Community-Associated Methicillin-Resistant *Staphylococcus aureus*: A Review

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common bacterial pathogen responsible for a variety of infections in both children and adults. Treatment of infections caused by this organism is problematic due to its resistance to many drugs. Recent reports of community-associated MRSA (CA-MRSA) infections in patients with no known risk factors have serious public health implications. Therapeutic options for these infections are untested; therefore, the potential exists for high morbidity and mortality. Recently, clinical definitions have been established, and new molecular approaches have allowed investigators to distinguish CA-MRSA more easily from traditional nosocomial-derived MRSA strains. Identifying potential risk factors for CA-MRSA acquisition and fully characterizing the epidemiologic, clinical, and molecular properties of these strains are necessary to provide effective therapeutic guidelines.

**Keywords:** community-associated methicillin-resistant *Staphylococcus aureus*, community-associated MRSA, CA-MRSA, SCCmec IV, staphylococcal cassette chromosome, Panton-Valentine leucocidin, MRSA, disk diffusion test, clindamycin, daptomycin, trimethoprim-sulfamethoxazole.

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**OUTLINE**

- Epidemiology
- Risk Factors
- Molecular Analysis of Community- and Health Care–Associated MRSA
- Virulence Factors and Toxins
- Outbreaks
- Treatment Options
- Nonantimicrobial Treatment Option
- Conclusion

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a formidable bacterial pathogen responsible for a variety of infections commonly seen in patients of all ages.\(^1\)–\(^3\) Acquisition of this organism is typically associated with particular settings (health care institutions, such as hospitals and long-term care facilities) and patient groups (patients with prolonged hospitalization, past antimicrobial use, indwelling catheters, decubitis ulcers, postoperative surgical wounds, and use of intravenous drugs or treatment with enteral feedings or dialysis).\(^4\)–\(^7\)

Infections due to MRSA present a considerable dilemma to clinicians, since therapeutic options are limited and suboptimal dosing contributes to heightened mortality and increased length of hospital stay.\(^5\)–\(^9\)

Although alteration of target penicillin-binding proteins is the primary mechanism of resistance to β-lactam antibiotics, over the years MRSA strains have gained multiple mechanisms of resistance to several classes of antimicrobials,
including macrolides, aminoglycosides, fluoroquinolones, tetracyclines, and lincosamide antibiotics such as clindamycin. For the past several decades, glycopeptide antibiotics, such as vancomycin, have been considered the only agents to which MRSA have not developed resistance. Unfortunately, due to overuse of glycopeptide antibiotics, MRSA have emerged with reduced susceptibility to these agents as well.10, 11

In recent years, there have been several reports of community-associated MRSA (CA-MRSA) infections throughout the world, including several outbreaks in the United States.12–15 Most of these outbreaks have been associated with a single-clone strain. Transmission has occurred by close physical contact in situations involving children in day-care centers, children and adults on Indian reservations, athletes, military personnel, correctional facilities, and men having sex with men.16–18 Of concern, these patients are otherwise healthy individuals with no known risk factors for MRSA acquisition.3, 7, 13, 15, 19–26

The prevalence of MRSA infections is increasing in the community.27–29 Recent investigations have revealed several characteristics that differentiate CA-MRSA from health care–associated MRSA (HA-MRSA) strains. Community isolates tend to be susceptible to a variety of non–β-lactam antibiotics, whereas HA-MRSA are typically resistant to multiple antibiotics. Other differences are that genotypes of community isolates are not the same as those of health care–derived isolates, community strains harbor a novel methicillin resistance cassette gene element not identified to date among strains that are endemic to health care settings, and community isolates occur in patients lacking typical risk factors for MRSA.1–5

Finally, community isolates are more likely than health care–derived isolates to encode putative virulence factors, such as Panton-Valentine leucocidin, a cytotoxin virulence factor that has been associated with severe pneumonia in children and with skin and soft tissue infections in adults.

The Centers for Disease Control and Prevention (CDC) has established criteria to distinguish CA-MRSA from HA-MRSA isolates.30 According to these criteria, the diagnosis of CA-MRSA must be made in an outpatient setting or by culture showing MRSA within 48 hours after admission to the hospital. The patient must not have experienced any of the following during the year before infection: hospitalization; admission to a nursing home, skilled nursing facility, or hospice; dialysis; or surgery. In addition, the patient must be without permanent indwelling catheters or medical devices that pass through the skin into the body.

