

National
Foundation for
Infectious
Diseases

CLINICAL UPDATES IN

Infectious Diseases

Supported by an unrestricted educational grant from Cubist Pharmaceuticals

Volume XI Issue 2 July 2008

Therapy for Community-Associated MRSA Infections: Antibiotics and More

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Introduction

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) outbreaks have become a worldwide problem. Patients originally reported what appeared to be spider bites, even in locales without biting spiders. Soon it was recognized that infection was frequently spread by close contact in various settings, including among participants in various contact sports, such as football and wrestling, within correctional facilities with crowded conditions, among military recruits, in day care and other institutional settings, and among men who have sex with men.^{1,2}

Most CA-MRSA infections involve the skin and soft tissues. Deep-seated infection, although much less common, can be extremely serious. Rapidly fatal bacteremia and necrotizing pneumonia are examples.³ The organisms causing these infections are differentiated from other MRSA by several features, including a unique resistance gene, the *meclV* gene, carried on a small cassette known as the staphylococcal chromosomal cassette (SCC) IV. Additional characteristics of these strains are the Panton-Valentine leukocidin (PVL), which may be a marker for resistance, and, from a clinical and treatment standpoint of greater importance, a resistance profile considerably different from the usual hospital-associated MRSA.^{4,5} Unlike their hospital-associated counterparts, CA-MRSA tends to remain susceptible to a wide range of antibiotics, thus making a variety of options available to the treating clinician.

Management of Skin/Soft Tissue Infections

In view of the favorable antibiogram associated with CA-MRSA and the relatively mild nature of the superficial infections most often seen, the clinician can choose from several different classes of antibiotics. **Table 1.** As with other MRSA, all but a very few isolates remain susceptible to vancomycin, which remains the "gold standard" for treatment of MRSA. However, recent studies verify that approximately half of the patients treated with antibiotics for superficial skin/soft tissue infections have responded well despite being treated with

Table 1. Antibiotics with Activity Against CA-MRSA
PO=Oral, IV=Intravenous

Antibiotic	Usual Route of Administration	Comment
Clindamycin	PO, IV	Inducible resistance; D-test recommended
Daptomycin	IV	Cannot be used for pneumonia due to inactivation by surfactant
Erythromycin	PO, IV	Intravenous toxic to veins
Gentamicin	IV, IM	May provide synergy, not used as monotherapy
Linezolid	PO, IV	Bacterostatic
Quinupristin-dalfoprisin	IV	Must be administered via central vein
Rifampin	PO, IV	Resistance rapidly develops if used as monotherapy
Tetracyclines (doxycycline, minocycline)	PO, IV	Sparse data in MRSA infection; resistance may be present at baseline or develop during therapy
Tigecycline	IV	Especially useful in mixed infection
Trimethoprim/sulfamethoxazole	PO, IV	Sparse data in MRSA infection
Vancomycin	IV	Heteroresistance may limit activity

antibiotics to which the isolate was resistant. This emphasizes the importance of drainage and, indeed, most such patients have responded to incision and drainage of their skin lesions regardless of the antibiotic they received for therapy.⁶ For clinicians wishing to use an oral agent in addition to any drainage procedure or for cases not amenable to drainage, a number of antibiotics are available. Fridkin *et al* studied isolates from Atlanta, Baltimore and Minnesota and verified that most isolates are susceptible *in vitro* to clindamycin (85-88%), rifampin (67-98%), tetracycline (61-91%), linezolid (92-100%), trimethoprim-sulfamethoxazole (TMP/SMX) (83-97%), as well as vancomycin. Erythromycin and clindamycin present a special problem. Some MRSA that appear to be susceptible to clindamycin have inducible resistance that is not detected by routine automated laboratory techniques. Comparing the susceptibility to erythromycin may identify such isolates. If the organism is susceptible to both erythromycin and clindamycin, either antibiotic may be used. However, if susceptible to clindamycin but resistant to erythromycin, monotherapy with clindamycin should not be prescribed unless a disk diffusion test (D-test) evaluating for the presence of inducible macrolide-lincosamide-streptogramin B (iMLS_B) resistance.^{7,8} This test is performed on agar and involves placing disks impregnated with both antibiotics on a lawn of the *S. aureus* in question. If there is inducible clindamycin resistance, a flattened zone of inhibition appears at the diffusion interface of the two antibiotics and neither drug should be used for treatment. Selecting the best antibiotic in these cases depends more on the clinician's preference than any published data. Aside from a single published study indicating linezolid was superior to vancomycin, few data exist to inform the choice.⁹ The combination TMP/SMX was studied in patients with *S. aureus* bacteremia, though not those with CA-MRSA strains.¹⁰ Nevertheless, based on these earlier results and recent susceptibility data showing the antibiotic remains active against current MRSA isolates, TMP/SMX is widely used to treat patients with CA-MRSA infections.¹¹⁻¹³ Minocycline is another oral antibiotic that has useful activity against MRSA. There are no controlled studies demonstrating its utility; however, it does gain access to a variety of tissue compartments and has been used successfully to treat superficial staphylococcal infection.¹²⁻¹⁵


