure. Peritonitis due to *S. aureus* with intermediate resistance to glycopeptides developed after 18 weeks of vancomycin treatment for recurrent methicillin-resistant *S. aureus* peritonitis associated with dialysis. The removal of the peritoneal catheter plus treatment with rifampin and trimethoprim-sulfamethoxazole eradicated the infection. The second patient was a 66-year-old man with diabetes in New Jersey. A bloodstream infection due to *S. aureus* with intermediate resistance to glycopeptides developed after 18 weeks of vancomycin treatment for recurrent methicillin-resistant *S. aureus* bacteremia. This infection was eradicated with vancomycin, gentamicin, and rifampin. Both patients died. The glycopeptide-intermediate *S. aureus* isolates differed by two bands on pulsed-field gel electrophoresis. On electron microscopy, the isolates from the infected patients had thicker extracellular matrixes than control methicillin-resistant *S. aureus* isolates. No carriage was documented among 177 contacts of the two patients.

Conclusions The emergence of *S. aureus* with intermediate resistance to glycopeptides emphasizes the importance of the prudent use of antibiotics, the laboratory capacity to identify resistant strains, and the use of infection-control precautions to prevent transmission. (N Engl J Med 1999;340:493-501.)

©1999, Massachusetts Medical Society.

S*TAPHYLOCOCCUS AUREUS* is one of the most common causes of nosocomial and community-acquired infection.^{1,2} It is the most common cause of surgical-wound infections and second only to coagulase-negative staphylococci as a cause of nosocomial bloodstream infection.¹ After the initial success of penicillin in treating *S. aureus* infections, resistance to this drug began to emerge. Now, 70 to 80 percent of *S. aureus* isolates are resistant to penicillin.³ Methicillin and other semisynthetic penicillins were successful in treating penicillin-resistant *S. aureus* infections until the 1980s, when methicillin-resistant *S. aureus* became endemic in many hospitals.⁴

Since the emergence of methicillin-resistant *S. aureus*, the glycopeptide vancomycin has been the only uniformly effective treatment for staphylococcal infections. The recent emergence of glycopeptide resistance in coagulase-negative staphylococci has heightened concern about whether *S. aureus* could acquire glycopeptide resistance⁵⁻¹²; the emergence of such resistance could produce morbidity and mortality similar to that caused by *S. aureus* infections in the era before antibiotics became available.

In May 1996, the world's first documented clinical infection due to *S. aureus* with intermediate resistance to glycopeptides (glycopeptide-intermediate *S. aureus*) was diagnosed in a patient in Japan.^{13,14} In this report, we describe our investigation of the first documented glycopeptide-intermediate *S. aureus* infections

From the Hospital Infections Program (T.L.S., M.L.P., M.V.L., F.C.T., W.R.J.) and the Division of Viral and Rickettsial Disease (E.W.), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta; the Michigan Department of Community Health, Lansing (K.R.W., B.R.-D.); and William Beaumont Hospital, Royal Oak, Mich. (C.C., M.J.Z., J.D.B.). Address reprint requests to Dr. Pearson at the Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, MS E-69, Atlanta, GA 30333.

*Other members of the Glycopeptide-Intermediate *Staphylococcus aureus* Working Group are listed in the Appendix.

in the United States and discuss the clinical significance and public health implications of the emergence of these organisms.

METHODS

Definition, Ascertainment, and Review of Cases

An *S. aureus* isolate with intermediate resistance to glycopeptides was defined as an *S. aureus* isolate associated with a minimal inhibitory concentration of vancomycin of 8 to 16 μg per milliliter.¹⁵ A patient who had an infection caused by glycopeptide-intermediate *S. aureus* at William Beaumont Hospital, Royal Oak, Michigan, or Our Lady of Lourdes Hospital, Camden, New Jersey, from August 1996 to August 1997 was considered a case patient.

To identify *S. aureus* isolates with intermediate resistance to glycopeptides, we reviewed the hospitals' laboratory records to identify any *S. aureus* isolate associated with a minimal inhibitory concentration of vancomycin that was 4 μg per milliliter or higher for retesting. For each patient who had an infection with *S. aureus* with intermediate resistance, we reviewed the available medical records to obtain information on the clinical course and outcome, any antecedent use of antimicrobial agents, therapy, and contacts with health care personnel. These patients were interviewed to determine their activities and details of their recent medical care.

Infection-Control Policies and Practices

Next, we reviewed infection-control policies and practices at facilities and agencies where patients found to have resistant isolates had received care. To assess infection-control practices, we administered a standardized questionnaire to personnel who had provided direct care to the patients with resistant infection. We asked them about their knowledge of the patient's infection or carriage status, and their use of barrier precautions (e.g., gloves, gown, and mask) when caring for the infected patients.

Investigation of Contacts

To assess potential transmission of *S. aureus* with intermediate resistance to glycopeptides, we identified the hospital roommates, health care providers, and household contacts of patients with resistant isolates and cultured specimens from their hands and nares.

Laboratory Methods

Glycopeptide-intermediate *S. aureus* and epidemiologically related *S. aureus* isolates were sent to the Centers for Disease Control and Prevention (CDC) for confirmation of the species by standard reference methods¹⁶ and for antimicrobial-susceptibility testing with broth-microdilution methods.¹⁷ Isolates of *S. aureus* with intermediate resistance to glycopeptides were typed by pulsed-field gel electrophoresis.^{17,18}

S. aureus isolates with intermediate glycopeptide resistance were examined by scanning and transmission electron microscopy. For scanning electron microscopy, modifications of standard scanning electron microscopical techniques¹⁹ were used to fix, embed, and stain the organisms, which were then observed with a Philips XL20 scanning electron microscope (Philips Electronic Instruments, Mahwah, N.J.). To obtain transmission electron micrographs, modifications of standard transmission electron microscopy techniques²⁰ were used to fix, embed, and stain the organisms, which were then observed with a Philips 410 TEM transmission electron microscope (Philips Electronic Instruments).

Specimens for culture were obtained by swabbing the anterior nares with a dry sterile swab and were inoculated onto mannitol salt agar and incubated at 35°C. Specimens for culture from the hands were obtained by the wipe-rinse technique.²¹ Rinse fluid obtained with the wipe-rinse technique was passed through a 0.45- μm membrane filter (Advantec MFS, Pleasanton, Calif.). The filters were then implanted on Columbia nutrient agar (Becton Dickinson Microbiology Systems, Cockeysville, Md.) and mannitol salt agar. The cultures of specimens from the hands were incubated

for up to seven days at 35°C. Isolates were screened by the Staph-aurex Rapid latex test (Murex Diagnostics, Norcross, Ga.) and the coagulase tests.¹⁶ All *S. aureus* isolates were tested for susceptibility to vancomycin by agar-plate dilution.²² In Michigan, cultures of specimens from the hands and nares of the patient and contacts were transported to the Michigan Department of Community Health for identification of the species and testing for susceptibility to vancomycin. All specimens from New Jersey were sent directly to the CDC.

