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Staphylococcus aureus: The new adventures of a legendary pathogen

■ ABSTRACT

Nosocomial infections with strains of methicillin-resistant *Staphylococcus aureus* (MRSA) began to emerge in the 1960s, are increasing in frequency, and tend to have worse outcomes than infections due to methicillin-susceptible *S aureus*. Community-associated MRSA infections emerged in the 1990s. Community-associated MRSA strains have up to now been epidemiologically and bacteriologically distinct from hospital-associated MRSA strains, but in a new twist, MRSA strains that have so far been only community-associated are invading the hospital. Another worrisome trend is increasing resistance to vancomycin (Vancocin).

■ KEY POINTS

Community-associated MRSA infections tend to affect patients younger than those who traditionally get hospital-associated MRSA infections. Most of these infections are of the skin and soft tissues, but this pathogen can also affect deeper tissues, and bacteremia and necrotizing pneumonia have been reported.

For patients with skin and soft-tissue infections due to MRSA, incision and drainage rather than antibiotic therapy is often the key intervention.

Vancomycin has been our stalwart for treating MRSA infections for more than 40 years, but it is not working as well as it used to, at least in certain situations. Vancomycin should not be used to treat infections due to methicillin-susceptible *S aureus*.

Needed are better understanding of the factors that influence persistent *S aureus* bacteremia, well-controlled, prospective studies, and continued antibiotic development.

STAPHYLOCOCCUS AUREUS is rearing its ugly head in new and interesting ways, both in the hospital and in the community.

Rates of invasive infections with methicillin-resistant *S aureus* (MRSA) have been increasing both in the hospital and in the community, a trend that has attracted considerable interest in the lay media. Curiously, the most common community-associated MRSA strain, which up to now has been distinct from hospital-associated MRSA strains, is invading our hospitals. Alarming, vancomycin (Vancocin), the drug of last resort for MRSA infections for the past 40 years, does not seem to be as effective as it used to be.

This paper summarizes the changing epidemiology of *S aureus*, particularly the emergence of MRSA outside of the hospital; reviews the difficulties associated with *S aureus* bacteremia and its treatment in view of; some changes in vancomycin susceptibility; and appraises the old and new treatment options.

■ MRSA IS ON THE RISE IN THE HOSPITAL

S aureus, a gram-positive, coagulase-positive bacterium, is one of the leading nosocomial bloodstream pathogens, second only to coagulase-negative staphylococci.¹ And the incidence of *S aureus* infections is increasing. MRSA in particular is increasingly causing infections throughout hospitals, including intensive care units. As of 2004, nearly two-thirds of isolates of *S aureus* from intensive care units were MRSA.²

*Dr. Rehm has disclosed that she has served on the speaker's bureaus of Cubist and Wyeth, has served on advisory boards for Cubist and Pfizer, and has received research support from Cubist.

