The Widening Challenge: How to Manage MRSA

This once-limited organism is now thriving outside the hospital.

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Staphylococcus Aureus, an Evolving Pathogen

Staphylococcus aureus is one of the most common organisms encountered in podiatric practice. For decades, beta-lactam antibiotics have been the mainstay of therapy. Unfortunately, this treatment paradigm is changing. Methicillin-resistant...
MRSA... 

Staphylococcus aureus (MRSA) has been isolated with increasing frequency from lower extremity infections. In some settings, MRSA has become the predominant form of S. aureus isolated from uncomplicated skin infections in the community. Some strains of MRSA produce cytotoxic virulence factors, resulting in severe necrotizing infections. In the era of resistance, the importance of taking a culture has taken on new meaning.

MRSA: Thriving Outside the Hospital

Since the introduction of penicillin in 1941, S. aureus has undergone a slow but steady metamorphosis. Methicillin was first introduced for clinical use in 1960 to combat the growing incidence of beta-lactamase production among S. aureus. Within a year of its introduction, the first strains of S. aureus resistant to methicillin began to emerge in the United Kingdom. Shortly afterwards, in 1963, MRSA appeared among staphylococci causing blood stream infections in Danish hospitals. Originally a nosocomial pathogen, MRSA has become endemic in the United States and many parts of the world and has become increasingly common in the community, occurring in patients with and without established risk factors.

Mechanism of Resistance

To understand why some drugs are active against MRSA and others are not, it is helpful to look at the mechanism of resistance. Methicillin resistance is associated with the presence of penicillin binding protein 2a (PBP2a). PBP2a, encoded by the mec A gene, has a low affinity for Beta-lactam antibiotics, resulting in resistance to all currently available Beta-lactam drugs. By definition, penicillins, cephalosporins, carbapenems and monobactams have no activity against MRSA. Horizontal transfer of the mec A gene into known MSSA strains converts the strains into MRSA in all cases.

Why is oxacillin tested instead of methicillin?

A useful drug in its day, methicillin has fallen out of use in favor of safer, more active antibiotics. When reviewing a culture and sensitivity report, we now look to oxacillin as a surrogate marker for methicillin resistance. Oxacillin is more resistant to degradation in storage and is more likely to detect heteroresistant strains than methicillin. The acronym MRSA is still used to describe these isolates because of its historic role. For all practical purposes, resistance to oxacillin (ORSA) is synonymous with resistance to methicillin (MRSA). MRSA is defined as having an oxacillin MIC90 =\geq 4\mu g/ml.

All MRSA is Not Created Equal

MRSA can be divided into two main types: community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA). The distinction between the two has become more difficult over the years as HA-MRSA strains move into the community and CA-MRSA strains move into the hospital. Each, however, has important distinguishing features.

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beta-lactam antibiotics. This explains why HA-MRSA strains are multi-drug resistant. Type II is the most prevalent of these HA-MRSA strains found in the United States. SCC mec elements IV and V found in CA-MRSA strains lack antibiotic resistance genes other than mecA, thereby explaining resistance only toward beta-lactam drugs. CA-MRSA can be considered, by comparison, to be a multi-drug susceptible type of MRSA.

CA-MRSA: Multi-Drug Susceptible, But More Virulent

Although originally thought to be a less virulent organism, MRSA has recently been shown to be more virulent than MSSA. In a study by Engemann in 2003, patients with MRSA skin and skin structure infections had a greater 90-day mortality, a longer duration of infection and incurred twice the amount of hospital charges versus those patients with MSSA infections.

Paradoxically, although more susceptible to antibiotics, CA-MRSA has the potential to be more tissue destructive than its hospital counterpart. This is in part due to the production of cytotoxic virulence factors known as Panton Valentine Leukocidins (PVL’s). CA-MRSA isolates containing PVL genes have been linked to recurrent, severe necrotizing skin infections similar to those seen in Group A Streptococcal disease. PVL’s create pores in the leukocyte membrane causing cell death and are thought to be in part responsible for the rapid spread of infection. PVL genes are less commonly found in HA-MRSA or MSSA community isolates.