CASE REPORTS

Patient 1

Patient 1 was a 59-year-old man in Michigan who had diabetes mellitus, hypertension, metastatic small-cell carcinoma of unknown primary origin, and chronic renal failure that had required continuous ambulatory peritoneal dialysis since 1992. In February 1997, he was given a diagnosis, as an outpatient, of peritonitis after nausea and vomiting developed (Fig. 1). The peritoneal-fluid cell count was 790 white cells per deciliter, of which 88 percent were polymorphonuclear leukocytes. Gram's staining of the peritoneal fluid revealed gram-positive cocci, and cultures grew methicillin-resistant *S. aureus*. The patient was treated with intravenous vancomycin (1 g every 72 hours) for 14 days. The indwelling peritoneal catheter had no insertion-site inflammation and was not removed. Cultures of peritoneal fluid obtained after the completion of intravenous vancomycin therapy were negative. Over the subsequent five months, the patient had four additional episodes of culture-confirmed methicillin-resistant *S. aureus* peritonitis; each was treated with intravenous vancomycin, predominantly on an outpatient basis. The patient received vancomycin for a total of 18 weeks before glycopeptide-intermediate *S. aureus* was identified; peak serum levels of vancomycin (median, 33 μg per milliliter; range, 20.6 to 42.3) and trough levels (median, 10.4 μg per milliliter; range, 6.2 to 19.7) were within recommended limits.²³

On July 19, 1997, *S. aureus* with intermediate glycopeptide resistance was cultured from the patient's peritoneal fluid. Antimicrobial agents to which the isolate was susceptible included chloramphenicol, rifampin, trimethoprim-sulfamethoxazole, and tetracycline. Initially, the patient was treated as an outpatient with intravenous vancomycin (1 g every 72 hours) and intramuscular tobramycin (120 mg every 5 days). However, he continued to have abdominal pain and was hospitalized. Vancomycin was administered intraperitoneally at a dosage of 50 mg per 2 liters of dialysate twice a day and intravenously at 1 g every 72 hours. Cultures of peritoneal fluid obtained on days 12 and 19 of vancomycin therapy remained positive for *S. aureus* with intermediate glycopeptide resistance. On August 18, oral rifampin (300 mg daily) was added to the patient's regimen. On August 21, oral trimethoprim-sulfamethoxazole (160 mg and 800 mg daily) was also added; vancomycin and gentamicin were discontinued. At the time of our investigation, 23 days after the initiation of therapy, *S. aureus* was cultured from the patient's hands; no *S. aureus* with intermediate glycopeptide resistance was detected.

On September 5, 49 days after antimicrobial therapy for glycopeptide-intermediate *S. aureus* was begun, peritoneal-fluid cultures became negative; the peritoneal catheter was removed 4 days later. Culture of material from the catheter revealed no *S. aureus*. The patient had received a total of 16 days of rifampin and trimethoprim-sulfamethoxazole and was discharged on hemodialysis. The patient resumed continuous ambulatory peritoneal dialysis with no recurrence of peritonitis.

Surveillance cultures of specimens from the axilla, nares, vascular catheters, and peritoneal catheters were performed until January 6, 1998, and remained negative for *S. aureus* with intermediate glycopeptide resistance. The patient died at home, under hospice care. No autopsy was performed.

Patient 2

Patient 2 was a 66-year-old man in New Jersey who had congestive heart failure and diabetes mellitus; he was admitted to the hos-

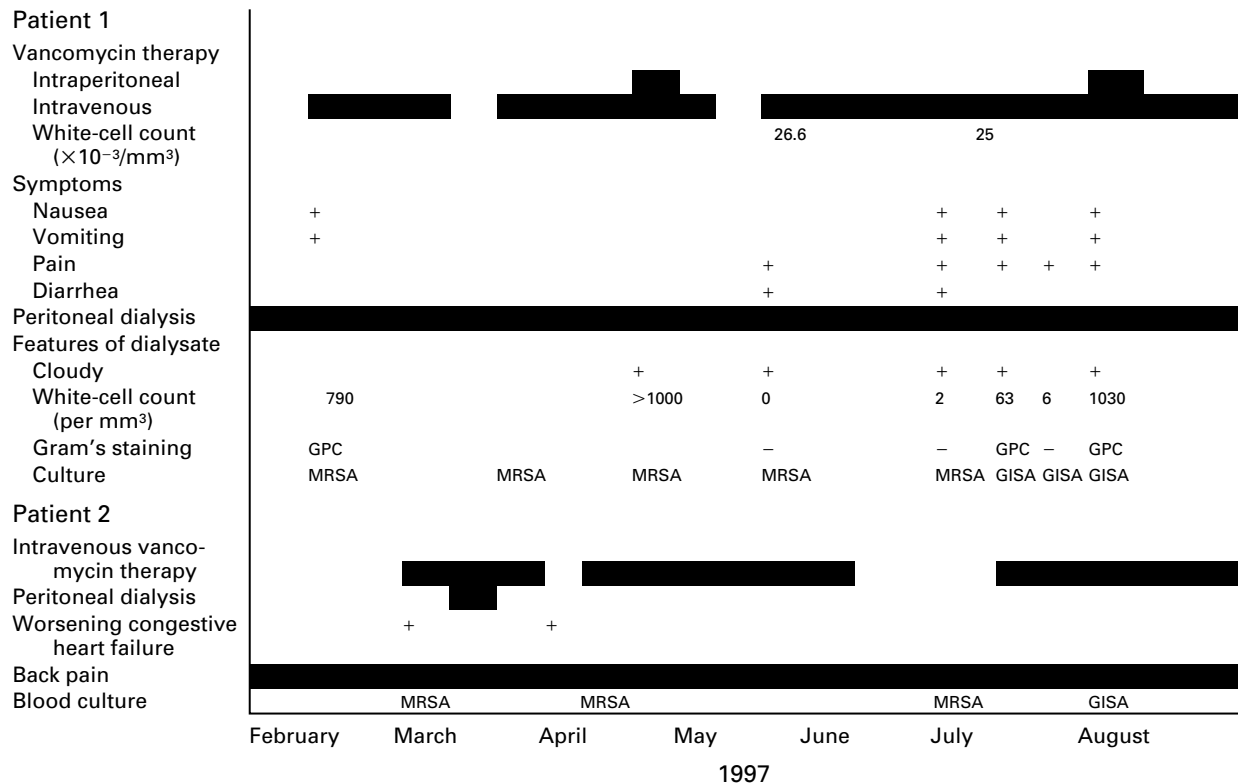


Figure 1. Time Line Showing the Clinical Course of Patients 1 and 2.