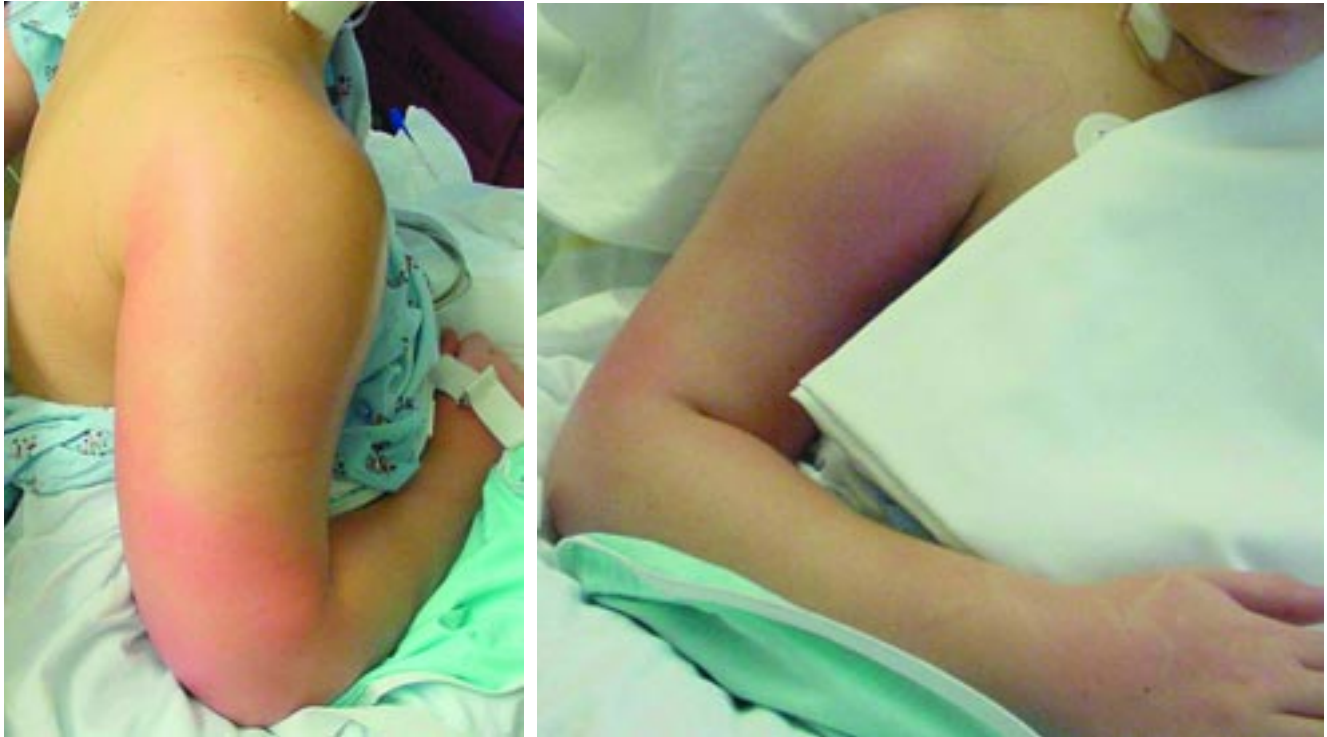


FIGURE 1. Necrotizing fasciitis due to community-associated methicillin-resistant *Staphylococcus aureus*.

When you see a skin or soft tissue infection, think about MRSA

MRSA infections are worse than methicillin-susceptible *S aureus* (MSSA) infections in terms of the rates of death and other undesirable outcomes.³ Several factors may be responsible: MRSA infection may be a marker of severity of illness (sicker patients may be more likely to have MRSA), our treatment for MRSA may not be as effective as it is for MSSA, and the organism may be inherently more virulent.

■ **METHICILLIN RESISTANCE IS ALSO ON THE RISE IN THE COMMUNITY**

Community-associated MRSA began emerging clinically about 10 years ago. It was first described in a cohort of children with necrotizing pneumonia in Minnesota, but soon other populations at risk began to emerge, such as residents of correctional facilities, men who had sex with men, competitive athletes (eg, fencers, wrestlers, and football players), and Alaskan natives and other native populations. A common factor in all these groups was close proximity of the members to each other. Later, it began to spread beyond these tradi-

tional risk groups into the community at large.

Community-associated MRSA strains have a characteristic pattern of antimicrobial susceptibility (see below). In the laboratory, they grow somewhat faster than health-care-associated MRSA strains, but not as fast as MSSA. They have a strong association with skin and soft-tissue infections: when you see a skin or soft-tissue infection, be it in an outpatient or an inpatient, think about MRSA. Their virulence varies, but rapid onset and progression of illness are quite common. Their most common strain in the United States at present is USA 300.

**Case 1:
A young woman with necrotizing fasciitis**

A 21-year-old college student presented to our service in May 2004 with high fever and severe arm pain, which had been worsening for several days. She had been previously healthy, had not had any contact with the health care system, and had not received any antibiotics.

Her arm was red and extremely painful (FIGURE 1). Pain out of proportion to findings is

a cardinal sign of necrotizing fasciitis, and this is indeed what she had.

Her blood cultures were positive for MRSA, as were cultures of the deep tissue of the deltoid muscle and fascia when she underwent emergency surgical debridement. The infection required several additional surgical debridements and removal of one head of her deltoid muscle, but she was fortunate: in the past, some patients with this problem might have undergone radical amputation of the arm or even more extensive surgery. This patient continued to have positive blood cultures 4 days postoperatively, but she ultimately recovered, completing 28 days of daptomycin (Cubicin) therapy at a dose of 6 mg/kg every 24 hours. The last 10 days of daptomycin therapy were given at home via a percutaneous intravenous central catheter.