Inducible Clindamycin Resistance: MLS

Clindamycin continues to be a commonly-prescribed antibiotic for the treatment of methicillin-susceptible Staphylococcal infections, and has even shown to have activity against some strains of CA-MRSA. It is likely, however, that the true incidence of clindamycin resistance has been underestimated.

It is standard practice to rely on Continued on page 142

MRSA can be divided into two main types: community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA).

There are currently five known allotypes, designated SCCmec types I-IV. HA-MRSA strains contain SCCmec types I, II and III. Whereas CA-MRSA strains contain SCC mec types IV and V (Figure 3).

The genetic sequence of type SCCmec found in HA-MRSA reveals plasmids and transposons that mediate resistance to non-beta-lactam antibiotics. This explains why HA-MRSA strains are multi-drug resistant. Type II is the most prevalent of these HA-MRSA strains found in the United States. SCC mec elements IV and V found in CA-MRSA strains lack antibiotic resistance genes other than mecA, thereby explaining resistance only toward beta-lactam drugs. CA-MRSA can be considered, by comparison, to be a multi-drug susceptible type of MRSA.

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MRSA Differences

<table>
<thead>
<tr>
<th>Feature</th>
<th>HA-MRSA</th>
<th>CA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mec-A</td>
<td>Type I, II, III</td>
<td>Type IV, V</td>
</tr>
<tr>
<td>Toxins</td>
<td>Fewer</td>
<td>More</td>
</tr>
<tr>
<td>PVL</td>
<td>Rare</td>
<td>More Common</td>
</tr>
<tr>
<td>Abx Resistant</td>
<td>Multiply resistant</td>
<td>Sensitive except Beta-lactams</td>
</tr>
</tbody>
</table>

### FIGURE 3

**MRSA Differences**

<table>
<thead>
<tr>
<th>Community-acquired MRSA produce more toxins and virulence factors than its hospital counterpart.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA-MRSA with Inducible Clindamycin Resistance</strong></td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
</tr>
<tr>
<td>Cefazolin</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Oxacillin</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
<tr>
<td>TMP/SMX</td>
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<tr>
<td>Vancomycin</td>
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MRSA...

A culture and sensitivity report to choose an antibiotic for directed therapy. In the case of clindamycin, however, culture and sensitivity results may not always be reliable. A phenomenon known as inducible clindamycin resistance (ICR) may mislead the clinician into thinking that a particular strain of S. aureus is susceptible to clindamycin, when in fact it is not.

During laboratory testing, S. aureus appears to be resistant to erythromycin and susceptible to clindamycin, however, once the patient is exposed to clindamycin, he or she may quickly develop resistance (Figure 4).

Staphylococcal strains which possess the erm gene prevent macrolides and lincosamides (erythromycin and clindamycin) from binding to their target site. Clindamycin is a poor inducer of the erm gene compared to erythromycin. The isolate may appear sensitive on laboratory testing but the patient may fail to respond clinically. Inducible clindamycin resistance is seen in both MRSA and MSSA isolates. It has also been found that this inducible resistance extends to streptogramin B antibiotics, giving rise to the acronym MLS (macrolide, lincosamide, streptogramin) resistance.

In some regions of the United States, a high proportion of CA-MRSA isolates are clindamycin resistant. If the proportion of clindamycin resistant MRSA isolates exceeds 10-15 percent, it is recommended that clindamycin not be used as empiric treatment of suspected S. aureus infections.

Although clindamycin should be used with caution if erythromycin resistance is present, it is possible to have resistance to erythromycin without it signifying inducible clindamycin resistance. To determine if this is the case, the microbiology laboratory must perform the “D” test.

The “D” Test

The “D” test is a double-disc diffusion test in which an erythromycin disc is placed 15 mm. away from a clindamycin disc on an agar plate inoculated with S. aureus. If inducible resistance is present, a flattening of the zone of inhibition around the clindamycin disc will be seen (Figure 5). This flattened zone of inhibition resembles the letter “D,” hence the name “D” test.