Dark bands show the duration of therapy or symptoms, plus signs the presence of symptoms or abnormalities or positive test results, and minus signs negative test results. GPC denotes gram-positive cocci, MRSA methicillin-resistant *Staphylococcus aureus*, and GISA glycopeptide-intermediate *S. aureus*.

pital on February 4, 1997, for evaluation of shortness of breath. A urinary tract infection due to methicillin-resistant *S. aureus* and vancomycin-resistant enterococci was diagnosed; the patient was treated with intravenous vancomycin (1 g on day 1) and oral doxycycline (100 mg daily for 10 days). Seven days into treatment, acute renal failure developed that required peritoneal dialysis. Cultures of peritoneal fluid obtained at the time of catheter insertion grew methicillin-resistant *S. aureus*. After 11 days, when dialysis was no longer required, the peritoneal catheter was removed, and no further peritoneal fluid for culture was obtained. On day 16 of hospitalization, a methicillin-resistant *S. aureus* bloodstream infection was diagnosed, and the patient received intravenous vancomycin (1 g every three days) for four more weeks. Blood cultures were negative after two weeks of intravenous vancomycin.

In April and July, the patient had three recurrences of methicillin-resistant *S. aureus* bloodstream infection; no localized infections were identified, and no foreign bodies were present at the time each infection was diagnosed. Bone scanning and white-cell scanning to detect possible occult infection were also negative. Transesophageal echocardiography showed clinically insignificant aortic and mitral insufficiency, but no valvular vegetations. Each episode was treated with intravenous vancomycin (1 g every three days). The peak serum vancomycin levels measured on two occasions were 32.5 μg per milliliter and 26.4 μg per milliliter. Trough levels and randomly measured serum vancomycin levels ranged from 4.6 to 26.2 μg per milliliter (median, 16.6). Only one randomly measured vancomycin level (4.6 μg per milliliter) fell below the recommended range for the trough serum level of vancomycin.²³

On August 6, 1997, after a total of 18 weeks of vancomycin therapy, a culture of blood drawn to evaluate the response to therapy grew *S. aureus* with intermediate resistance to glycopep-

tides. The bloodstream infection was initially treated on an outpatient basis with intravenous vancomycin (1 g every 10 days). On August 11, after the *S. aureus* isolate was recognized as having intermediate resistance to vancomycin, intravenous gentamicin (80 mg per day) was added. At the time of our investigation, four days after the addition of gentamicin, no *S. aureus* was cultured from specimens obtained from the patient's hands or nares.

On August 26, pedal and pulmonary edema developed, and oral rifampin (300 mg daily) was added to the patient's regimen. Two days later, he was admitted to the hospital for rapidly progressive renal insufficiency, thought to be due to his nephrotoxic medications, and peritoneal dialysis was begun. After four weeks of antimicrobial therapy for *S. aureus* infection with intermediate resistance to glycopeptides, all antimicrobial drugs were discontinued. On September 23, his temperature was 38.0°C (100.4°F), and blood cultures grew *Candida glabrata* and *C. parapsilosis*; peritoneal-fluid cultures grew *S. epidermidis*; urine cultures grew klebsiella and pseudomonas species. No *S. aureus* with intermediate resistance to glycopeptides was isolated from these cultures. Despite treatment with intravenous amphotericin B (45 mg per day) and oral doxycycline (100 mg twice a day) and ciprofloxacin (500 mg every 12 hours), the patient died 34 days after admission. Consent for an autopsy was refused.

RESULTS

Infection-Control Policies and Practices

While infected with *S. aureus* with intermediate resistance to glycopeptide, these two patients received care at three hospitals and affiliated outpa-

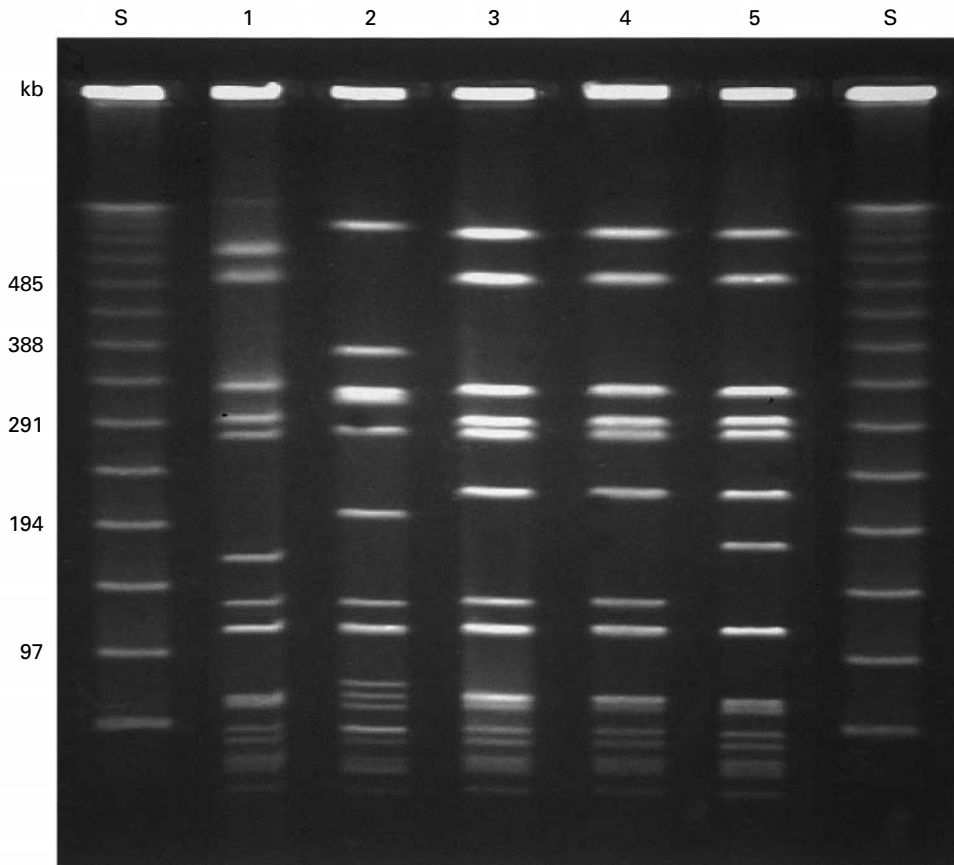


Figure 2. Patterns of *Smal*-Digested DNA of *S. aureus* Isolates on Pulsed-Field Gel Electrophoresis.