Comment. The epidemiology of MRSA infections is changing. More patients who have no traditional risk factors, specifically health care contact, are getting MRSA infections. A recent report from the US Centers for Disease Control and Prevention (CDC) indicates that the proportion of patients with invasive disease due to MRSA has doubled since 2001-2002.⁴ Part of the reason undoubtedly is that MRSA, particularly community-associated MRSA, often carries specific virulence factors that make it more invasive. The CDC estimated that in 2005 there were nearly 100,000 cases of invasive MRSA infection in the United States, and nearly a fifth of these infections resulted in death.

Resistance and virulence factors in community-associated MRSA

Most community-associated MRSA strains carry a mobile genetic element called type IV SCCmec (staphylococcal chromosomal cassette mec) that enhances its antimicrobial resistance. This genetic component was probably borrowed from coagulase-negative staphylococci, in which it is quite common but does not cause as much of a problem. It is now present in a wide range of *S aureus* strains. Most of the *S aureus* strains that carry type IV SCCmec are MRSA, but a few MSSA strains do carry it as well.

The potent toxin Pantone-Valentine leukocidin is an extracellular product that is

detected in fewer than 5% of hospital strains but is more common in community-associated strains. It kills leukocytes by forming pores in the cell membrane and causing skin necrosis in cutaneous infections. It is associated with skin abscesses and rapidly progressive necrotizing pneumonia in MSSA or MRSA.

Epidemiologic differences between community- and health-care-associated MRSA

Patients with community-associated MRSA infections tend to be younger than those who traditionally get health-care-associated MRSA infections: in a study from Naimi et al in 2003, the mean ages were 23 vs 68 years.⁵ A greater proportion of patients with community-associated MRSA strains are nonwhite.^{4,5}

Most community-associated MRSA infections are of the skin and soft tissue (75% in the series from Naimi et al⁵), but this pathogen causes other infections as well. Bacteremia of unknown origin has been seen, as has necrotizing pneumonia. Most of the skin and soft-tissue infections are relatively superficial, such as folliculitis or furunculosis, but deeper tissue infections such as necrotizing fasciitis and pyomyositis have also been seen.⁶

The incidence of community-associated MRSA infections varies greatly by geographic region.⁷ The northeastern United States has so far been relatively spared, but in Atlanta, Houston, and Los Angeles up to 80% of cases of characteristic skin or soft-tissue infections seen in emergency or outpatient departments are due to community-associated MRSA. Physicians at the Texas Children's Hospital in Houston assume that all skin or soft-tissue infections are due to community-associated MRSA unless proven otherwise.⁸

Differences in antibiotic susceptibility

Community-associated MRSA is more susceptible to various antibiotics than health-care-associated MRSA,⁵ but not by much. Strains are usually susceptible to vancomycin, tetracyclines, trimethoprim-sulfamethoxazole (Bactrim, Septra), and rifampin (Rifadin). Unlike hospital strains, a fair number of community-acquired strains are susceptible to clindamycin (Cleocin) in the laboratory, but with a caveat: some of these clindamycin-susceptible strains actually may harbor the tools

Any patient who has a skin or soft-tissue infection with a collection of pus needs incision and drainage

for inducible resistance. In fact, they can become resistant to clindamycin even without being exposed to it.

The laboratory test for inducible clindamycin resistance is called the D test. After coating an agar plate with *S aureus*, the technician places erythromycin and clindamycin disks. If the erythromycin induces clindamycin resistance, the plate is clear of growth around the clindamycin disk except for the portion nearest the erythromycin disk, leaving a characteristic D-shaped area of lucency.

Risk factors for MRSA

Moran et al⁷ analyzed the risk factors for community-associated MRSA in patients with skin or soft-tissue infections seen in the emergency department. The infection was more likely to be due to community-associated MRSA if the patient was black, had used any antibiotic in the past month, had a history of MRSA infection, or had close contact with a person with a similar infection. Many patients interpreted the infections as spider bites because the lesions tended to have a dark center surrounded by a tender area. These infections were not associated with underlying illness. In some cases, community-associated MRSA skin infections have been associated with tattooing and even manicuring.

However, it is very difficult to distinguish between community-associated MRSA and MSSA skin and soft-tissue infections on the basis of clinical and epidemiologic characteristics. Miller et al⁹ studied a large group of patients in Los Angeles who were hospitalized with community-associated skin and soft-tissue *S aureus* infections. All the patients were followed up for 30 days after hospital discharge. Regardless of whether they had MRSA or MSSA, they had similar outcomes. Close contacts of the patients also tended to develop infection.

