REVIEW ARTICLE

# Current Treatment Options for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infection

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**During the past decade, there has been a marked increase in the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* infection in the United States and elsewhere. The most common such infections are those involving the skin and skin structures. Although a number of these lesions (including small furuncles and abscesses) respond well to surgical incision and drainage, oral antimicrobial agents are commonly used to treat these infections in outpatients. Unfortunately, with the exception of linezolid, none of the agents presently being used in this fashion has been subjected to rigorous clinical trial. Thus, current therapy is based largely on anecdotal evidence. For more-serious infections requiring hospitalization, parenteral antimicrobials such as vancomycin, teicoplanin, daptomycin, linezolid, and tigecycline are presently available and have demonstrated effectiveness in randomized, prospective, double-blind trials.**

Although occasional infections due to community-acquired (or community-associated [CA]) methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported for a number of years [1], the current epidemic of CA MRSA infection in the United States and elsewhere began in the late 1990s, when 4 fatal cases of CA MRSA infection in Native American children were reported in the United States [2, 3]. In nearly the same time frame, CA MRSA infections were reported in a number of other parts of the world, including Australia, Switzerland, France, the United Kingdom, New Zealand, Finland, Canada, and Samoa [4]. The majority (but not all) of the isolates causing these infections contain genes encoding the Panton-Valentine leukocidin and possess unique cassettes containing the *mecA* gene, which is associated with methicillin resistance (*mec*IV or, less commonly, *mec*V or *mec*VI) [5, 6]. Although infections due to CA MRSA have occurred throughout the world, they have become a particularly acute problem in the United States, where 1 clone (USA300) has achieved predominance and, over the course of ~5 years, has spread throughout the country. This organism now comprises 60%–75% of *S. aureus* isolates in most areas of the United States where it has been sought [7, 8]. USA300 and related Panton-Valentine leukocidin–containing clones, such as USA400, USA500, USA1000, and USA1110, are capable of causing a variety of very serious infections, including necrotizing fasciitis, pyomyositis, septic thrombophlebitis of the extremities, the "pelvic syndrome" (septic arthritis of the hips, pelvic osteomyelitis, pelvic abscesses, and septic thrombophlebitis in children), Waterhouse-Friderichsen syndrome, rapidly progressive pneumonia, and ocular infections [2, 5]. Nonetheless, the majority of infections currently caused by these organisms are relatively minor, purulent and/or pustular skin and soft-tissue infections [9]. Until the advent of CA MRSA infection, *S. aureus* infections in the United States were routinely treated with oral antistaphylococcal penicillins, such as dicloxacillin, or cephalosporins, such as cephalexin or cefadroxil [10, 11]. Alternative antimicrobial drugs were rarely used and were even less frequently subjected to rigorous clinical evaluation. Nonetheless, a variety of oral agents, such as trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, doxycycline (and less commonly minocycline), linezolid, rifampin, and occasionally, fluoroquinolones,

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**Table 1. Oral antimicrobial agents for treatment of community-acquired methicillin-resistant *Staphylococcus aureus* infection.**

| Agent | Adult dosage |
|---|---|
| Trimethoprim-sulfamethoxazole | 1–2 double-strength tablets (160/800 mg) every 12 h |
| Doxycycline | 100 mg every 12 h |
| Minocycline | 100 mg every 12 h |
| Rifampin | 600 mg every day |
| Clindamycin | 300–600 mg every 6-8 h (pediatric dosage, 2–8 mg/kg every 6-8 h) |
| Linezolid | 400–600 mg every 12 h |
| Fusidic acid (usually given in combination with rifampin) | 500 mg every 8 h |

have been used by clinicians in the United States for these infections. In Australia, the United Kingdom, and several other countries, fusidic acid (usually in combination with rifampin to prevent the emergence of resistance) has also been used in the outpatient setting. A newly released topical agent, retapamulin, has been approved for minor skin infections, such as impetigo, but has not been approved for MRSA and will not be further discussed here [12]. For more-serious infections requiring hospitalization, a variety of parenteral agents are available, including vancomycin (and outside the United States, teicoplanin), daptomycin, linezolid, and tigecycline (table 1 and table 2).