In one study, D tests of 91 clindamycin-susceptible, erythromycin resistant, S. aureus isolates showed that 68% of MSSA and 12.3% of MRSA cultures were D test positive. It is recommended that the clinician contact a microbiology laboratory to see if the “D” test is routinely performed.

Treatment Options

Because of the increasing incidence of MRSA and the realization that there are, in fact, two distinct genetic strains causing human infection, there has been a corresponding interest in finding new therapies against these organisms. As discussed in detail above, not all MRSA has the same susceptibility patterns. While HA-MRSA is usually only treated with non-beta lactam antibiotics specifically designed to be used against MRSA, CA-MRSA is usually susceptible to a wide range of both old and new drugs.

Some of these would never have been considered appropriate therapy for MRSA before this recognition of two distinct genotypes. Although, with the exception of clindamycin as mentioned previously, just about any drug that is shown on the C&S report to be effective against the particular organism which has been isolated, can be selected. Some of the most frequently mentioned and prescribed antibiotics include the later generation tetracyclines and trimethoprim/sulfamethoxazole. It should be noted that few of these drugs have much medical evidence behind their efficacy as the studies have not been performed on these older compounds. Furthermore, the FDA has not approved any of these older agents as being specifically effective against MRSA. FDA risk categories will help the physician choose the safest agent for treatment of MRSA infections in pregnant patients (Figure 6).

Probably the largest study to date dealing with this issue was recently published by Ruhe. In his study of 24 patients with serious tetracycline sensitive MRSA infections (67% had complicated skin and skin structure infections) both doxycycline and minocycline were used. Clinical cure was achieved in 83% of these patients. Both drugs were well-tolerated.

The conclusion of this study was that long-acting tetracyclines may be a reasonable treatment alternative'. The remainder of this section will deal with those drugs that are specifically designed and approved for use against MRSA.

Vancomycin

First approved in 1988, vancomycin has long been the mainstay in the treatment of patients with serious MRSA infections. Despite recognized issues with inadequate tissue penetration, the ability...
to only dose it IV and concerns about toxicity, it has established itself as an overall effective and safe drug for most MRSA infections. Its acceptance was further bolstered by the perception that, quite frankly, it was “all there is.” In fact, it was; however, despite the development of newer agents that have shown remarkably higher efficacy rates and rather staggering vancomycin failure rates against MRSA for skin and skin structure infections (SSSI), the drug remains the mainstay of treatment in many hospitals and in the minds of many physicians. Much of this may be attributed to a “comfort zone” situation where docs have used the drug for almost half a century and they are comfortable with it, shortcomings and all.

Furthermore, the cost of some of the new drugs is quite off-putting to many physicians, patients and pharmacies that need to stock the newer, expensive drugs. There is also a widely held theory that all new antibiotics should be “reserved” or restricted only to cases in which “Old Faithful” fails. The problem with this approach is that by the time the new drug is started, the patient may have lost limb or life.

More recently there have been concerns about the development of tolerance and frank resistance of staphylococcus to vancomycin. Vancomycin Intermediate Staphylococcus aureus (VISA) was first reported in Japan in 1997. As of 2004, there are at least nine reported cases in the US. Furthermore, the first reports of vancomycin-resistant Staphylococcus aureus (VRSA) was found in patients with diabetic foot ulcerations. All cases were reversible.

**Linezolid**

Linezolid was the first of the newer generation of anti-MRSA antibiotics to have clinical relevance to podiatric medicine. This novel oxazolidinone antibiotic has been shown in a number of randomized, controlled clinical trials to be a very effective drug for the treatment of MRSA in complicated SSSI, including diabetic foot infections. In fact, it is one of a very few antibiotics that is specifically FDA-indicated for the treatment of diabetic foot infections. It has the further advantage of being 100% bioavailable in the oral formulation so its efficacy would be comparable whether given IV or PO.