A key point from this and many other studies: patients were more likely to remain infected if they did not undergo incision and drainage. This key intervention is indicated for any patient who has a skin and soft-tissue infection with an undrained focus of infection.

COMMUNITY-ASSOCIATED MRSA IS INVADING THE HOSPITAL

In a new development, community-associated MRSA strains are now appearing in the hospital. This is not only because patients are bacteremic when they come in: patients in the hospital are getting nosocomial infections due to community-associated MRSA strains.

Seybold et al¹⁰ analyzed 116 cases of MRSA bloodstream infections in Atlanta, GA. In 9 (8%) of the cases the patient had not had any contact with the health care system within the past year, and these cases were classified as truly community-associated. Of the remaining 107 cases, 49 (42%) were nosocomial, and the USA 300 strain—the predominant community-associated MRSA strain—accounted for 10 (20%) of the nosocomial cases.

In the recent CDC study of invasive MRSA infections, Klevens et al⁴ reported that nearly a third of cases of bacteremia were due to community-associated MRSA, and these strains accounted for a greater proportion of cases of cellulitis and endocarditis than did health-care-associated strains.

In a study of hospital-associated MRSA, Maree et al¹¹ found that the percentage of cases in which the bacteria carried the SCCmec type IV marker had increased from less than 20% in 1999 to more than 50% in 2004.

Comment. Suffice it to say that we are surrounded by MRSA. Community-associated MRSA is here to stay. It is even invading our hospitals, and we need to consider this very carefully when choosing antimicrobial therapy.

NAGGING QUESTIONS ABOUT VANCOMYCIN

Case 2: Vancomycin-intermediate *S aureus* (VISA) bacteremia and endocarditis

In December 2006 we saw a very ill 60-year-old woman who was hospitalized with MRSA bacteremia, pacemaker endocarditis, and superior vena cava thrombosis. Although she was treated with vancomycin and rifampin, her condition worsened, she had a stroke, and she developed renal failure. In a difficult operation, the pacemaker was removed, but the

We are surrounded by MRSA, both inside and outside the hospital

bacteremia persisted. In early February 2007 she underwent another difficult operation in which the superior vena cava clot was debrided, a right atrial clot was removed, and her mitral valve was replaced. Less than 2 weeks later, and despite ongoing vancomycin and rifampin therapy, the MRSA bacteremia recurred.

During the approximately 6 weeks that the patient had been receiving these antibiotics, the minimal inhibitory concentration (MIC) of rifampin against the *S aureus* isolate increased from less than 1 µg/mL (susceptible) to 2 µg/mL (resistant). The MIC of vancomycin went from 2 µg/mL (susceptible) to 4 µg/mL (intermediately susceptible). Vancomycin and rifampin were discontinued, and daptomycin and gentamicin (Garamycin) therapy were started. (Her daptomycin MIC was 0.5 µg/mL). The patient's condition stabilized, and she was discharged to a long-term nursing facility. She had no relapse of MRSA bacteremia, but she died in early April of that year.

Is vancomycin becoming less effective?

Degrees of vancomycin resistance

Vancomycin has been our stalwart for treating MRSA infections for more than 40 years but it is not working as well as it used to, at least in certain situations.

Various terms describe the degrees of susceptibility or resistance to vancomycin (FIGURE 2).¹²

VRSA (vancomycin-resistant *S aureus*) is rare. These fully resistant strains probably acquired a resistance mechanism (the *vanA* operon) from vancomycin-resistant enterococci. Infections tend to occur in patients simultaneously infected with both *S aureus* and vancomycin-resistant enterococci, giving the bacteria an opportunity to exchange genetic material.

VISA (vancomycin-intermediate *S aureus*) infections tend to occur in patients like the one described above who have had long-term vancomycin therapy. VISA strains appear to overproduce a matrix that captures vancomycin and keeps it from entering the cell. On electron microscopy, these bacteria have a very thick cell wall.¹³

Vancomycin tolerance is a state in which the bacteria are “stunned” or kept in check