Unlike patients with superficial infection, those with deep-seated infection present a more difficult challenge. Among these more serious problems, necrotizing fasciitis carries a unique concern because it appears to present differently from the usual

clinical pattern. A recent report demonstrated that patients with necrotizing fasciitis due to CA-MRSA often present with subtle disease, masking the serious nature of the infection.³ Frequently *S. aureus* is the only pathogen involved, unlike many other cases in which multiple pathogens play a role. There are no published studies specifically addressing which antibiotic is preferred in this setting; however, routine practice dictates that a parenteral antibiotic should be used in order to guarantee that a sufficient concentration of drug is delivered to the site of infection. Fortunately, several antibiotics that have activity against MRSA have been recently approved, giving the clinician options other than vancomycin. The need for additional options has been emphasized by a number of studies verifying what has long been suspected; that vancomycin, for decades the drug of choice for MRSA infection, is actually a relatively ineffective antibiotic.

Antibiotic Options

The effectiveness of vancomycin was called into question in a study performed in patients with MRSA endocarditis in which the median duration of bacteremia was seven days, nearly twice as long as occurred in a previous study of β -lactam treatment of methicillin-sensitive *S. aureus* (MSSA) endocarditis.¹⁶ More recently, two meta-analyses showed a significantly higher mortality rate in patients with MRSA bacteremia compared to those with MSSA bacteremia.^{17,18} Several hypotheses may explain this difference. First, therapy may be delayed in patients with MRSA infection because physicians do not expect MRSA to be involved. Hence, they begin an empiric regimen that does not provide coverage for resistant strains. Lodise *et al* showed that the mortality rate is significantly higher when appropriate therapy is delayed for patients with MRSA infection.¹⁹ Such a delay may be due to the time it takes for the microbiology laboratory to identify and verify the susceptibility profile of the organism isolated. Another potential reason that worse outcomes are associated with MRSA infection is that the organism itself is more virulent than methicillin-sensitive isolates. Although there is a suspicion that some isolates of MRSA are more virulent than MSSA, perhaps due to toxins such as PVL, the same toxins have been identified in sensitive strains and thus far there are no convincing data to support the notion that MRSA are more virulent than MSSA. The third hypothesis, and most likely the most important reason for the differences in outcome between patients with MSSA and MRSA, is that the drug used most often to treat MRSA, vancomycin, is inferior to other antibiotics.

Vancomycin has long been known to eradicate bacteria at a much slower rate than β -lactam antibiotics. Numerous reasons may explain the failure of vancomycin to rapidly eradicate infection due to MRSA. One growing concern is the discovery that among staphylococcal isolates there may be clones with heterogeneous resistance to vancomycin.²⁰⁻²⁴ Routine laboratory testing does not identify this resistance, but a number of studies document that these strains, known as heteroresistant vancomycin intermediate *Staphylococcus aureus* (hVISA), are responsible for an increased failure rate among patients treated with vancomycin.^{23,25,26} Even among sensitive strains, there is accumulating evidence that a favorable outcome is not assured by vancomycin

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Published by the National Foundation
for Infectious Diseases
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301-656-0003 • www.nfid.org
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treatment. Sakoulas *et al* studied patients treated with vancomycin and found a failure rate of 90% if the MIC of the organism was 1.0-2.0 µg/mL, compared to a success rate of 56% if the MIC was ≤ 0.5 µg/mL.²⁷ In a similar recent study, Moise-Broder *et al* reported a failure rate among patients treated with vancomycin for *S. aureus* infection to be approximately 50% among patients whose organism had a MIC of 0.5µg/mL. When the isolate had an MIC of 1.0 µg/mL or 2.0 µg/mL, the failure rates were approximately 70% and 90%, respectively.²⁸ It is noteworthy that this study was conducted among patients with MSSA infection, suggesting that vancomycin is substantially inferior to β-lactams, the typical therapeutic choice for sensitive staphylococci, and further contributing to the notion that it is vancomycin, rather than the MRSA itself, that is responsible for the poor outcomes in these patients. In an effort to achieve better results when using vancomycin, perhaps in the hope of providing a synergistic combination, many clinicians add rifampin to vancomycin. Although the practice is widespread and is supported by *in-vitro* data, in the trial of patients with endocarditis who received either vancomycin alone or vancomycin plus rifampin mentioned above, the median duration of bacteremia was 7.0 days for the vancomycin regimen and 9.0 days for those receiving the combination.¹⁶ These data raise a concern about the utility of adding rifampin to a vancomycin regimen. Such experiences have stimulated a search for alternatives to vancomycin, several of which have become recently available.