S denotes lambda molecular-size standards; lane 1, *S. aureus* American Type Culture Collection 29213 control; lane 2, a methicillin-resistant *S. aureus* isolate from Georgia; lane 3, a glycopeptide-intermediate *S. aureus* isolate from Patient 1 in Michigan; lane 4, a methicillin-resistant *S. aureus* isolate from Patient 1 in Michigan; and lane 5, a glycopeptide-intermediate *S. aureus* isolate from Patient 2 in New Jersey.

tient clinics, at five physicians' offices, and through two home health agencies. Each of these medical care settings had written infection-control policies that were consistent with the CDC's recommended precautions for the care of patients infected with antimicrobial-resistant pathogens. In Michigan, contact isolation precautions (i.e., private rooms, gowns, gloves, and use of antimicrobial soap) were used for Patient 1 on his admission to the hospital because of his carriage of methicillin-resistant *S. aureus*; while he was receiving outpatient care in physicians' offices and hospital clinics and at home, standard precautions were generally used. In New Jersey, Patient 2 was also placed on contact isolation precautions at the time of hospitalization, because of a prior infection with vancomycin-resistant enterococci.

Among the 151 health care workers who provided direct care to these patients, 62 (41 percent) knew the patients were colonized or infected with methicillin-resistant *S. aureus* or vancomycin-resistant enterococci, and 118 (78 percent) used gloves, with or with-

out further barrier methods, when delivering care to the patients.

Investigation of Contacts

We identified 235 contacts (79 in Michigan and 156 in New Jersey); 58 hospital employees (25 percent) were unavailable because of vacations (33 workers) or hospital policy (25 workers). The remaining 177 contacts (54 in Michigan and 123 in New Jersey) were 86 nurses or nurse's assistants, 23 physicians, 15 home health aides, 11 phlebotomists, 10 household contacts, 8 hospital roommates, 7 technicians, 4 orderlies, 4 emergency-response personnel, 3 physical therapists, 3 medical students, 2 hospital chaplains, and 1 dietitian. All agreed to provide material for culture. Sixty (34 percent) of these contacts (21 in Michigan and 39 in New Jersey) were positive for *S. aureus*; 10 (17 percent) had hand carriage only, 40 (67 percent) had nares carriage only, and 10 (17 percent) had both. No carriage of *S. aureus* with intermediate resistance to glycopeptides was found.

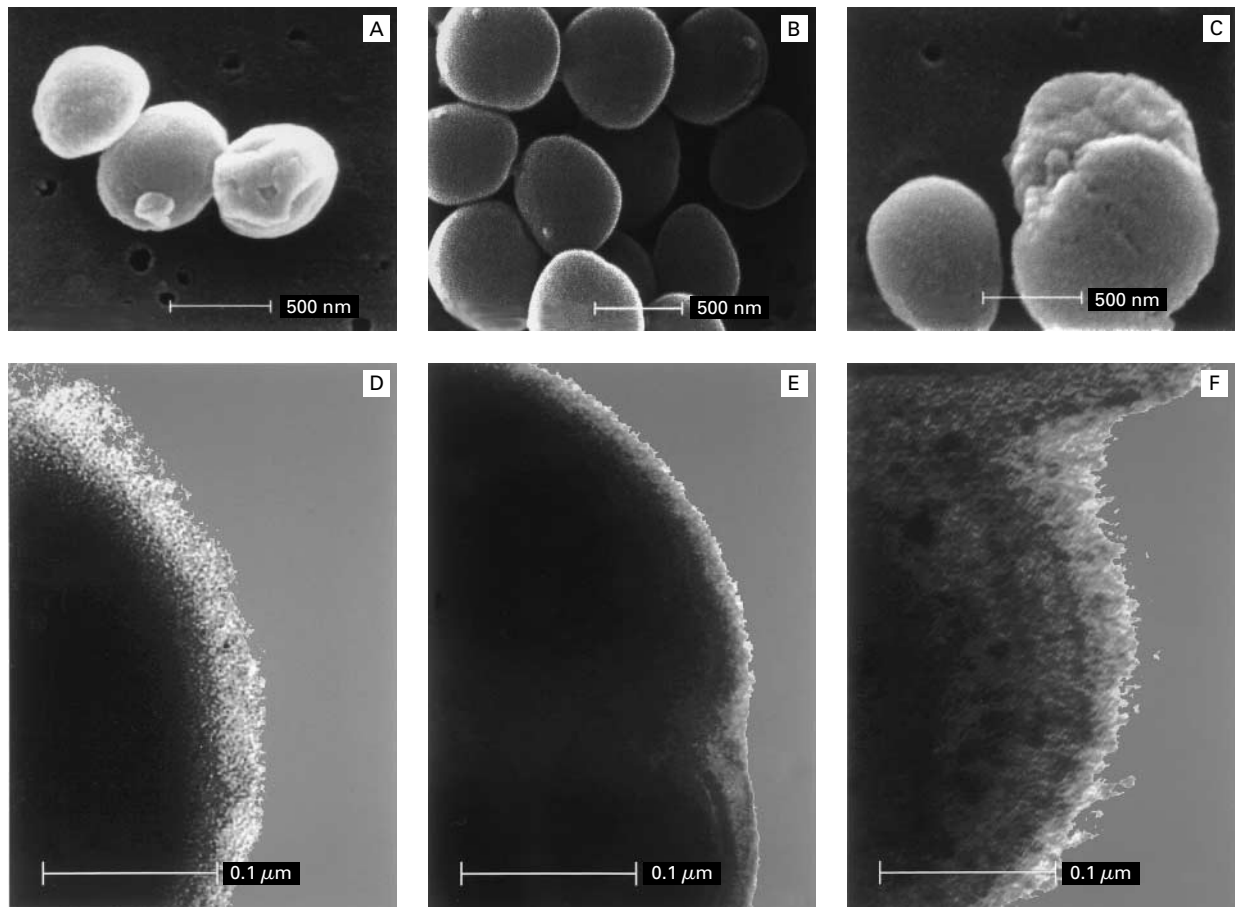


Figure 3. Electron Micrographs of *S. aureus* Isolates.