Degrees of vancomycin resistance in *Staphylococcus aureus*

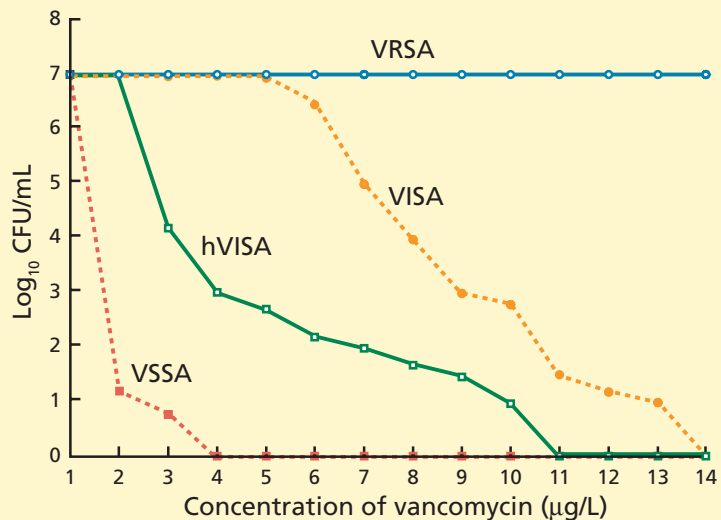


FIGURE 2. Population analysis of vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-intermediate *S aureus* (VISA), heteroresistant VISA (hVISA), and vancomycin-susceptible *S aureus* (VSSA). The population analysis shows how many cells in a fixed number of cells (usually about 10⁷ colony-forming units [CFU]) of each strain are resistant to various concentrations of vancomycin. VRSA is a highly resistant and homogeneously resistant strain, with 100% of the population growing at each of the vancomycin concentrations tested. VISA is intermediately resistant, with 100% of the population growing at 4 µg of vancomycin per mL and also with significant subpopulations growing at 8 µg/mL. hVISA demonstrates heterogeneous resistance, having subpopulations of cells with various levels of resistance to vancomycin and including small populations of vancomycin-intermediate resistant cells with growth at 8 µg of vancomycin per mL.

LIU C, CHAMBERS HF. STAPHYLOCOCCUS AUREUS WITH HETEROGENEOUS RESISTANCE TO VANCOMYCIN: EPIDEMIOLOGY, CLINICAL SIGNIFICANCE, AND CRITICAL ASSESSMENT OF DIAGNOSTIC METHODS. ANTIMICROB AGENTS CHEMOTHER 2003; 47:3040–3045

but not killed by vancomycin. That is manifested in the laboratory by a ratio of minimum bactericidal concentration to MIC greater than 32.

hVISA (heteroresistant VISA) is new and worrisome. These organisms have an overall MIC in the susceptible range, but within that population are individual isolates with an MIC that is much higher—in the intermediate or perhaps even in the resistant range.¹⁴

Reported rates of hVISA vary from less than 2% to as high as 76%, because the methods for detecting it are still very poorly standardized. The usual automated laboratory tests do not detect hVISA.

hVISA is probably clinically relevant, as evidence is emerging both *in vitro* and *in vivo* that the higher the MIC for vancomycin, the worse the clinical outcome.¹⁵ hVISA has been associated with failures of therapy in several situations, usually in cases of severe invasive or deep infection, endocarditis, and bacteremia with vertebral osteomyelitis where vancomycin concentrations at the site of infection may be suboptimal.^{16–19} While most hVISA strains that have been described were resistant to methicillin, some were susceptible.

The E test is emerging as the standard test for hVISA. This test uses a plastic strip that contains gradually increasing concentrations of vancomycin along its length. Placed in the culture dish, the strip inhibits growth of the organism at its high-concentration end but not at its low-concentration end. If the sample contains hVISA, the cutoff is not well defined, with a few colonies growing at higher concentrations.

New definition of vancomycin susceptibility

Recognizing that the MICs for vancomycin have been rising in the last few years, the Clinical and Laboratory Standards Institute last year changed the break points between susceptibility and resistance. The new definitions are:

- **Susceptible**—an MIC of 2.0 µg/mL or less (formerly 4.0 µg/mL or less)
- **Intermediate**—4.0 to 8.0 µg/mL (formerly 8.0 to 16 µg/mL)
- **Resistant**—16 µg/mL or greater (formerly 32 µg/mL or greater).

One should pay attention to the MIC numbers on the laboratory reports, not just to the words “susceptible” or “not susceptible.” If the number is, say, 0.5 µg/mL or less, the organism should really be susceptible. If the number is 1 or 2, it is still in the susceptible range, but those are the organisms that may cause problems later on.