Providing definitive recommendations for antimicrobial therapy of skin and soft-tissue infections due to CA MRSA is problematic for several reasons. First, many of these infections (especially furuncles, pustules, and small abscesses) will likely respond favorably to effective surgical incision and drainage and may not even require antimicrobial therapy. Evidence in support of this can be gleaned from a recent study of CA MRSA infections seen in emergency departments across the United States [7]. Because the majority of patients in this study underwent surgical incision and drainage of their lesions, the authors concluded that it was impossible to draw strong conclusions concerning the relative efficacy of antimicrobial therapy. In another study from San Francisco, patients with CA MRSA skin and soft-tissue infections were randomized to receive cephalexin or placebo after undergoing incision and drainage (essentially a double-placebo study) [13]. The patients in this study did well, and in fact, placebo was slightly better than cephalexin therapy, strongly supporting the value of appropriate incision and drainage in treating these infections. In essence, this was a double-placebo study, because all of the infections were caused by MRSA, against which cephalexin therapy should not be effective. When the lesions are large, are surrounded by cellulitis, or do not involve drainable foci and occur in patients with fever or other systemic symptoms, most clinicians treat with antimicrobial drugs, even in the absence of controlled trials defining benefit [14]. Unfortunately, there are no randomized, prospective trials of the agents most commonly used to treat skin and soft-tissue infection due to CA MRSA; thus, we are forced to rely solely on anecdotal evidence. This may soon change, however. The National Institutes of Health has recently funded 2 clinical trials in the United States that will provide data on the effectiveness of oral antimicrobial agents for skin and soft-tissue infections due to CA MRSA in adults and children [15]. Unfortunately, it will likely be several years before the results of these studies are available.

At present, in the United States, TMP-SMX and clindamycin are the most commonly used antimicrobial drugs for the outpatient treatment of CA MRSA infections. Fusidic acid plus rifampin combination therapy is frequently used in other parts of the world. It appears that TMP-SMX is the agent primarily preferred for the therapy of adults in the United States, and clindamycin is favored by many pediatricians [2].

The use of TMP-SMX to treat CA MRSA infections is primarily based on a 1992 study by Markowitz et al. [16], which was a randomized, nonblinded trial involving 101 injection drug users with *S. aureus* infections (47% of the infections were due to MRSA, and 65% were bacteremic). Intravenous TMP-SMX therapy was compared with vancomycin therapy. Infections were cured in 57 of 58 vancomycin recipients and in 37 of 43 TMP-SMX recipients ($P < .02$). Interestingly, all of the treatment failures occurred in patients with methicillin-susceptible strains of *S. aureus* (MSSA), and the authors concluded very conservatively that "vancomycin is superior to TMP-SMX in efficacy and safety when treating intravenous drug users who

**Table 2. Parenteral agents for the treatment of community-acquired methicillin-resistant *Staphylococcus aureus* infection.**

| Agent | Dosage |
|---|---|
| Vancomycin | 1 g intravenously every 12 h |
| Daptomycin | 4 mg/kg intravenously every 24 h |
| Linezolid | 600 mg intravenously every 12 h |
| Tigecycline | 100 mg intravenously once, then 50 mg intravenously every 12 h |

have staphylococcal infections. However, all treatment failures occurred in patients with MSSA infections at any site. Therefore, TMP-SMX may be considered as an alternative to vancomycin in selected cases of MRSA infection" [16, p. 390]. In vitro evidence supporting the use of TMP-SMX to treat MRSA infections may be gleaned from a recent study in which TMP-SMX exhibited greater bactericidal activity against MRSA than did linezolid, rifampicin, clindamycin, or minocycline [17]. Interestingly, adding rifampicin to the TMP-SMX regimen showed a trend toward antagonism in vitro [17]. As already noted, there are no randomized, prospective trials to define the effectiveness of TMP-SMX therapy for CA MRSA infections. However, a recent retrospective chart review of skin and soft-tissue infections seen during the period 1998–2005 at the Fenway Community Health Center in Boston, Massachusetts, concluded that empirical therapy of CA MRSA infections treated with TMP-SMX was associated with a favorable response, compared with therapy with agents to which the organisms were resistant (OR, 5.91), when controlled for incision and drainage and HIV infection status [18]. A small randomized, prospective study of TMP-SMX (160/800 mg twice daily) versus doxycycline (100 mg twice daily) resulted in 3 clinical failures in 14 patients treated with TMP-SMX. There were no treatment failures in the small (20-patient) doxycycline treatment arm [19]. A potential drawback of using TMP-SMX alone for the treatment of skin and soft-tissue infections in the absence of available cultures is that the efficacy of TMP-SMX for infections due to group A streptococci is probably less than optimal, although this has not been rigorously studied in the context of skin and skin-structure infections. Another issue regarding the use of TMP-SMX in this context relates to the appropriate dosage. Most clinicians have used a dosage of 2 double-strength TMP-SMX tablets twice daily, although this has not been universally used, and it has not been definitely proven that 2 double-strength TMP-SMX tablets twice daily is superior to 1 double-strength tablet twice daily. Interestingly, in the study by Cenizal et al. [19] that was quoted above, the treatment failures occurred when patients received lower dosages (1 double-strength tablet twice daily) of TMP-SMX.