The top row shows scanning electron micrographs magnified 50,000 times; the bottom row, transmission electron micrographs magnified 348,000 times. Panels A and D show a glycopeptide-intermediate *S. aureus* isolate from Patient 1 in Michigan, in which increased extracellular material is evident; Panels B and E, methicillin-resistant *S. aureus* from Georgia, showing a normal cell wall without increased extracellular material; and Panels C and F, a glycopeptide-intermediate *S. aureus* isolate from Patient 2 in New Jersey, with evidence of increased extracellular material.

Results of Laboratory Tests

According to broth-microdilution methods, the isolates of *S. aureus* with intermediate resistance to glycopeptides from both patients had minimal inhibitory concentrations of 8 μg per milliliter of vancomycin both on initial testing and after passage through 20 subcultures. In contrast, on disk-diffusion testing, the Michigan and New Jersey isolates were read as susceptible to vancomycin at 18 and 17 mm, respectively. Both isolates were resistant to penicillin, oxacillin, ciprofloxacin, erythromycin, and clindamycin, but both remained susceptible to chloramphenicol, dalfopristin, quinupristin, tetracycline, and trimethoprim-sulfamethoxazole. Patient 1's isolate was resistant to gentamicin and teicoplanin and susceptible to rifampin, whereas Patient 2's isolate was resistant to rifampin and susceptible to gentamicin and teicoplanin.¹⁷ With the exception of intermediate resistance to vancomycin, the susceptibility patterns of the *S. aureus*

isolates were similar to those of each patient's previous strain of methicillin-resistant *S. aureus*. Population analysis confirmed the presence of glycopeptide-intermediate subpopulations of *S. aureus*.

Pulsed-field gel electrophoresis revealed a difference of two bands between the two *S. aureus* isolates with intermediate resistance to glycopeptides (Fig. 2). Patient 1's glycopeptide-intermediate *S. aureus* isolate and a methicillin-resistant *S. aureus* isolate from the patient's hands had indistinguishable patterns on pulsed-field gel electrophoresis (Fig. 2). No methicillin-resistant *S. aureus* isolate from Patient 2 was available for comparison.

Scanning and transmission electron microscopy showed a layer of extracellular material of unknown chemical composition in the *S. aureus* isolates with intermediate resistance to vancomycin that was thicker than that in the methicillin-resistant *S. aureus* control isolates (Fig. 3).

DISCUSSION

We investigated the first two documented infections with *S. aureus* with intermediate resistance to glycopeptides in the United States. To date, a total of four glycopeptide-intermediate *S. aureus* infections have been documented worldwide,¹³ the first in Japan and, more recently, the fourth in New York. The emergence of *S. aureus* with intermediate glycopeptide resistance raises a number of questions: Who is at risk for infection with these strains of *S. aureus*? Are these strains clinically important? What is the mechanism of resistance? Finally, how can infection with *S. aureus* with intermediate resistance to glycopeptides be prevented and controlled?

Although the small number of documented infections due to glycopeptide-intermediate *S. aureus* precludes a formal risk assessment, there are certain common features among the four documented cases. First, all four patients had prior infections with methicillin-resistant *S. aureus*, for which they received repeated and prolonged vancomycin therapy. Second, three of the four received long-term or temporary dialysis. Third, three of the four had poor clinical response to vancomycin therapy. These findings suggest that monitoring for colonization or infection with *S. aureus* with intermediate glycopeptide resistance may be warranted among patients who are often treated with vancomycin, such as patients on dialysis.

The clinical course of the patients infected with *S. aureus* with intermediate vancomycin resistance suggests that even partial glycopeptide resistance among *S. aureus* is clinically important. Eradication of the glycopeptide-intermediate *S. aureus* infection in the patient in Japan required surgical débridement and prolonged therapy with ampicillin-sulbactam and arbekacin, an aminoglycoside unavailable in the United States.¹⁴ The first U.S. patient required seven weeks of combination antimicrobial therapy and removal of a peritoneal catheter for successful eradication of the infection. The second U.S. patient also required prolonged antimicrobial therapy, which was complicated by impaired renal function that required continuous ambulatory peritoneal dialysis. *S. aureus* with intermediate glycopeptide resistance should be suspected in any patient in whom otherwise appropriate vancomycin therapy for *S. aureus* infection appears to be ineffective.

Recently advocated approaches to the treatment of infections include the treatment of abscesses without drainage²⁴ and the use of vancomycin without surveillance of serum vancomycin levels.²⁵ Although these approaches may prove successful in some cases, the recent experience with infections caused by *S. aureus* with intermediate glycopeptide resistance suggests that abscesses must be drained and that adequate antimicrobial levels must be maintained for therapy to be successful.^{23,26-29}

Options for the treatment of infections caused by

S. aureus with intermediate glycopeptide resistance should be based on the organism's antimicrobial-susceptibility profile. An expanded antimicrobial-susceptibility profile may be necessary, depending on the laboratory's standard susceptibility panel. Some patients with *S. aureus* infection also benefit from consultation with an infectious-disease specialist.²⁹ Fortunately, to date all *S. aureus* isolates with intermediate glycopeptide resistance have been susceptible to alternative agents, including newly developed agents.¹⁷

Glycopeptide resistance may have emerged in *S. aureus* because of interspecies transfer of resistance genes or selection of resistant mutants as a result of prolonged antimicrobial therapy. The ability of gram-positive organisms to acquire glycopeptide-resistance genes became a matter of concern with the emergence of vancomycin-resistant enterococci, and vancomycin-resistance genes have been transferred from vancomycin-resistant enterococci to *S. aureus* in vitro.⁶ However, none of the *S. aureus* isolates with intermediate glycopeptide resistance have had *vanA*, *vanB*, *vanC1*, *vanC2*, or *vanC3* genes,¹⁷ suggesting that interspecies transfer of resistant genes from vancomycin-resistant enterococci³⁰ is not the mechanism by which glycopeptide resistance developed in these *S. aureus* isolates.