Further, even if the vancomycin MIC is in the susceptible range, higher MICs may affect outcomes. The average duration of MRSA

bacteremia on therapy is 8 to 9 days, vs 3 to 4 days with MSSA bacteremia.^{20,21} But Sakoulas et al¹⁵ found that, in MRSA bacteremia, the success rate with vancomycin therapy was 56% if the MIC was 0.5 or lower, compared with 10% if the MIC was 1.0 to 2.0 µg/mL. Examined in another way, the success rate was 50% if the logarithm of killing was 6.27 colony-forming units per mL or greater, 23% if 4.71 to 6.26, and zero if less than 4.71.

Case 3: Prolonged MRSA bacteremia

In the summer of 2006, a 66-year-old woman with a history of gastric bypass and cirrhosis underwent a long stay in the surgical intensive care unit because of a recurrent enterocutaneous fistula and chronic renal insufficiency. On November 5th, she had a positive blood culture for MRSA, which was treated appropriately with vancomycin for 4 weeks. She was discharged to subacute care but came back 2 days later, again with MRSA bacteremia. At that time her Hickman catheter, which had been inserted for total parenteral nutrition because of the enterocutaneous fistula, was removed.

Transthoracic echocardiography revealed no vegetations, but her bacteremia persisted. Her mental status was poor this entire time: she was mute and could barely be awakened. We looked for clots and infected clots; duplex ultrasonographic examinations of all four extremities were negative. Finally, magnetic resonance imaging of her back—performed empirically because of the persistent bacteremia—revealed vertebral osteomyelitis at level T12-L1. We also noticed on serial evaluations that the vancomycin MIC for her organism increased from 0.5 to 2.0 µg/mL, so therapy was changed from vancomycin to daptomycin.

Her bacteremia cleared. Follow-up echocardiography was negative, but she had two subsequent relapses of MRSA bacteremia, one in April 2007 and one before she died in the summer of 2007.

Prolonged bacteremia: Is it vancomycin resistance, or something else?

The MRSA isolates that cause prolonged bacteremia seem to have certain characteristics.²² Higher MICs are probably associated with

Pay attention to the MIC numbers on the lab report, not just the words ‘susceptible’ or ‘not susceptible’

longer periods of bacteremia. But some genetic components within some strains of *S aureus* give them a survival advantage. They have less susceptibility to the body's thrombin-induced platelet microbicidal protein. These isolates are not only associated with prolonged bacteremia: they are also associated with osteomyelitis, deep abscesses, endocarditis, recurrent infection, and increased death rate.²² Clinical laboratories do not test for these genetic components. One wonders whether our patient may have had an isolate with these mutations that gave it a survival advantage.

Do not use vancomycin for MSSA

Avoid using vancomycin for MSSA infections. It has been shown time and time again that MSSA infections do not respond as well to vancomycin as they do to beta-lactam antibiotics, specifically to the semisynthetic penicillins such as oxacillin and nafcillin, and even some of the first-generation cephalosporins. Chang et al²³ found that patients with MSSA bacteremia had higher rates of persistent infections, relapse, and bacteriologic failure if they received vancomycin than if they received nafcillin.

Do vancomycin trough levels affect toxicity?

The vancomycin trough levels that we aimed for in the past (5 to 10 µg/mL) were probably too low. Today, we aim for trough levels of 15 to 20 µg/mL, and many physicians are aiming for 20 to 25 µg/mL. Part of the reason is that vancomycin MICs are higher than they used to be: in order to keep the vancomycin level above the MIC for a longer period of time, the vancomycin trough level needs to be higher. In theory, keeping the vancomycin levels above the MIC for longer periods should improve outcomes. Yet Fowler et al²² found that vancomycin trough levels among patients who had persistent MRSA bacteremia were actually higher than trough levels among those in whom the bacteremia resolved, although the difference was not statistically significant.

We measure the vancomycin trough level to make sure it is high enough (and give larger doses if it is not); among adults, peak levels

need not be monitored on a routine basis because of the predictable pharmacokinetics of vancomycin.

Vancomycin toxicity can be either idiosyncratic or synergistic. Idiosyncratic toxicity occurs when a patient who has been on vancomycin for a long time develops a fixed rash, not associated with infusion. This is an immunologic phenomenon. It is a rare and very serious situation and may require steroid therapy.