Epidemiology

In 2000, the CDC began working closely with four states with a combined population of about 12 million persons to study the epidemiology of CA-MRSA infections. Information from these studies is helping the CDC understand the nature of the disease, the reasons why people get infected, and the types of research needed to help prevent these infections. These data are being collected in Connecticut, Minnesota, Georgia, and Maryland as part of CDC’s Emerging Infections Program. This program was expanded to six states in 2004.

In one of the more recent studies, a group of investigators characterized the epidemiologic and microbiologic characteristics of both CA- and HA-MRSA in 1100 MRSA infections.31 Based on pulsed field gel electrophoresis (PFGE) and staphylococcal exotoxin gene testing, they determined that 12% of the infecting strains were CA-MRSA and 85% were HA-MRSA. Seventy-five percent of skin and soft tissue infections were caused by CA-MRSA, whereas 37% were caused by HA-MRSA (odds ratio [OR] 4.25; 95% confidence interval [CI] 2.97–5.90). The CA-MRSA isolates typically possessed different exotoxin gene profiles than the HA-MRSA isolates.

Earlier studies investigated the epidemiology and clonality of CA-MRSA in Minnesota health care facilities.23 Ten health care facilities contributed data on 354 patients with CA-MRSA from 1996–1998. Patient records were examined for demographic data, and all infection types were recorded. All available isolates were analyzed with PFGE to determine if they were of hospital or community origin. The median age of patients was 16 years (range 1–78 yrs), and the most common infection type was skin and soft tissue infections. In adults, the most common infection type was skin and soft tissue (84%). Examination of the isolates by PFGE indicated that most (86%) were distinctly different from HA-MRSA organisms. In addition, as has been found in other evaluations of CA-MRSA strains, these pathogens tended to be more susceptible to antimicrobial agents than HA-MRSA.

To estimate the prevalence of CA-MRSA infections in Finland, a study evaluated MRSA culture–positive patients from a national hospital
The definition for CA-MRSA was the lack of hospitalization for a minimum of 2 years. Of the 526 patients identified with MRSA-positive status, 21% were determined to have MRSA of community origin. Three MRSA strains were identified as community strains on the basis of phage typing, PFGE, and ribotyping. Of interest, none of the community-acquired strains were multidrug resistant, and all strains demonstrated a mec hypervariable region. The authors concluded that CA-MRSA may arise de novo, through acquisition of the mecA gene.

A hospital-based observational study compared nosocomial and community-acquired S. aureus bacteremias. The researchers classified 32% of all bacteremias as hospital acquired, whereas 18.5% were deemed community acquired. However, on further examination, all patients with CA-MRSA were found to have regular contact with health care settings, making the term community-acquired misleading.

A meta-analysis applied to various types of CA-MRSA publications yielded several sets of key statistics. In nine studies where researchers obtained culture samples before making risk assessments, the pooled MRSA colonization rate was 2.1% (among 4825 patients). Another revealing finding was that nearly one half of patients with CA-MRSA had one or more risk factors for HA-MRSA, and among the remaining 3525 patients the colonization rate of CA-MRSA strains dropped to only 0.2%. Patients from whom samples were obtained in a health care facility were 2.4 times more likely to carry MRSA than community members cultured outside of a health care setting (95% CI 1.56–3.53). Finally, 17.8% of household contacts of patients colonized with HA-MRSA were found to also carry the index strain. To date, the true incidence of CA-MRSA is unknown, since most studies have characterized this organism in a relatively small group of patients over a short, fixed time interval.

Risk Factors

It is of vital importance to identify risk factors for CA-MRSA to enable clinicians to rapidly recognize and appropriately treat infected patients. Several studies have demonstrated an increase in the prevalence of CA-MRSA; however, risk factors have not been fully characterized. Children and young adults have served as the primary patient source for a significant number of these studies. Other than injection drug use, no other community-associated risk factors have been identified. Unfortunately, great inconsistencies exist in the definitions of CA-MRSA in these investigations. Early studies did not discuss exclusion criteria, whereas other studies discussed exclusion criteria for health care contact ranging from a few months to up to 1 year after MRSA colonization. Most report that routine contact with health care facilities was a significant risk factor for CA-MRSA acquisition.