Certain common factors in the cases of the two U.S. patients suggest that cellular modification due to prolonged vancomycin exposure was probably responsible for the emergence of glycopeptide resistance in these isolates. Both patients had received multiple prolonged courses of vancomycin for methicillin-resistant *S. aureus* infections. The patients' methicillin-resistant *S. aureus* isolates and their *S. aureus* isolates with intermediate glycopeptide resistance had similar minimal inhibitory concentrations of antimicrobials other than vancomycin. In addition, *S. aureus* isolates that had intermediate vancomycin resistance had increased extracellular material associated with the cell wall — a finding similar to that observed in *S. aureus* organisms with intermediate glycopeptide resistance induced in vitro.^{7,31,32} The thickened extracellular material has been shown to sequester vancomycin⁷ and to reduce the susceptibility of *S. aureus* to vancomycin.³² Although the exact mechanism of vancomycin resistance has not been determined, these data suggest that it emerged through the selection of naturally occurring resistant mutants during prolonged exposure to vancomycin. Elucidation of these mechanisms will be essential for the development of effective therapeutic agents.

The two *S. aureus* isolates with intermediate resistance to glycopeptides that were isolated from U.S. patients had similar patterns on pulsed-field gel electrophoresis. The *S. aureus* isolates with intermediate glycopeptide resistance and the colonizing methicillin-resistant *S. aureus* isolates from one patient were indistinguishable, suggesting that the methicil-

TABLE 1. SITUATIONS IN WHICH THE USE OF VANCOMYCIN SHOULD BE DISCOURAGED.*

Routine prophylaxis
Surgical patients without life-threatening allergy to beta-lactam antibiotics ²⁴
Low-birth-weight infants ²⁵
Patients on dialysis ^{26,27}
Patients with neutropenia
Patients with central venous catheters ^{26,28-43}
Empirical treatment
Febrile patients with neutropenia who are not at high risk for resistant gram-positive infection ⁴⁴⁻⁵⁰
Febrile low-birth-weight infants
Decontamination of the digestive tract
Treatment based on indications
Patients with single blood cultures positive for coagulase-negative staphylococci ⁵¹⁻⁵³
Patients colonized with methicillin-resistant <i>S. aureus</i> ^{54,55}
Patients with <i>Clostridium difficile</i> colitis (first-line therapy) ⁵⁶
Patients on dialysis for whom convenience in treating infections is desirable ⁵⁷⁻⁶⁰
Patients with gram-positive infections not due to resistant organisms

*Data are from the Hospital Infection Control Practices Advisory Committee.³³

lin-resistant *S. aureus* isolate may have been the progenitor of the *S. aureus* with intermediate glycopeptide resistance. The apparent similarity between the two geographically distant and epidemiologically unrelated isolates from the patients in Michigan and New Jersey probably reflects our inability to distinguish the genetic ancestry of the methicillin-resistant *S. aureus* isolates in the United States because of the limited number of strains. The two *S. aureus* isolates with intermediate glycopeptide resistance in the U.S. patients differed from the Japanese isolate.¹⁷

The widespread use of vancomycin and other antimicrobial agents that resulted in the dramatic increase in the prevalence of vancomycin-resistant enterococci in U.S. hospitals³³ may cause a similar increase in the prevalence of *S. aureus* with intermediate glycopeptide resistance. Data from Japan show that methicillin-resistant *S. aureus* with heteroresistance to vancomycin (heteroresistance is the manifestation of the resistance phenotype by only small subpopulations of the strain) is present in a number of hospitals.¹⁴ The prevalence of heteroresistant methicillin-resistant *S. aureus* isolates in U.S. hospitals is unknown. Fortunately, each of the hospitals to which the U.S. patients were admitted had infection-control policies in place for patients with antimicrobial-resistant infections or colonization, and we documented no carriage of *S. aureus* with intermediate glycopeptide resistance among the household or medical contacts of either patient. The lack of transmission of these resistant *S. aureus* infections suggests that adherence to recommended infection-con-

TABLE 2. RECOMMENDATIONS FOR PREVENTING THE SPREAD OF GLYCOPEPTIDE-RESISTANT STAPHYLOCOCCI.*

Laboratory

- Ensure presence of pure *S. aureus* isolate
- Use one of the following quantitative methods to determine the minimal inhibitory concentration with 24-hour incubation
 - Broth microdilution
 - Agar dilution
 - Agar-gradient diffusion
- Retest isolates associated with minimal inhibitory concentrations ≥ 4 μg per milliliter and those from patients whose condition does not improve with glycopeptide therapy
- Report all *S. aureus* isolates associated with minimal inhibitory concentrations ≥ 4 μg per milliliter of glycopeptide to the state health department and the CDC
- Immediately notify infection-control personnel, the clinical care unit, and attending physician when an *S. aureus* isolate associated with a minimal inhibitory concentration ≥ 4 μg per milliliter is recognized

Infection control

- Isolate the patient in a private room
 - Minimize the number of persons caring for the patient
 - Begin one-on-one care by specified personnel
- Initiate epidemiologic and laboratory investigations with the assistance of the state health department and the CDC
- Educate all health care personnel about the epidemiology of *S. aureus* with intermediate resistance to glycopeptides and about appropriate infection-control precautions
- Monitor and strictly enforce compliance with contact precautions⁶²
- Determine whether transmission has already occurred by performing baseline cultures of specimens from hands and nares of the following:
 - Those with physical contact with the patient
 - The patient's health care providers
 - The patient's roommates
- Use contact precautions (gown, mask, gloves, and antibacterial soap for hand washing)⁶²
- Assess efficacy of precautions by monitoring personnel for acquisition of the isolate
- Consult with the state health department and CDC before transferring the patient (for emergencies only) or discharging him or her
- Inform the following appropriate personnel about the presence of a patient with glycopeptide-intermediate *S. aureus*:
 - Patient's accepting physician
 - Admitting or emergency room personnel
 - Personnel admitting patients to unit

*Recommendations were modified from CDC guidelines.⁶¹

control practices may prevent the transmission of *S. aureus* with intermediate glycopeptide resistance from patient to patient and from patient to health care worker. Nevertheless, continuing education of clinicians about the indications for vancomycin use is needed to reduce the overuse and misuse of vancomycin and other antimicrobial agents in all health care settings, including inpatient and outpatient facilities (such as dialysis units). The development of innovative intervention programs, such as clinical practice guidelines and "antibiotic stop orders," which lead to automatic discontinuation of a prescribed antimicrobial agent after a predetermined interval, may increase compliance with the recommendations of the Hospital Infection Control Practices Advisory Committee and reduce overall use of antimicrobials (Table 1).²²

Recently, the CDC issued specific recommendations intended to reduce the development and trans-

mission of *S. aureus* with intermediate glycopeptide resistance (Table 2). First, laboratory personnel should use a quantitative method based on the minimal inhibitory concentration to detect *S. aureus* isolates with intermediate glycopeptide resistance. Vancomycin disk diffusion does not reliably identify *S. aureus* isolates with decreased susceptibility to glycopeptides.¹⁷ Second, programs to educate health care personnel about infection-control precautions against *S. aureus* with intermediate glycopeptide resistance should be developed, and infection-control specialists should monitor compliance with these precautions. Third, infection-control and laboratory personnel should implement active surveillance for *S. aureus* with intermediate glycopeptide resistance, particularly in populations at high risk, such as patients on dialysis and patients in whom vancomycin therapy is unsuccessful.¹⁷ If an *S. aureus* isolate with potential intermediate resistance to glycopeptides is identified, prompt notification of the state health department and the CDC is critical so that epidemiologic and laboratory support can be provided.