Synergistic toxicity occurs when vancomycin is given with other nephrotoxic agents, notably gentamicin. Vancomycin plus gentamicin equals nephrotoxicity. Vancomycin alone is usually not nephrotoxic, but close monitoring of renal function parameters is warranted with the use of higher doses.²⁴

■ IN UNEXPLAINED BACTEREMIA, LOOK FOR ENDOCARDITIS

In blood cultures from patients with bacteremia, *S aureus* is never a contaminant. Even if just one blood culture is positive for *S aureus*, believe that *S aureus* is the culprit.

Reports in the 1950s suggested that at least half of patients who had *S aureus* bacteremia had endocarditis,²⁵ leading to recommendations that all patients with *S aureus* bacteremia without an obvious primary source of infection should be evaluated for endocarditis. Subsequent estimates were lower, in the range of 15% to 25%.^{26,27} However, throughout the world *S aureus* endocarditis continues to have a very high mortality rate: at least a third of patients die.²⁸

Clinical criteria (community acquisition, no primary focus, and metastatic sequelae) were developed to try to predict the risk of endocarditis in bacteremic patients.²⁶ However, these criteria did not work very well. The clinical definition of endocarditis has evolved. The criteria of von Reyn et al²⁹ from 1981 did not use echocardiography as part of the definition, but the 1994 Duke criteria,³⁰ which were refined³¹ in 2000, use both clinical and echocardiographic parameters.

Stratton et al³² performed transthoracic echocardiography in 14 patients with bacteremia and found 1 patient with cryptic tricuspid infective endocarditis. Bayer et al³³

MSSA infections do not respond as well to vancomycin as they do to oxacillin and nafcillin

subsequently reported that of 72 patients with bacteremia, 6 (18%) of those who had no clinical findings suggestive of infectious endocarditis had findings on echocardiography that led to changes in their regimen. Adding echocardiography to three clinical risk factors increased the sensitivity of diagnosing endocarditis from 70% to 85% with a specificity of 100% and predictive value of 96%.

The Duke criteria call for transesophageal echocardiography, which is not feasible in some patients, eg, those with cirrhosis and esophageal varices.

S aureus endocarditis has changed over the years as our patient population has changed, and MRSA endocarditis tends to hit some of our most vulnerable patients. In a study by Miro et al³⁴ in 2005, MRSA was the leading pathogen in patients who were diagnosed with *S aureus* endocarditis in 1990 or later. We will only see these numbers go up. Patients with diabetes tend to have more MRSA, and of diabetic patients with MRSA endocarditis, 30% to 40% die in the hospital.

Indications for surgery

Certain conditions are indications for surgery among patients with endocarditis, and no antibiotic will cure the endocarditis if the patient has one of these conditions, eg:

- Persistent bacteremia during antibiotic therapy
- Recurrent emboli
- Heart failure that cannot be controlled
- Perivalvular or myocardial abscesses
- Large vegetations
- Early prosthetic valve infection
- Certain arrhythmias.

How long should *S aureus* bacteremia be treated?

In cases of bacteremia in which endocarditis has been ruled out and removable foci of infection (eg, intravascular catheters) have been removed, some evidence indicates that treatment for 2 weeks would be as effective as the 4 to 6 weeks that we would use for endocarditis or other severe or invasive infections.³⁵ The issue is controversial. If the patient has had frequent hospitalizations or a chronic medical condition I would hesitate to treat for less than 4 weeks, even if the infec-

tion appears to be associated with a removable focus.

Treatment of endocarditis

In the guidelines for treatment of endocarditis from the American Heart Association and Infectious Diseases Society of America,³⁶ all the recommendations are relatively old and many of them are somewhat empiric—they are not based on evidence from randomized clinical trials. Rather, they are best opinions based on clinical experience and some observational studies over the years.

For MSSA. In cases of native-valve endocarditis, oxacillin (Bactocill), nafcillin (Unipen), or another semisynthetic beta-lactam antibiotic is recommended. For penicillin-allergic patients, we have other options, such as cefazolin (Ancef, Kefzol).

Combination therapy is frequently recommended for native valve endocarditis as well as for prosthetic valve endocarditis, with either rifampin or gentamicin along with a primary agent. There is some evidence that one can clear staphylococcal bacteremia a day or two more quickly by use of combination therapy with nafcillin plus an aminoglycoside than with nafcillin alone.^{37,38} For MSSA-associated endocarditis, vancomycin does not work as well as beta-lactam antibiotics.^{39,40}

Korzeniowski and Sande³⁷ and Chambers et al³⁸ reported that the mean duration of bacteremia was 3.4 days for patients treated with nafcillin alone and 2.9 days for those treated with nafcillin plus an aminoglycoside. These studies led to consideration of a short course of gentamicin to clear the bacteremia quickly.