Looking at the data in a comparative trial of infected foot ulcerations in diabetic patients, linezolid was compared to ampicillin-sulbactam and amoxicillin-clavulanate, and found to be statistically more effective. Against vancomycin for complicated SSSI, Weigelt found that microbiological cures against MRSA were found with linezolid 87% of the time versus only 48% of the time with vancomycin (p=0.0022). Given the superiority of this drug against commonly used antibiotics in podiatric medicine, where does this fit? Certainly, in patients with diabetes who have MSSA infections, you would not use linezolid. Standard therapy with a cephalosporin or other beta-lactam agent would be most appropriate. In patients with diabetes who have a confirmed MRSA infection, however, this drug, even given orally, could very well be statistically more effective than vancomycin.

Much has been made about the potential for thrombocytopenia or pancytopenia in patients receiving this drug for longer than 10 days. This is something that does need to be monitored if the patient will be on a prolonged course of therapy. Interestingly, at least two studies have looked at the potential to cause hematologic adverse events versus that for vancomycin. In a study of 686 patients with nosocomial pneumonia, linezolid-induced thrombocytopenia was found 6.4% of the time. With vancomycin, the same was found 7.7% of the time. Rao looked at patients given long term therapy for orthopedic infections and likewise found that there were similar hematologic effects with a trend towards greater effect with vancomycin. Also, patients placed on vancomycin first, followed by linezolid actually did have a higher rate of thrombocytopenia. All cases were reversible.

**Daptomycin**

The second of the newer anti-MRSA antibiotics to have data specific for SSSI is the cyclic lipopeptide drug daptomycin. This drug is effective against Staphylococcus aureus-resistant to methicillin, vancomycin and linezolid. In its clinical trials, daptomycin was tested against vancomycin for MRSA isolates and a penicillinase-resistant penicillin for MSSA. Of the 902 available patients, only about 10%

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**FIGURE 6**

**FDA Risk Categories for Pregnancy**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Category</th>
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<tbody>
<tr>
<td>Clindamycin</td>
<td>B</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>B</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>C</td>
</tr>
<tr>
<td>Linezolid</td>
<td>C</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>C</td>
</tr>
<tr>
<td>Minocycline</td>
<td>D</td>
</tr>
</tbody>
</table>

Antibiotics with activity against MRSA and their FDA risk categories for pregnancy.
had MRSA. Clinical success rates were 81.1% for daptomycin vs. 73.8% for vancomycin. This is most interesting to again demonstrate the rather significant vancomycin failure rates that have been found across a range of trials for different antibiotics. If between one-quarter to one-half of patients do not respond on vancomycin can it still be considered first line therapy? Data specifically against diabetic infections is somewhat sparse in that only about 12% of this population had a diabetic foot infection.

Daptomycin can only be given parentally as no PO formulation exists. It does have the theoretical advantage of being considered a bactericidal agent but the validity of that advantage has been called into question. At this point, its use in podiatric medicine remains to be elucidated. It could be effective in more resistant organisms, even those found resistant to linezolid. Also, the theoretical advantage of its bactericidal activity may be useful in osteomyelitis but no studies yet exist to demonstrate its efficacy.

Tigecycline

The latest drug to receive FDA approval for the treatment of MRSA SSSI is the tetracycline derivative tigecycline. This drug is particularly exciting because up to this point all other anti-MRSA drugs have been specifically targeted against gram positive organisms only. Tigecycline is a broad spectrum agent effective against a wide range of both sensitive and multi-resistant gram positives, gram negatives and even anaerobic organisms. In the pivotal phase 3 trials tigecycline was compared to vancomycin with aztreonam for SSSI. 1,116 patients were enrolled and 833 were clinically available. Clinical response rates were found to be similar between the two arms. The conclusion was that tigecycline was as safe and efficacious as the vancomycin-aztreonam combination in treating patients with complicated SSSI.

At least on the surface this looks to be an ideal drug for podiatric infections, especially in those with severe diabetic foot infections.

Monotherapy would be usable because combination drug therapy to cover MRSA, gram negatives and anaerobes would be eliminated. It may be a bit too early to get overly enthusiastic, however. Careful analysis of this data shows that in the tigecycline group of 422 patients, only 83 (<20%) had diabetes and only 7.1% had infected ulcers. Of greatest concern is the incredibly high rate of gastrointestinal adverse events. Nausea occurred in 34.5% of the patients, vs. 8.2% for the comparator, and vomiting occurred in almost 20% of patients vs. 3.6% for the comparator. It will be interesting to see how this drug is positioned and whether or not more clinical experience bears out the problem with the GI events.