The emergence of *S. aureus* with intermediate glycopeptide resistance threatens to return us to the era before the development of antibiotics. To prevent further emergence of *S. aureus* strains with intermediate glycopeptide resistance and the emergence of *S. aureus* with full vancomycin resistance, the use of vancomycin must be optimized, laboratory methods for the detection of resistant pathogens must be enhanced, and infection-control precautions must be strictly followed for infected or colonized patients.

The use of company or trade names is for identification only and does not imply endorsement by the Public Health Service or the Department of Health and Human Services.

We are indebted to Lori Boschetto, B.S.N., Catherine Crain, M.T., B.S.N., and Sandy Pine, B.S., Our Lady of Lourdes Medical Center, Camden, N.J.; Gary Burke, D.O., Haddon Cardiology Associates, Haddon Heights, N.J.; Colin Campbell, D.V.M., and Herman Ellis, M.D., New Jersey Department of Health and Senior Services, Trenton; Gael Rodgers, R.N., B.S.N., Bon Secours of Michigan Health-care System, Grosse Pointe; and James Sunstrum, M.D., Oakwood Hospital, Dearborn, Mich., for their invaluable contributions to our investigation.

APPENDIX

In addition to the authors, the members of the Glycopeptide-Intermediate *Staphylococcus aureus* Working Group were as follows: M.J. Arduino, J.H. Carr, N. Clark, B. Hill, S. McAllister, and J.M. Miller, Hospital Infections Program, National Center for Infectious Diseases, CDC, Atlanta; and G. Jennings, Michigan Department of Community Health, Lansing.

REFERENCES

- National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986–April 1996, issued May 1996. *Am J Infect Control* 1996;24:380-8.
- Waldvogel FA. *Staphylococcus aureus* (including toxic shock syndrome). In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1995:1754-77.
- Atkinson BA, Lorian V. Antimicrobial agent susceptibility patterns of bacteria in hospitals from 1971 to 1982. *J Clin Microbiol* 1984;20:791-6.
- Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975–1991. *Infect Control Hosp Epidemiol* 1992;13:582-6.
- Edmond MB, Wenzel RP, Pasculle AW. Vancomycin-resistant *Staphylococcus aureus*: perspectives on measures needed for control. *Ann Intern Med* 1996;124:329-34.
- Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett* 1992;93:195-8.
- 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;179:2557-66.
- Garrett DO, Jochimsen E, Murfitt K, et al. The impending apocalypse, the emergence of vancomycin resistance in *Staphylococcus* spp. *Infect Control Hosp Epidemiol* 1997;18:Suppl:P32. abstract.
- Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococci. *N Engl J Med* 1987;316:927-31.
- Veach LA, Pfaller MA, Barrett M, Koontz FP, Wenzel RP. Vancomycin resistance in *Staphylococcus haemolyticus* causing colonization and bloodstream infection. *J Clin Microbiol* 1990;28:2064-8.
- Sanyal D, Johnson AP, George RC, Cookson BD, Williams AJ. Peritonitis due to vancomycin-resistant *Staphylococcus epidermidis*. *Lancet* 1991;337:54.
- Aubert G, Passot S, Lucht F, Dorche G. Selection of vancomycin- and teicoplanin-resistant *Staphylococcus haemolyticus* during teicoplanin treatment of *S. epidermidis* infection. *J Antimicrob Chemother* 1990;25:491-3.
- Reduced susceptibility of *Staphylococcus aureus* to vancomycin — Japan, 1996. *MMWR Morb Mortal Wkly Rep* 1997;46:624-6.
- Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 1997;40:135-6.
- Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically — approved standard. 4th ed. Vol. 17. No. 2. Wayne, Pa.: National Committee for Clinical Laboratory Standards, 1997. (NCCLS publication no. M7-A4.)
- Kloos WE, Bannerman TL. *Staphylococcus* and *Micrococcus*. In: Murray PR, ed. *Manual of clinical microbiology*. 6th ed. Washington, D.C.: American Society for Microbiology, 1995:282-98.
- Tenover FC, Lancaster MV, Hill BC, et al. Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. *J Clin Microbiol* 1998;36:1020-7. [Erratum, *J Clin Microbiol* 1998;36:2167.]
- Bannerman TL, Hancock GA, Tenover FC, Miller JM. Pulsed-field gel electrophoresis as a replacement for bacteriophage typing of *Staphylococcus aureus*. *J Clin Microbiol* 1995;33:551-5.
- Costerton JW, Irvin RT, Cheng K-J. The bacterial glycocalyx in nature and disease. *Annu Rev Microbiol* 1981;35:299-324.
- Newman GR, Jasani B. Post-embedding immunoenzyme techniques. In: Polak JM, Vardell IM, eds. *Immunolabelling for electron microscopy*. Amsterdam: Elsevier Science, 1984:53-70.
- Petersen NJ, Collins DE, Marshall JH. A microbiological assay technique for hands. *Health Lab Sci* 1973;10:18-22.
- Jorgensen JH. Laboratory issues in the detection and reporting of antibacterial resistance. *Infect Dis Clin North Am* 1997;11:785-802.
- Ingerman MJ, Santoro J. Vancomycin: a new old agent. *Infect Dis Clin North Am* 1989;3:641-51.
- Bamberger DM. Outcome of medical treatment of bacterial abscesses without therapeutic drainage: review of cases reported in the literature. *Clin Infect Dis* 1996;23:591-603.
- Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis* 1994;18:533-43.
- Mollitt DL. Pediatric surgical infection and antibiotic usage. *Pediatr Infect Dis* 1985;4:326-9.
- Serry C, Bleck PC, Javid H, et al. Sternal wound complications: management and results. *J Thorac Cardiovasc Surg* 1980;80:861-7.
- Hermans PE, Wilhelm MP. Vancomycin. *Mayo Clin Proc* 1987;62:901-5.
- Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis* 1998;27:478-86.
- Clark NC, Cooksey RC, Hill BC, Swenson JM, Tenover FC. Characterization of glycopeptide-resistant enterococci from U.S. hospitals. *Antimicrob Agents Chemother* 1993;37:2311-7.
- Daum RS, Gupta S, Sabbagh R, Milewski WM. Characterization of *Staphylococcus aureus* isolates with decreased susceptibility to vancomycin and teicoplanin: isolation and purification of a constitutively produced protein associated with decreased susceptibility. *J Infect Dis* 1992;166:1066-72.