Molecular Analysis of Community- and Health Care–Associated MRSA

Several investigations have explored the molecular aspects of CA-MRSA. One research group investigated the potential for a shared common origin of HA-MRSA and CA-MRSA. Twenty-three well characterized strains of CA-MRSA were compared with 12 non–multidrug-resistant, oxacillin-resistant S. aureus (NORSA) strains—strains that are frequently isolated in hospitals but are considered to be decedents of CA-MRSA isolates—and with representative hospital isolates. This indicated that CA-MRSA strains can acquire resistance to non–β-lactams through exposure. The CA-MRSA strains were also found to have lower levels of resistance to oxacillin and imipenem-cilastatin (minimum inhibitory concentrations of 8–32 µg/ml), implying that CA-MRSA strains, unlike HA-MRSA strains, were not selected by exposure to the potent β-lactam agents typically used in hospital settings. It was also observed that doubling times were significantly shorter for CA-MRSA than for HA-MRSA. The authors speculated that this high growth rate may help CA-MRSA achieve successful colonization by enabling it to outcompete other bacterial species that are normally part of the commensal flora.

Application of multilocus sequence typing and evolutionary mathematical models to an international collection of 359 MRSA isolates has revealed that all MRSA share a common genetic lineage and can be traced to a single MRSA clone. This strain, known as ST-250, appears to have evolved from a methicillin-susceptible S. aureus (MSSA) isolate, which subsequently acquired the mec gene from an unknown source. Minor variations of this organism, such as ST-247; the Iberian clone; and ST-5, 22, and 45, have evolved...
into some of the more common MRSA isolates that have been found around the world. The diversity of MRSA strains is secondary to horizontal transfer of genetic elements that insert into the bacterial genome. Current MRSA isolates are either descendants of preexisting clones or have been created by horizontal transfer of the mec determinant into successful MSSA.39 The mecA gene in staphylococci is responsible for β-lactam resistance. This gene encodes a penicillin-binding protein that has low affinity for β-lactam–type antibiotics. The mecA gene complex is carried on a specific integrative genetic element known as the staphylococcal cassette chromosome (SCC). These mobile cassettes consist of the mec complex and the cassette recombinase genes, which are responsible for encoding integration and excision of the SCCmec element on the staphylococcal chromosome (Figure 1).

Five SCCmec types have been identified for *S. aureus*. The gene elements differ in size, composition, and associated antimicrobial resistance expression (Table 1).30–42 The SCCmec types I, II, and III are found predominately in HA-MRSA isolates. These isolates carry a number of inserted plasmids and transposable genetic elements downstream of the mecA complex. The SCCmec types II and III are responsible for the

### Table 1. The Five Types of the mec Gene Complex

<table>
<thead>
<tr>
<th>SCCmec Type</th>
<th>Size (kb)</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34.3</td>
<td>Lacks other resistance genes</td>
</tr>
<tr>
<td>II</td>
<td>53.0</td>
<td>Associated with multiple drug resistance</td>
</tr>
<tr>
<td>III</td>
<td>66.9</td>
<td>Associated with multiple drug resistance</td>
</tr>
<tr>
<td>IV</td>
<td>20.9–24.3</td>
<td>Resistant to β-lactam antibiotics</td>
</tr>
<tr>
<td>V</td>
<td>28.0</td>
<td>Lacks antibiotic resistance genes other than mecA</td>
</tr>
</tbody>
</table>

SCC = staphylococcal cassette chromosome.

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Figure 1. Structure of the staphylococcal cassette chromosome mec, with the recombinase genes complex upstream of the mec complex. The mec complex contains the mecA gene responsible for β-lactam resistance in *Staphylococcus aureus*. IS1272 = insertion sequence–like element; ccrA and ccrB = cassette chromosome recombinase genes A and B that mobilize the mec element; mecR1 = mec sensor transducer and repressor genes that regulate production of PBP-2A, which is responsible for β-lactam resistance; IS431 = integrated plasmid that encodes tetracycline resistance; and orfx = open reading frame in which the mobile elements (staphylococcal cassette chromosome) are located. (Adapted in part from reference 37.)
multiple non–β-lactam antimicrobial resistance often expressed in these health care–related strains. The SCC\textit{mec} type IV is typically found in CA-MRSA strains and in NORSA isolates. This SCC\textit{mec} type is smaller in size and lacks other multidrug-resistance genes. Recently, a SCC\textit{mec} type V was described. Similar to type IV, it is small in size, does not contain antimicrobial resistance genes other than \textit{mecA}, and is found predominately in CA-MRSA and NORSA strains.