The No Treatment Option

Although an anathema to many podiatric physicians, there comes a time when no treatment may be the best treatment. This is particularly true of MRSA. Studies are starting to show that just because MRSA is cultured from a wound, it may not be necessary to utilize specific anti-MRSA therapy.

Looking specifically at diabetic foot infections, Dang found that although the overall number of patients growing MRSA doubled over a three year period, MRSA was eradicated with debridement, topical treatment and isolation without the use of specific anti-MRSA antibiotics.

Looking at CA-MRSA in a more general group of 453 patients, Fridkin found that initial antibiotic therapy that was inactive against CA-MRSA did not increase the chance for an adverse outcome versus those that received anti-MRSA antibiotics.

This last section emphasizes one of the oldest axioms of clinical infectious diseases: It is important to treat your patient and not the culture report. If the patient is improving despite a culture report showing MRSA resistant to the prescribed antibiotic, do not change therapy—monitor the patient.

Yes, MRSA is an increasing problem. It has become much more common than ever before. Furthermore, we now have the added challenge of determining whether or not the patient presents with CA or HA-MRSA. Fortunately, new therapies are arriving to treat those who really need them.

References


5 Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. Ad...


MRSA...

1) Which of the following antibiotics is active against CA-MRSA?
   - A) cephalexin
   - B) minocycline
   - C) amoxicillin/clavulanate
   - D) dicloxacillin

2) You are treating an uncomplicated skin infection in a pregnant patient. Which of the following antibiotics is the least safe to use?
   - A) linezolid
   - B) vancomycin
   - C) minocycline
   - D) daptomycin

3) Which of the following has 100% bioavailable after oral administration?
   - A) vancomycin
   - B) linezolid
   - C) minocycline
   - D) clindamycin

4) Which of the following antibiotics cannot be used to treat an MRSA infection?
   - A) imipenem/cilistatin
   - B) daptomycin
   - C) vancomycin
   - D) linezolid

5) Penicillin binding protein 2a (PBP2a) is encoded by the
   - A) erm gene
   - B) mec A gene
   - C) MLS gene
   - D) PVL gene

6) Which of the following antibiotics cannot be used in a patient with a history of sulfa allergy?
   - A) minocycline
12) Vancomycin intermediate S. sureus (VISA) was first reported in
   A) 1961
   B) 1985
   C) 1997
   D) 2005

13) Which of the following has shown activity against S. aureus resistant to methicillin, vancomycin and linezolid?
   A) minocycline
   B) TMP/SMX
   C) Daptomycin
   D) Clindamycin

14) Which of the following is available in oral form for treatment of MRSA?
   A) linezolid
   B) daptomycin
   C) vancomycin
   D) tigecycline

15) Which of the following is safest to use in a pregnant patient?
   A) linezolid
   B) clindamycin
   C) trimethoprim/sul-famethoxazole
   D) vancomycin

16) The “D” test is used to detect
   A) inducible clindamycin resistance
   B) resistance to methicillin
   C) susceptibility to erythromycin
   D) susceptibility to daptomycin

17) Which of the following has shown reliable activity against hospital acquired MRSA (HA-MRSA)?
   A) Clindamycin
   B) TMP/SMX
   C) Tetracycline
   D) Vancomycin

18) Which is true about community-acquired MRSA (CA-MRSA)?
   A) It is sensitive to antibiotics except beta-lactams
   B) It produces fewer toxins than HA-MRSA
   C) It rarely produces pan-ton valentine leukocidins (PVL)
   D) It is associated with mec A type I, II, III

19) Resistance to which of the following antibiotics implies resistance to methicillin?
   A) oxacillin
   B) erythromycin
   C) clindamycin
   D) cephaolthin

20) Penicillin was introduced for clinical use in
   A) 1938
   B) 1941
   C) 1952
   D) 1956