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ADVENT OF VANCOMYCIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

From the time of Paul Ehrlich's silver bullet, bacteria have been evolving means of resisting antimicrobial agents and medical scientists have been working to develop ever newer ones. Vancomycin, introduced in 1956, has been the drug of last resort for infections caused by resistant Gram-positive organisms like methicillin-resistant *Staphylococcus aureus* and ampicillin-resistant enterococci. In 1986, however, enterococci resistant to vancomycin were isolated in Europe,[1, 2] and by early 1987, vancomycin-resistant enterococci (VRE) were showing up in U.S. patients.[3]

If there were any good news in this, it would be that the resistance was appearing in enterococci—organisms with limited virulence. But pessimists among us immediately began to fear the worst – i.e., that such resistance might be transferred to a nastier bacterium like *S. aureus*. The publication of an *in vitro* transfer of the vancomycin-resistance gene to *S. aureus* didn't do much to quell our fears.[4] And then the appearance of *S. aureus* with reduced susceptibility to vancomycin in Japan in 1996 and the subsequent appearance of similar strains in the eastern U.S. seemed to portend yet worse things.[5, 6]

As Goethe might have said, "*und jetzt ist die Wurst gekommen*." In the July 5 issue of the MMWR, CDC reported the first case of documented vancomycin-resistant *S. aureus* (VRSA) infection in the world.[7] This issue of the *CD Summary* recaps the case report and discusses prevention and control of VRSA.

CASE REPORT

In June 2002, VRSA was isolated from a catheter exit site in a 40-year-old patient in Michigan with diabetes, peripheral vascular disease and dialysis-dependent chronic renal failure. Since April 2001, the patient had been treated for chronic foot ulcerations with multiple courses of antimicrobial therapy, including vancomycin. In April 2002, the patient underwent amputation of a gangrenous toe and subsequently developed methicillin-resistant *S. aureus* bacteremia that was treated with vancomycin and rifampin. In June 2002, the patient developed a suspected catheter exit-site infection; cultures of the exit site and catheter tip subsequently grew *S. aureus* resistant to oxacillin (minimum inhibitory concentration [MIC] >16 µg/ml) and vancomycin (MIC >128 µg/ml). VRE and *Klebsiella oxytoca* were also isolated from a culture of the ulcer. As of early July, the patient was clinically stable, and the infection was responding to outpatient treatment consisting of aggressive wound care and systemic antimicrobial therapy with trimethoprim/sulfamethoxazole.

The VRSA isolate recovered from the catheter exit site was initially identified at a local hospital laboratory and was confirmed by the Michigan Department of Community Health and CDC.

The National Committee on Clinical Laboratory Standards MIC breakpoints for vancomycin are as follows: susceptible, <4 µg/ml; intermediate, 8-16 µg/ml; and resistant, >32 µg/ml. Using the broth microdilution method, the MIC was >128 µg/ml. The Michigan VRSA isolate, unlike the previous isolates of *S. aureus* with intermediate susceptibility to vancomycin, carried the *vanA* vancomycin resistance gene, and it seems likely that the *S. aureus* acquired this gene from the VRE.

Epidemiologic and laboratory investigations are under way to assess the risk for transmission of VRSA to other patients, health-care workers, family members, and other close contacts. To date, no spread to others has been found.

SO WHAT DO WE DO NOW?

The Michigan case demonstrates that transfer of resistance from the enterococcus to *S. aureus* can, unfortunately, occur spontaneously *in vivo*. Given the current prevalence of both methicillin-resistant *S. aureus* and VRE, it seems likely or even inevitable that such transfer will occur again. We expect, however, to be able to delay the re-emergence and slow the spread of VRSA by lessening the pressure exerted by antibiotics—especially vancomycin—that select for VRE. In 1995, CDC and the Hospital Infection Control Practices Advisory Committee (HICPAC) promulgated recommendations to assist clinicians in their prescribing of vancomycin.[8]

In 1994, the then-Health Division surveyed hospitals in Oregon regarding pharmacy policies to optimize vancomycin use and reviewed all new vancomycin orders for appropriateness during a 3-week period. Only four (6%) of the 66 hospitals in Oregon had pharmacy restrictions on initial vancomycin orders, and 40% of vancomycin orders were judged inappropriate according to CDC-HICPAC guidelines.[9] We repeated the study in 1999, hoping to find an improvement in vancomycin use in the intervening years. Although at least 13 hospitals had adopted vancomycin-use policies, we were disappointed to find that overall inpatient vancomycin use had increased significantly since 1994. The good news was that the vancomycin policies had worked: hospitals with policies restricting vancomycin use to selected indications had substantially lower rates of inappropriate vancomycin use than hospitals without such policies (1.0 orders/1,000 patient-days vs. 1.8; P = 0.01).[10] Hospitals should review their vancomycin use and develop policies targeted to problems identified within each institution. A special boxed edition of situations where vancomycin should and should not be used is shown, *verso*.

WHAT IF?

What will we do if this nightmare bug emerges here? First, we need to detect it. All *Staph* should be tested using a MIC method (broth microdilution, agar dilution or agar-gradient diffusion) using a full 24-hour incubation.[11] If VRSA is detected,[11] the laboratory should immediately notify infection-control personnel, the clinical unit and the attending physician. All strains with a MIC ≥4 µg/ml should be re-tested; if repeat results are consistent, the laboratory should immediately notify the local health department.

Re-test staphylococci from patients who fail to respond to vancomycin therapy, because resistance may have emerged during therapy.

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Infection-control personnel should initiate an epidemiologic and laboratory investigation in collaboration with the local/state health department and CDC.

Medical and nursing staff should isolate the patient in a private room and implement contact precautions (gown, mask, glove and antibacterial soap for handwashing).

Staff should minimize the number of persons with access to colonized/infected patients and dedicate specific health-care workers to provide one-on-one care.

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VANCOMYCIN IS APPROPRIATE FOR...

- Treatment of serious infections caused by β-lactam-resistant Gram-positive microorganisms. (Vancomycin may be less rapidly bactericidal than are β-lactam agents for β-lactam-susceptible staphylococci.)
- Treatment of infections caused by Gram-positive microorganisms in patients who have serious allergies to β-lactam antimicrobials.
- Treatment of antibiotic-associated colitis that 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
- Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices (e.g., cardiac and vascular procedures 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 greater than 6 hours, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses.)

DON'T USE VANCOMYCIN FOR...

- Routine surgical prophylaxis (except patients with a life-threatening allergy to β-lactams).
- Empiric antimicrobial therapy for febrile neutropenic patients, unless evidence indicates that infection is caused by Gram-positives (e.g., an inflamed Hickman catheter exit site) and the prevalence of MRSA in the hospital is substantial.
- Treatment in response to a single blood culture positive for coagulase-negative *Staph*, if other blood cultures taken during the same time frame are negative (i.e., if contamination is suspected). Because contamination of blood cultures with skin flora (e.g., *S. epidermidis*) can result in unnecessary treatment, phlebotomists should be trained to minimize contamination.
- Continued empiric treatment of patients whose cultures are negative for β-lactam-resistant Gram-positive microorganisms.
- Systemic or local (e.g., antibiotic lock) prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.
- Selective decontamination of the gut.
- Eradication of MRSA colonization.
- Primary treatment of antibiotic-associated colitis.
- Routine prophylaxis for very low-birthweight infants (<1,500 g).
- Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis.
- Treatment (for dosing convenience) of infections caused by β-lactam-sensitive Gram-positive microorganisms in patients with renal failure.
- Topical application or irrigation.