**Virulence Factors and Toxins**

\textit{Staphylococcus aureus} produces numerous unique toxins and virulence factors, such as the toxic shock syndrome toxin (TSST-1), enterotoxins, and exotoxins, that can inflict severe clinical syndromes, such as septic shock, necrotizing pneumonia, and complicated skin and soft tissue infections.\(^4^3\) Highly diverse and unique virulence genes appear to be characteristics of CA-MRSA that clearly distinguish them from typical HA-MRSA strains. Genomic studies have shown that CA-MRSA strains carry a range of virulence genes that are distinct from those found in other \textit{S. aureus} strains. A research group compared 32 CA-MRSA strains with respect to clonal relatedness and \textit{S. aureus} superantigen toxins.\(^3^5\) As expected, most isolates (81\%) were susceptible to a wide variety of non–β-lactam antimicrobials. Thirty-one of the 32 CA-MRSA isolates were highly related as determined by PFGE and superantigen testing, and were genetically unrelated to HA-MRSA strains. The 31 related CA-MRSA isolates produced either staphylococcal enterotoxin B or enterotoxin C. No isolates produced TSST-1. A study of the MW2 CA-MRSA strain isolated from North Dakota in 1998 identified 18 toxins that were not found in any of five comparative hospital-derived strains.\(^4^4\) The genes \textit{seh} and \textit{seo}, which encode for superantigen enterotoxins H and O, were found in close proximity to the SCC\textit{mec} complex. Enterotoxins H and O have particularly high binding affinities for the major histocompatibility complex type II molecules and were reported only in this CA-MRSA isolate. Of interest, enterotoxin H is produced in disproportionate amounts compared with other superantigens and is involved in acute toxic shock–like syndromes.\(^4^5\)

Another virulence factor specific to CA-MRSA strains is the Panton-Valentine leucocidin (PVL) toxin. This is a bicomponent cytotoxin previously reported to be produced by less than 5\% of \textit{S. aureus} isolates. The toxin is encoded by two genes, \textit{lukS-PV} and \textit{lukF-PV}, which are carried on a bacteriophage that has incorporated itself into the \textit{S. aureus} chromosome. It is capable of destroying human leukocytes and inflicting severe tissue damage. It has been associated with necrotic skin lesions and severe necrotizing pneumonia in both children and adults.\(^4^6\),\(^4^7\) One investigator characterized 14 CA-MRSA strains recovered from patients in France who had been healthy during the 18 months before becoming infected.\(^3^3\) Most patients had skin or soft tissue infections, and two patients had necrotizing pneumonia. The PVL gene and \textit{lukE-lukD} (leucocidin genes) were detected in all 14 isolates. Earlier studies have shown that PVL genes are rarely detected in MRSA isolates associated with hospital infections.\(^4^8\) The authors concluded that the combination of \textit{mecA} and the PVL gene have created a superadaptable \textit{S. aureus} strain capable of spreading rapidly through the community.\(^3^5\)

A recent study investigated the genetic relatedness of five community-acquired \textit{S. aureus} isolates obtained from four consecutive pediatric patients who presented with sepsis syndrome and severe pneumonia over a 3-week period in 2000.\(^3^7\) Two of the patients were infected with three MSSA isolates, whereas the other two were infected with MRSA. The two MRSA strains contained the SCC\textit{mec} IV element that characterizes CA-MRSA isolates. Of interest, all five isolates contained the staphylococcal toxin genes \textit{sea}, \textit{seh}, and \textit{seo} and the PVL genes \textit{lukS-PV} and \textit{lukF-PV}. Analysis with PFGE revealed only one difference among the strains: the two MRSA strains, unlike the MSSA strains, contained two bands reflecting the presence of the SCC\textit{mec} IV element that distinguishes CA-MRSA from HA-MSSA. According to the researchers, the genetic relatedness of these isolates suggests that CA-MRSA infections arose from MSSA isolates that successfully incorporated the SCC\textit{mec} IV element.

A small town in western Switzerland was the site of a large outbreak of skin infections from September 1999–2000.\(^4^3\) Twenty-two students from a single third-grade classroom had 13 episodes of skin infections that included furuncles, abscesses, and cellulitis. Two patients were hospitalized, and the rest were treated with systemic antibiotics, with or without surgical drainage. All cultures grew MSSA. One of three clones isolated was positive for PVL. This clone
was associated with nine persons, consisting of classmates, teachers, and family members who were either nasal carriers or infected. Nasal carriage was detected only after six students and three relatives were noted to have relapsing episodes of skin infections over a 13-month period. The authors suggested that PVL-positive \textit{S. aureus} may easily spread between persons in close contact, infecting otherwise healthy children and adults. Because of their high virulence capability, skin infections can rapidly progress to severe necrotizing pneumonia with a high mortality rate.