The combination antibiotic, TMP/SMX has the advantage of availability in both oral and parenteral forms. In the study by Fridkin *et al* assessing the susceptibility in three US cities of CA-MRSA to various antibiotics, the range of susceptibility for TMP/SMX was 83-99%.⁶ However, although as noted above that many clinicians use TMP/SMX for patients with MRSA infection, a substantial body of data supporting its use is lacking. Markowitz *et al* compared TMP/SMX to vancomycin in patients with MSSA and MRSA bacteremia.¹⁰ In the MRSA group, 26 of 26 patients responded to vancomycin, as did all 21 patients treated with TMP/SMX. It is interesting to note that among patients with MSSA bacteremia, only 16 of 22 patients treated with TMP/SMX had a successful outcome compared to 31 of 32 who received vancomycin. Since that study, there have been no published comparative data to guide the practitioner in the use of TMP/SMX for patients with CA-MRSA infection, in particular for patients with other deep-seated infections such as osteomyelitis, pneumonia or meningitis. Nevertheless, in the absence of data to the contrary, this combination appears to be a viable option for clinicians searching for an alternative to vancomycin.


The combination of quipristin-dalfopristin, two streptogramin antibiotics, is active against resistant staphylococci (including vancomycin-resistant isolates) and is available for parenteral use. The drug has been studied in a variety of infections, although few data are published regarding its use in patients with bacteremia.²⁹ In one study of patients with endocarditis, therapy was considered successful in six of eleven patients in the intent to treat analysis. However, none in the final population achieved clinical or bacteriologic cure.³⁰ The drug also has notable side effects, particularly infusion related

venous toxicity, arthralgia and myalgia that have led to it being used primarily as a third-line agent.

Tigecycline is a new tetracycline derivative that has broad antibacterial activity, including activity against MRSA.³¹ There are no published data of patients treated with tigecycline for MRSA bacteremia or endocarditis; however, randomized, controlled trials have demonstrated that tigecycline is non-inferior to the comparators for the treatment of complicated skin and skin structure infections, as well as complicated intra-abdominal infections due to susceptible organisms. The most frequent and problematic side effect associated with its administration to date has been nausea and/or vomiting. When MRSA are part of a polymicrobial infection, especially when anaerobic organisms are present, tigecycline may be an attractive alternative to vancomycin, bearing in mind that it has not been proven superior in clinical trials.

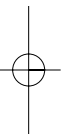
Linezolid has the advantage of availability in both parenteral and oral forms. It has been used to treat a variety of infections and, though it has not received FDA approval for use in bacteremia and endocarditis, there is some published literature describing its use in these conditions. Linezolid is a bacterostatic antibiotic but the overall cure rate with use of this drug is excellent.³² Compared to vancomycin, it appears to be especially useful in patients with *Staphylococcus aureus* pneumonia. In a small study by Gonzalez *et al* of patients with bacteremic MSSA pneumonia, the mortality rate of patients treated with vancomycin was 47% (8/17), whereas none of the ten patients treated with cloxacillin died.³³ One potential explanation for this disparity is the poor penetration of vancomycin into lung tissue. Cruciani *et al* found that in patients with a serum vancomycin concentration of approximately 40 µg/mL the corresponding lung concentration was only 10µg/mL and declined rapidly to less than half of that within three hours.³⁴ In an effort to improve the outcome of patients receiving vancomycin for pneumonia, Moise *et al* found that patients with a AUC >345 had a success rate of 78% compared to those with a AUC ≤ 345 who had a success rate of 24%. The difficulty of assuring an adequate outcome in patients with pneumonia prompted a search for alternative agents. In a study of 242 patients treated with vancomycin or linezolid for MRSA infection, including 18% who were bacteremic, Stevens *et al* found there were no statistically significant differences between treatment groups in ranges of clinical cure or microbiologic success.³⁶ However, Wunderink *et al* analyzed patients with MRSA pneumonia and reported a success rate of 59% for patients treated with linezolid and only 36.5% for those receiving vancomycin (p=.009).³⁷ These data need to be confirmed by additional studies, but they are encouraging that linezolid may be an excellent choice for the treatment of MRSA pneumonia. Additional data also suggest linezolid may be effective therapy for patients with bacteremia or endocarditis, with an overall cure rate of 73%.³² However, adverse reactions were common in this study and may prove to be a limiting feature of this antibiotic.