32. Shlaes DM, Shlaes JH, Vincent S, Etter L, Fey PD, Goering RV. Teicoplanin-resistant *Staphylococcus aureus* expresses a novel membrane protein and increases expression of penicillin-binding protein 2 complex. *Antimicrob Agents Chemother* 1993;37:2432-7.
33. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep* 1995;44(RR-12):1-13.
34. Conte JE Jr, Cohen SN, Roe BB, Elashoff RM. Antibiotic prophylaxis and cardiac surgery: a prospective double-blind comparison of single-dose versus multiple-dose regimens. *Ann Intern Med* 1972;76:943-9.
35. Kacica MA, Horgan MJ, Ochoa L, Sandler R, Lepow ML, Venezia RA. Prevention of gram-positive sepsis in neonates weighing less than 1500 grams. *J Pediatr* 1994;125:253-8.
36. Kaplan AH, Gilligan PH, Facklam RR. Recovery of resistant enterococci during vancomycin prophylaxis. *J Clin Microbiol* 1988;26:1216-8.
37. Lam TY, Vas SI, Oreopoulos DG. Long-term intraperitoneal vancomycin in the prevention of recurrent peritonitis during CAPD: preliminary results. *Perit Dial Int* 1991;11:281-2.
38. Ranson MR, Oppenheim BA, Jackson A, Kamthan AG, Scarffe JH. Double-blind placebo controlled study of vancomycin prophylaxis for central venous catheter insertion in cancer patients. *J Hosp Infect* 1990;15:95-102.
39. Henrickson KJ, Powell KR, Schwartz CL. A dilute solution of vancomycin and heparin retains antibacterial and anticoagulant activities. *J Infect Dis* 1988;157:600-1.
40. Schwartz CL, Henrickson KJ, Roghmann K, Powell KR. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin-susceptible organisms. *J Clin Oncol* 1990;8:1591-7.
41. Henrickson KJ, Dunne WM Jr. Modification of central venous catheter flush solution improves in vitro antimicrobial activity. *J Infect Dis* 1992;166:944-6.
42. Gaillard JL, Merlino R, Pajot N, et al. Conventional and nonconventional modes of vancomycin administration to decontaminate the internal surface of catheters colonized with coagulase-negative staphylococci. *J Parenter Enteral Nutr* 1990;14:593-7.
43. Spafford PS, Sinkin RA, Cox C, Reubens L, Powell KR. Prevention of central venous catheter-related coagulase-negative staphylococcal sepsis in neonates. *J Pediatr* 1994;125:259-63.
44. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA. Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med* 1988;108:30-5.
45. Shenep JL, Hughes WT, Roberson KP, et al. Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. *N Engl J Med* 1988;319:1053-8.
46. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986;315:552-8.
47. Karp JE, Dick JD, Angelopoulos C, et al. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia: randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *Am J Med* 1986;81:237-42.
48. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group, National Cancer Institute of Canada-Clinical Trials Group. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991;163:951-8. [Erratum, *J Infect Dis* 1991;164:832.]
49. Riikonen P. Imipenem compared with ceftazidime plus vancomycin as initial therapy for fever in neutropenic children with cancer. *Pediatr Infect Dis J* 1991;10:918-23.
50. Lamy T, Michelet C, Dauriac C, Grulois I, Donio PY, Le Prise PY. Benefit of prophylaxis by intravenous systemic vancomycin in granulocytopenic patients: a prospective, randomized trial among 59 patients. *Acta Haematol* 1993;90:109-13.
51. Isaacman DJ, Karasic RB. Lack of effect of changing needles on contamination of blood cultures. *Pediatr Infect Dis J* 1990;9:274-8.
52. Krumholz HN, Cummings S, York M. Blood culture phlebotomy: switching needles does not prevent contamination. *Ann Intern Med* 1990;113:290-2. [Erratum, *Ann Intern Med* 1990;113:723.]
53. Strand CL, Wajsbort RR, Sturmman K. Effect of iodophor vs iodine tincture skin preparation on blood culture contamination rate. *JAMA* 1993;269:1004-6.
54. Gradon JD, Wu EH, Lutwick LI. Aerosolized vancomycin therapy facilitating nursing home placement. *Ann Pharmacother* 1992;26:209-10.
55. Weathers L, Riggs D, Santeiro M, Weibley RE. Aerosolized vancomycin for treatment of airway colonization by methicillin-resistant *Staphylococcus aureus*. *Pediatr Infect Dis J* 1990;9:220-1.
56. Johnson S, Homann SR, Bettin KM, et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or metronidazole: a randomized, placebo-controlled trial. *Ann Intern Med* 1992;117:297-302.
57. Bastani B, Freer K, Read D, et al. Treatment of gram-positive peritonitis with two intraperitoneal doses of vancomycin in continuous ambulatory peritoneal dialysis patients. *Nephron* 1987;45:283-5.
58. Newman LN, Tessman M, Hanslik T, Schulak J, Mayes J, Friedlander M. A retrospective view of factors that affect catheter healing: four years of experience. *Adv Perit Dial* 1993;9:217-22.
59. Capdevila JA, Segarra A, Planes AM, et al. Successful treatment of haemodialysis catheter-related sepsis without catheter removal. *Nephrol Dial Transplant* 1993;8:231-4.
60. Edell LS, Westby GR, Gould SR. An improved method of vancomycin administration to dialysis patients. *Clin Nephrol* 1988;29:86-7.
61. Interim guidelines for prevention and control of Staphylococcal infection associated with reduced susceptibility to vancomycin. *MMWR Morb Mortal Wkly Rep* 1997;46:626-8, 635.
62. Garner JS, Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol* 1996;17:53-80. [Erratum, *Infect Control Hosp Epidemiol* 1996;17:214.]