Another investigation described the clonal distribution of PVL-carrying MRSA strains and their association with skin and soft tissue infections in the San Francisco Bay area. A total of 671 isolates collected from inpatients and outpatients during 1997–2002 were evaluated for strain relatedness and virulence factors. Approximately 70\% of PVL-carrying MRSA strains were isolated from jail inmates and patients receiving surgical treatment in outpatient settings specializing in skin and soft tissue infections. Although as many as nine clonal types were identified, the vast majority (88.5\%) of PVL-carrying MRSA belonged to only two clonal groups. Of interest, these two clonal groups also carried the SCC\textit{mec} IV resistance element and were more likely to be associated (p<0.0001) with skin and soft tissue infections than any other infection site. Overall, the data suggest that most CA-MRSA strains probably arose from successful MSSA strains that incorporated a variety of specific virulence factors, thus improving their ability to colonize and cause infection.

**Outbreaks**

Outbreaks of CA-MRSA were first described in the early 1980s. In the late 1990s, increasing reports began to emerge. Unfortunately, CA-MRSA is now a common community-based pathogen. It has demonstrated great geographic diversity, with outbreaks reported in the Unites States, Canada, Europe, Finland, Saudi Arabia, India, Asia, Australia, and New Zealand. The strains involved in these outbreaks have in common the \textit{mec} type IV cassette but are genetically distinct from one another. Outbreaks of CA-MRSA are typically characterized by clusters of skin and soft tissue infections among persons who have close contact with one another. Most concerning is that persons infected are otherwise healthy individuals with no known risk factors for infection by drug-resistant bacteria.

The first report of CA-MRSA came from a large urban Michigan hospital in 1982. It described community-associated \textit{S. aureus} infections in 24 intravenous drug users and 16 nonusers. All persons infected were otherwise healthy individuals with no risk factors for MRSA colonization. On the basis of PFGE data, investigators proposed that MRSA infection arose in the community as well as in the hospital and had the potential to disseminate in both settings. It has been subsequently noted that intravenous drug users have frequent contact with health care institutions, and the strains they are colonized with may have originated in the hospital.

During the 1980s and through the mid 1990s, CA-MRSA infections were infrequent in populations other than intravenous drug users. However, in October 2001, the Mississippi State Department of Health notified the CDC that 31 prison inmates had acquired MRSA skin or soft tissue infections. This number was unexpectedly high for a non–health care setting. The next year, inmates in the Los Angeles County Jail began reporting a high frequency of spider bites. Further investigation revealed that these so-called “bites” were actually MRSA skin infections. Also that same year, the Los Angeles County Department of Health Services investigated cases of invasive MRSA infection in two athletes on the same team who were hospitalized. In addition, outbreaks among men having sex with men were also reported. In 2003, researchers described an outbreak of MRSA skin infections among a military beneficiary population. An additional study reported CA-MRSA infections in roommates sharing instruments used for plucking and trimming hair. These reports of invasive MRSA skin infections emphasized the potential for rapid spread of the organism within the community among individuals who may acquire it through close personal contact.

Children are also vulnerable to CA-MRSA. One of the first major reports of invasive CA-MRSA infections occurred in Minnesota and North Dakota between 1997 and 1999. This outbreak was associated with four pediatric deaths from infections that progressed to pneumonia and sepsis syndrome.

Humans are not the only hosts for CA-MRSA, which has raised concern as a possible emerging zoonotic and veterinary disease. A report in 2003 discussed a common clonal \textit{mec} type IV
strain isolated from horses and their caretakers at an equine farm in Ontario. Horses are not known to harbor *S. aureus* naturally. Based on timing of isolation, subtyping, and evaluation of animal and human contact, combinations of horse-human, human-horse, or horse-horse transmission were suspected.74

Few surveillance studies have characterized how this pathogen develops within the community. One research group conducted *S. aureus* surveillance during an outbreak in a rural Alaska village that is not connected to other villages by roads.46 The researchers used PFGE and PVL production to identify the relatedness of the isolates. They discovered that patients living in a community associated with an outbreak had received more antibiotic courses during the past 12 months than patients in a nonoutbreak setting (p=0.01). Also, individuals involved in the outbreak were more likely to use a sauna that was known to be colonized by MRSA. The investigators determined that the likely cause for MRSA colonization was the sauna's plywood, which was semiporous and had an irregular shape that allowed for biofilm formation attachment and hence MRSA survival at high temperatures.