Daptomycin has been studied both in patients with skin/soft tissue infections as well as in bacteremia and endocarditis with encouraging results.^{38,39} Among patients with MRSA bacteremia or endocarditis there was a 12% difference, with success in 44.4% of

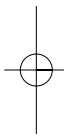


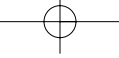
patients receiving daptomycin and only 32.6% among those receiving a combination of vancomycin and aminoglycoside.³⁹ The study was designed as a non-inferiority trial and this difference was not statistically significant. Of interest, the success rates among patients with MSSA infection were almost equal between the two treatment groups (44.6% and 46.7% for those treated with daptomycin and semisynthetic penicillin plus aminoglycoside, respectively). The difference between daptomycin and vancomycin plus gentamicin was even greater among patients with uncomplicated MRSA bacteremia (60.0% vs. 45.5% for daptomycin and vancomycin/gentamicin combination, respectively). Success rates in complicated MRSA bacteremia were 45.5% for daptomycin and 27.3% for those treated with vancomycin plus gentamicin. Again, due to the design of the study, neither difference is statistically significant.

Prevention of MRSA



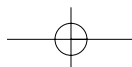
It should be noted that despite the availability of multiple effective agents for the treatment of MRSA, a primary goal remains prevention of such infections. This is an area in which health care providers can play an important role. In a recent study of patients with CA-MRSA infection, almost 20% of patients reported close contact with somebody who had a similar infection.⁴⁰ Several interventions have been proposed that probably would help reduce this patient-to-patient transmission, each of which involves educating patients. Simple measures, such as keeping their lesions covered with clean, dry dressings, maintaining good hand hygiene, and avoiding sharing contaminated items may prove to be very effective at reducing the spread of these infections. Also, since colonization with *S. aureus* is an antecedent step prior to infection, a number of studies have also been conducted to determine if carriage could be eliminated from *S. aureus* carriers. Numerous regimens have been tried, none of which have been very effective. However, in a recent study a combination of chlorhexidine gluconate wash, intranasal mupirocin plus oral rifampin and doxycycline was superior to placebo in eradication of *S. aureus* colonization.⁷ In this large trial of hospitalized patients, 74% of patients in the treatment arm remained free of colonization compared with only 32% in the placebo arm ($p=.001$). More work needs to be done to determine if this result can be generalized to other populations, but it is the most encouraging data to date and may prove to be a substantial tool in our efforts to control staphylococcal disease.



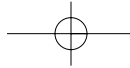


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Self Assessment Examination

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A minimum assessment score of 80% is required.

1) Which of the following statements about community-associated MRSA is incorrect?

- most of the time it causes invasive infections
- it usually produces PantonValentine leukocidin
- many cutaneous infections can be cured without using antibiotics
- it usually carries the *meclV* gene

Answer: _____

2) Which of the following is true regarding the activity of vancomycin against MRSA?

- it is rapidly bactericidal
- vancomycin's activity is not enhanced when it is given in combination with rifampin
- clinical outcome is independent of the vancomycin MIC within the susceptible range
- hVISA strains tend to respond rapidly to vancomycin treatment

Answer: _____

3) Clindamycin is an acceptable choice for the monotherapy of superficial skin/soft tissue infections caused by CA-MRSA if which test is negative?

- A-test
- B-test
- C-test
- D-test
- E-test

Answer: _____

4) The utility of vancomycin in the treatment of staphylococcal pneumonia is limited by:

- nephrotoxicity
- poor penetration into lung tissue
- necessity to monitor serum concentration
- common allergic reactions

Answer: _____

5) Each of the following has been recommended to prevent the spread of MRSA infections except:

- hand washing
- clean, dry dressings over infected wounds
- vancomycin therapy
- decontamination with chlorhexidine gluconate wash, intranasal mupirocin,

Answer: _____

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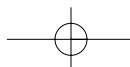
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Target Audience

Infectious disease physicians, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, practicing physicians, and other healthcare professionals interested in the treatment of serious infections due to CA-MRSA.

Learning Objectives

Participant will be able to list new and old antibiotics for treatment of CA-MRSA infections.

Participation in the Learning Process

Credit is based upon the approximate time it should take to read this publication and complete the assessment and evaluation. A minimum assessment score of 80% is required. Publication date is July 1, 2008. **Requests for credit or contact hours must be postmarked no later than January 1, 2009, after which this material is no longer certified for credit.**

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Susan J. Rehm, MD (senior editor) has received consulting fees, honoraria, paid meeting registration fees, paid travel, speaking fees or other financial compensation from Wyeth, CSL Laboratories, Roche, Pfizer and Cubist. Dr. Rehm has received a research grant, stipend and/or fellowship from Cubist.

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