Clindamycin has been widely used by pediatricians for therapy of skin and soft-tissue infections, including those due to CA MRSA [2]. Although there are no randomized, prospective, controlled trials of the use of clindamycin therapy for CA MRSA infections, available anecdotal experience suggests that it is likely to be effective, provided that the organism is susceptible in vitro [2]. Currently, the prevalence of clindamycin resistance among CA MRSA in the United States varies considerably by geographic location [20–22]. In San Francisco, the prevalence of clindamycin resistance has been <12% to date [21]. In Boston, however, a recent study has revealed that 49%–76% of CA MRSA isolates are clindamycin resistant [22]. Even in those areas where the prevalence of clindamycin resistance is low, however, susceptibility to clindamycin does not always predict outcome. Organisms that exhibit resistance to erythromycin and susceptibility to clindamycin (which accounted for almost 80% of the USA300 isolates in a recent study in San Francisco [21]) may exhibit resistance either because of efflux (in which case they remain clinically susceptible to clindamycin) or via the inducible expression of the $MLS_B$ gene, which methylates the binding site for erythromycin and clindamycin and renders the organism resistant. Because clindamycin does not induce the production of the methylase, these organisms will be found to be susceptible by clinical microbiology laboratory testing, unless a specific test, such as the double-disk D-test, is used to detect this type of inducible resistance [23]. The clinical significance of this finding is that a single-step mutation can convert these organisms to clindamycin resistance. There are numerous anecdotal reports of clinical failure of clindamycin because of the emergence of such resistance during treatment [24–27]. Unfortunately, the frequency with which this occurs is not known, but it is probably relatively low. Thus, it is likely that most patients infected with organisms that are found to be susceptible to clindamycin by laboratory testing will respond favorably to the drug. Nonetheless, to be certain of therapeutic outcome, it is prudent to test for inducible resistance (in organisms that are resistant to erythromycin) using the aforementioned D-test.

Another potential advantage of clindamycin (and of linezolid and fusidic acid) is that it suppresses production of Panton-Valentine leukocidin and other virulence factors in MRSA. Interestingly, subinhibitory concentrations of oxacillin or nafcillin actually increase production of these toxins [28, 29].

The long-acting tetracyclines (minocycline and doxycycline) were used extensively in Japan for the treatment of MRSA infections before the availability of vancomycin there. Until recently, however, they have not been used as frequently in the United States for that purpose. Ruhe et al. [30] published a small retrospective record review of 24 patients with tetracycline-susceptible MRSA infections treated with long-acting tetracyclines and noted a clinical cure rate of 83% among those patients. In an accompanying literature review, the authors found 73 additional patients in 9 studies who were treated for MRSA infections with long-acting tetracyclines. In general, the response rates in these studies varied from 80% to 100%. Another small, recently published, prospective trial suggested a response rate of 100% among 20 patients treated with doxycycline after incision and drainage of their abscesses due to MRSA infection [19]. Finally, Ruhe et al. [31] published a retrospective cohort study involving 276 patients who had 282 episodes of MRSA skin and soft-tissue infections and who presented to the emergency department or outpatient clinic at 2 tertiary medical centers in Arkansas from October 2002 through

February 2007. Treatment failure occurred in only 4 of 90 patients treated with tetracyclines but was seen in 24 of 192 patients treated with $\beta$-lactam antimicrobials ($P = .035$). The majority of patients in this study had abscesses that were surgically drained, and this undoubtedly explains the high cure rate associated with long-acting tetracycline therapy and the fact that a high percentage of these patients appeared to respond to inappropriate ($\beta$-lactam) therapy.

Although the initial isolates of CA MRSA from the United States were almost universally susceptible to the tetracyclines [9], several recent studies have documented increasing resistance to the tetracyclines among USA300 strains in San Francisco and Boston [21, 22]. If this trend continues, it will likely have a significant impact on the effectiveness of the long-acting tetracyclines for the treatment of CA MRSA infections.