Due to the rise in CA-MRSA outbreaks, the CDC has published recommendations to prevent the spread of MRSA among persons living in the same household.30 These recommendations include covering infections that drain or produce pus, washing hands frequently, avoiding the sharing of personal items (e.g., towels, washcloth, razor, clothing, or uniforms), washing soiled linens and clothes with hot water, and drying clothes in a hot dryer rather than air-drying.

### Treatment Options

Although the epidemiology of CA-MRSA has been widely explored, therapeutic management of this infection has not been well studied and is not well established. Infections caused by CA-MRSA fall into a broad spectrum, ranging from uncomplicated skin and soft tissue infections, which can be treated in outpatient settings, to severe sepsis and toxic shock syndrome, which require hospitalization and aggressive treatment. Because CA-MRSA strains tend to be susceptible to a wide variety of non-β-lactam antibiotics, it would seem that several treatment options are available (Table 2). However, most potential treatments have not been tested clinically, and their efficacy is therefore unknown. Moreover, there is great uncertainty about development of resistance. Researchers have expressed renewed interest in the use of clindamycin, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX) in treating MRSA infections, as these drugs generally have activity against CA-MRSA (Table 3).33, 40, 75 For severe infections requiring hospitalization together with intravenous antibiotics, vancomycin and newer agents, such as linezolid, quinupristin-dalfopristin, and daptomycin, can be feasible options.

Clindamycin remains a viable treatment option for CA-MRSA, as it demonstrates in vitro susceptibility to most MRSA isolates. However, inducible resistance and treatment failure have been reported.18, 77 The disk diffusion (D-test) method can detect *S. aureus* isolates with inducible macrolide-lincosamide-streptogramin B (iMLSB) resistance.78 However, this is a cumber-

### Table 2. Antimicrobial Agents with Potential for Use in Treating Methicillin-Resistant *Staphylococcus aureus*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Traditional Regimens</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>300–450 mg p.o. q6h 600–900 mg i.v. q8h</td>
<td>Caution is warranted due to iMLSB resistance</td>
</tr>
<tr>
<td>Daptomycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 mg/kg i.v. q24h</td>
<td>Approved for use in complicated skin and soft tissue infections</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg i.v. or p.o. q12h</td>
<td>Limited clinical data exists in treating MRSA infections</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg i.v. or p.o. q12h</td>
<td>Approved for complicated skin and soft tissue infections, concern for overuse and resistance due to oral availability</td>
</tr>
<tr>
<td>Quinupristin-dalfopristin</td>
<td>7.5 mg/kg i.v. q12h</td>
<td>Caution is warranted due to iMLSB resistance and poor tolerability</td>
</tr>
<tr>
<td>TMP-SMX&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160 mg p.o. q12h&lt;sup&gt;b&lt;/sup&gt; 2.5 mg/kg i.v. q12h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Caution is warranted in sulfa-allergic patients</td>
</tr>
<tr>
<td>Vancomycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 g i.v. q12h</td>
<td>Targeted concentrations are controversial</td>
</tr>
</tbody>
</table>

iMLSB = inducible macrolide-lincosamide-streptogramin B; MRSA = methicillin-resistant *Staphylococcus aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.

<sup>a</sup>Dosage should be adjusted for renal function.

<sup>b</sup>Dosage is based on the trimethoprim component.
some procedure, and hospital laboratories have had difficulty applying this method to each S. aureus isolate. The D-test is conducted with erythromycin-clindamycin disk pairs placed by hand on an agar dish streaked with the isolate in question. After incubation, zone diameters are measured, and significant ingrowth within a zone up to the edge of the disk is considered constitutive (already present) resistance. In contrast, flattening or blunting of the clindamycin zone (D shape) indicates inducible resistance (Figure 2).78

Inducible isolates (those with positive results on the D-test) are a source of concern because they may have a heightened rate of mutations, which would enable them to develop constitutive resistance to clindamycin during therapy. One clinical laboratory screened over 150 S. aureus isolates for iMLS\textsubscript{B} resistance in erythromycin-resistant and clindamycin-susceptible clinical S. aureus isolates and found 56% of isolates to have inducible resistance by the D-test.76 Little information is available to characterize iMLS\textsubscript{B} resistance in CA-MRSA. However, a recent investigation examined 85 clinical MRSA isolates for iMLSB resistance.75 Isolates were evaluated based on CDC definition and molecular typing. In SCC\textit{mec} type II isolates (HA-MRSA), 50% of strains harbored iMLS\textsubscript{B} resistance, whereas only 17% of SCC\textit{mec} type IV isolates (CA-MRSA) had this type of resistance pattern. The number of CA-MRSA strains worldwide harboring this inducible type of resistance is unknown. It is therefore not recommended to use clindamycin to treat MRSA infections unless the appropriate D-test for iMLS\textsubscript{B} resistance is conducted on the specified isolate according to the guidelines of the National Committee for Clinical Laboratory Standards.79, 80