With MRSA, bacteremia often requires a week or more to clear. Levine et al²¹ reported a study in 42 patients, mostly injection-drug users, with right-sided native-valve endocarditis. The median duration of bacteremia was 7 days in patients who received vancomycin alone vs 9 days in those who received vancomycin plus rifampin; however, some patients were bacteremic for up to 27 days. Fever persisted for a median of 7 days, probably partly due to septic pulmonary emboli. Three patients died, and three required valve replacement.

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Even if just one blood culture is positive for *S aureus*, believe it

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■ NEW ANTIBIOTICS

Several new antibiotics are active against gram-positive cocci.^{41–44} However, the majority of them have not been prospectively studied for treating bacteremia or endocarditis.

Quinupristin/dalfopristin (Synercid) has not been formally studied for treatment of MRSA bacteremia or endocarditis. There are a few case reports of its use in these conditions.⁴⁵ Quinupristin/dalfopristin is bacteriostatic, and its use may be associated with phlebitis, myalgias, and arthralgias.⁴⁶

Linezolid (Zyvox) is approved for treatment of complicated skin and soft-tissue infections and for hospital-acquired pneumonia. There have been no specific studies of linezolid in the treatment of *S aureus* bacteremia or endocarditis. However, Shorr et al⁴⁷ retrospectively looked at the bacteremic patients in five previous studies of linezolid vs vancomycin and found 144 cases of *S aureus* bacteremia, half of which were due to MRSA. Of 53 assessable patients with MRSA bacteremia, the primary infection was cured in 14 (56%) of the linezolid patients and 13 (46%) of the vancomycin patients.

The oral form is 100% bioavailable. One should avoid concomitant use of serotonin-reuptake inhibitors because of the risk of serotonin syndrome. Adverse effects include altered taste sensation and peripheral neuropathy. There are other potential toxicities, including hematologic changes (thrombocytopenia, leukopenia) and metabolic effects (lactic acidosis), so clinical and laboratory monitoring is important.⁴⁸ The role of linezolid in the treatment of patients with *S aureus* bacteremia or endocarditis remains to be defined.

Daptomycin is indicated for complicated skin and soft-tissue infections, bacteremia, and right-sided endocarditis due to *S aureus*. Fowler et al²⁰ found that daptomycin was not inferior to beta-lactam antibiotics for treatment of MSSA bacteremia and right-sided endocarditis, and for MRSA infections it outperformed vancomycin, but the difference was not statistically significant.

The dosing interval should be increased from once every 24 hours to every 48 hours if

the creatinine clearance is 30 mL/minute or less. Adverse effects include myalgia, rhabdomyolysis (rare), and elevations in creatine phosphokinase. Reports of rising MICs during daptomycin therapy, in some cases associated with persistent infection,⁴⁹ suggest that careful attention be paid to dosing and clinical monitoring.

Tigecycline (Tygacil) is indicated for complicated skin and soft-tissue infections and complicated intra-abdominal infections due to susceptible organisms. It is active against both MSSA and MRSA, but clinical experience with its use in invasive infections is somewhat limited.⁵⁰ The dose of tigecycline should be reduced in advanced cirrhosis. Adverse effects include nausea and vomiting.

Telavancin, dalbavancin, and oritavancin, investigational parenteral antibiotics that are derivatives of vancomycin, are in clinical trials. The pharmacokinetic activity of these agents is of interest: telavancin is being studied with a once-daily dosing interval and

dalbavancin's half-life allows once-weekly dosing. In a limited trial, dalbavancin was found to be safe and effective in the treatment of catheter-related bloodstream infections.⁵¹ None of the antibiotics in this group has been studied for treatment of *S aureus* endocarditis. Telavancin therapy has been associated with rash, hypokalemia, QT prolongation, and creatinine elevations. Gastrointestinal symptoms have been reported with the use of dalbavancin.

Ceftobiprole, another investigational agent, is the only cephalosporin antibiotic that is active against MRSA. It is given every 12 hours. Adverse effects include nausea and taste disturbance.

Iclaprim is a novel diaminopyrimidine and a dihydrofolate reductase inhibitor. In vitro, it is active against gram-positive bacteria, including MRSA, VISA, and VRSA; clinical investigations at this point are limited to the treatment of skin and soft-tissue infections. ■

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