Rifampicin has excellent in vitro activity against CA MRSA infections but cannot be used as a single agent to treat such infections because of the rapid emergence of resistance that occurs even during therapy [32]. Combinations of rifampin and TMP-SMX have been shown to exhibit in vitro antagonism [17]. There are no published studies demonstrating the benefit of such combination therapy, but nonetheless, some clinicians have added rifampin to TMP-SMX or long-acting tetracycline regimens. Rifampin is also commonly used with fusidic acid to prevent mutual emergence of resistance during therapy. Linezolid is the only orally available agent for which efficacy against MRSA infection has been demonstrated in controlled trials [33]. This drug has excellent activity against infections due to group A streptococci and has also demonstrated efficacy for diabetic foot infections [34]. Because it is a relatively expensive drug, however, the use of linezolid for treating outpatients has been limited thus far.

The agents currently available for parenteral therapy of serious CA MRSA infections are listed in table 2. These include vancomycin (or teicoplanin), daptomycin, linezolid, and tigecycline. Vancomycin (or teicoplanin, in countries where it is available) remains the gold standard of therapy for serious MRSA infections. That standard, however, is now tarnished by decreasing efficacy because of increasing resistance among MRSA strains [35, 36]. Unfortunately, this resistance is not easily demonstrable by clinical microbiology laboratory testing, because many of the strains that fail to respond to therapy with vancomycin exhibit a heteroresistance phenomenon, which requires special methodology for detection [37]. A detailed discussion of mechanisms associated with the diminishing efficacy of vancomycin therapy for MRSA infections is beyond the scope of this paper, but such mechanisms are reviewed in detail in articles by Sakoulas and Moellering [35] and Tenover and Moellering [36].

Daptomycin is a new lipoglycopeptide antimicrobial drug that is rapidly bactericidal for MRSA infection. It has recently been approved for the treatment of bacteremia and right-sided endocarditis due to *S. aureus* (including MRSA) on the basis of a study that revealed that daptomycin therapy was noninferior to vancomycin therapy for this indication [38]. In the subgroup of patients with MRSA infections, daptomycin therapy was numerically but not statistically significantly superior to vancomycin therapy. Daptomycin has not been studied extensively for infections due to CA MRSA. It should be noted, however, that MRSA strains with heteroresistance to vancomycin may exhibit heteroresistance to daptomycin (clinical significance has not been fully determined to date), even when the MRSA strains have never been exposed to daptomycin [39].

Linezolid has clearly been demonstrated to be effective for the treatment of MRSA infections on the basis of controlled, clinical trials and may be superior to vancomycin for the treatment of complicated skin infections due to MRSA [40]. Although resistance to linezolid in MRSA has been described, this has not been a significant clinical problem to date [41].

Tigecycline is the fourth parenteral drug available for the treatment of serious MRSA infections. In controlled clinical trials, it has been shown to be noninferior to vancomycin for this indication [42, 43]. Nonetheless, the number of patients with MRSA infections in studies to date are relatively limited.

Because these 3 agents have not been tested against one another in controlled trials, their relative efficacies are not known. However, some preliminary observations may be useful in guiding their application for particularly severe infections due to CA MRSA. For serious skin and skin-structure infections, such as necrotizing fasciitis, linezolid may be particularly useful because of its ability to impair toxin production [28]. The addition of clindamycin to a vancomycin regimen for this purpose is also reasonable. The same rationale leads to the consideration of the use of linezolid for the treatment of pneumonia due to CA MRSA. It should be noted, however, that, although linezolid has been shown to be noninferior (and possibly superior) to vancomycin for the treatment of hospital-associated pneumonia and ventilator-associated pneumonia due to MRSA, there are no published data supporting its use for CA pneumonia [44]. Daptomycin is inactivated by pulmonary surfactant and should not be used for CA pneumonia due to CA MRSA [45].

As noted above, a number of parenteral agents are available for the treatment of serious infections due to CA MRSA. The efficacy of daptomycin, linezolid, and tigecycline for MRSA infections has been demonstrated in prospective, controlled clinical trials. Unfortunately, with the exception of linezolid, no such data are available for the oral agents that are currently widely used for the therapy of CA MRSA infections in outpatients. It is hoped that 2 trials being initiated under National Institutes of Health sponsorship will provide much needed data

on the efficacy of oral antimicrobial drugs for treating these increasingly important infections.

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