Trimethoprim-sulfamethoxazole is another antibiotic with potential for treatment of CA-MRSA. However, limited clinical studies and patient cases have found TMP-SMX to be useful in treating MRSA infections. The reported rate of TMP-SMX resistance in S. aureus is highly variable, but most CA-MRSA strains appear to be susceptible. The sulfa moiety of TMP-SMX, sulfamethoxazole, is bacteriostatic, whereas the trimethoprim component blocks dihydrofolate reductase, thus inhibiting production of metabolically active folic acid. When both agents are used together, TMP-SMX appears to produce

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**Table 3. Phenotypic Expression of SCC\textit{mec} Types II, III, and IV Isolates**

<table>
<thead>
<tr>
<th>Agent</th>
<th>\textit{mec} IV (n=55)</th>
<th>\textit{mec} II and III (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin\textsuperscript{75}</td>
<td>0.0625–1.0</td>
<td>0.0625–2.0</td>
</tr>
<tr>
<td>Clindamycin\textsuperscript{73}</td>
<td>0.06–0.125.0</td>
<td>0.125 to &gt; 32.0</td>
</tr>
<tr>
<td>Linezolid\textsuperscript{73}</td>
<td>1.0–4.0</td>
<td>1.0–4.0</td>
</tr>
<tr>
<td>Erythromycin\textsuperscript{38, 41, 75}</td>
<td>0.5–32.0</td>
<td>&gt; 32.0 to &gt; 512.0</td>
</tr>
<tr>
<td>Doxycycline\textsuperscript{38, 75}</td>
<td>0.125–8.0</td>
<td>0.25 to &gt; 512.0</td>
</tr>
<tr>
<td>Oxacillin\textsuperscript{38, 41, 75}</td>
<td>4–64.0</td>
<td>32.0 to &gt; 512.0</td>
</tr>
<tr>
<td>Vancomycin\textsuperscript{75}</td>
<td>1.0–4.0</td>
<td>2.0–8.0</td>
</tr>
<tr>
<td>TMP-SMX\textsuperscript{75}</td>
<td>0.06/1.2 to 1.0/20.0</td>
<td>0.06/1.5 to &gt; 32.0/640.0</td>
</tr>
<tr>
<td>Imipenem\textsuperscript{38, 41, 75}</td>
<td>0.063–2.0</td>
<td>0.5–128.0</td>
</tr>
<tr>
<td>Cefaclor\textsuperscript{75}</td>
<td>64–128.0</td>
<td>&gt; 128.0</td>
</tr>
<tr>
<td>Ciprofloxacin\textsuperscript{75}</td>
<td>0.5–64.0</td>
<td>2.0 to &gt; 64.0</td>
</tr>
</tbody>
</table>


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**Figure 2.** Double disk diffusion test (D-test) demonstrating erythromycin induction of clindamycin resistance. Blunting of the clindamycin inhibition zone produces a D shape as indicated.
a bactericidal effect against most isolates. One study investigated the use of TMP-SMX in MRSA bacteremia in intravenous drug users. The investigators reported that TMP-SMX may be considered as an alternative to vancomycin in selected cases of MRSA infection; however, treatment failures were reported. More recent studies report allergic reactions to sulfonamide antibiotics in approximately 10% of patients; therefore, caution is warranted in this patient population. The development of resistance and the therapeutic use of TMP-SMX in MRSA have not been fully established. However, a small retrospective study suggested that prompt incision and drainage, followed by a 2–3-week course of TMP-SMX in combination with rifampin was an effective treatment option for cutaneous infections caused by CA-MRSA. Although in vitro testing revealed susceptibility to TMP-SMX and rifampin, infection recurred in a patient treated with TMP-SMX alone compared with the combination of TMP-SMX and rifampin. Resistance to rifampin develops rapidly when it is given as monotherapy. Therefore, rifampin should be considered only when given in combination.

Minocycline is a tetracycline antibiotic that has been used in the past for the treatment of MRSA. Doxycycline, another tetracycline compound, has a similar susceptibility profile. Although these agents have been used clinically, limited published data are available on the use of tetracyclines in the treatment of MRSA; therefore, the efficacy of doxycycline and minocycline in the treatment of MRSA have not been established.

Caution is warranted in using fluoroquinolones to treat MRSA infections. Historically, overuse of fluoroquinolones has been associated with MRSA selection. Moreover, use of fluoroquinolones for treating MRSA infections is correlated with rapid acquisition of fluoroquinolone-resistant MRSA. The newer fluoroquinolones may have a role in the treatment of complicated skin and soft tissue infections, especially in patients who are allergic to penicillin. More clinical studies are needed before a formal recommendation can be made.

Until the arrival of newer agents, most clinicians would agree that vancomycin, a glycopeptide antibiotic, is the drug of choice for treating serious MRSA infections. However, recent reports have described glycopeptide–intermediately susceptible S. aureus (GISA) and heteroresistant GISA. Vancomycin-resistant S. aureus (VRSA) has been identified in Michigan, Pennsylvania, and New York. These organisms are often not responsive to vancomycin.

Although vancomycin has been proved as a safe and effective treatment option for MRSA, increasing reports document glycopeptide resistance. These reports have heightened awareness of the need for newer and more effective agents. The relationship between CA-MRSA and heteroresistant GISA has not yet been described.

Linezolid, which in 2000 became the first oxazolidinone to be approved by the Food and Drug Administration (FDA), has good penetration into skin and soft tissue infections and is available in an oral formulation. Although it is considered a bacteriostatic agent, linezolid has demonstrated effectiveness in skin and soft tissue infections, bacteremia, and pneumonia caused by gram-positive bacteria. Linezolid shows activity against MRSA, although S. aureus resistance has been reported. Researchers have expressed concern that linezolid is being overused.

Quinupristin-dalfopristin is a streptogramin combination product with a gram-positive spectrum of activity that includes MRSA. Although the FDA has not approved quinupristin-dalfopristin for use in MRSA infections, the product is approved for use in complicated skin and soft tissue infections. The poor tolerability profile of quinupristin-dalfopristin limits its use. Moreover, S. aureus may demonstrate inducible or constitutive MLSB. Cross-resistance to macrolides, lincosamides, and streptogramin B-type antibiotics by methylation of the ribosomal target is the most common mechanism of S. aureus resistance to streptogramin combination products. If inducible resistance is present, quinupristin remains active because it is not an inducer of the methylase. However, if constitutive, quinupristin is inactive, and quinupristin-dalfopristin becomes bacteriostatic rather than bactericidal. Thus, loss of activity may occur. This process has been demonstrated both in vitro and in vivo.

Daptomycin is a novel lipopeptide antibiotic approved by the FDA in 2003 for treatment of complicated skin and soft tissue infections, including those caused by MRSA. This drug has received much interest because of its activity against multidrug-resistant gram-positive bacteria, especially MRSA. Daptomycin has demonstrated rapid bactericidal (99.9% kill) activity in several in vitro and animal pharmacodynamic studies.
viable treatment option, its role in the treatment of CA-MRSA has not yet been fully established.

Overall, there appear to be several antimicrobial therapeutic options for treating CA-MRSA infections. However, as stated above, no definitive studies have tested these options clinically. Since a number of toxins are associated with CA-MRSA, research is needed to address the appropriate selection of antimicrobial agents with regard to the threat posed by toxin release.

Nonantimicrobial Options

For noncomplicated S. aureus skin and soft tissue abscesses, incision and drainage therapy, without the use of antibiotics, is generally adequate. One retrospective chart review addressed 69 children with skin and soft tissue abscesses caused by culture-proved CA-MRSA. Treatment consisted of drainage and wound packing. All children received antibiotics; however, only 7% of patients were prescribed an antibiotic to which their CA-MRSA isolate was susceptible (treatment began before culture results were known). The investigators addressed the status of each infection at 2–6 months after presentation. They concluded that incision and drainage, without adjunctive antibiotic therapy, were effective for CA-MRSA skin and soft tissue abscesses with a diameter of less than 5 cm in immunocompetent children.

Conclusion

Evidence suggests that CA-MRSA—the newest staphylococcal threat—will be increasingly prevalent in the near future. Moreover, although most strains are now susceptible to multiple non-β-lactam antibiotics, this may change due to exposure to multiple antimicrobials in various settings. Epidemiologic studies are needed to specify the patient populations likely to harbor this pathogen. Alternative treatment options to β-lactams must be assessed under investigational trial conditions before specific treatment guidelines can be recommended.

References