

# Evidence based approach to the treatment of community-associated methicillin-resistant *Staphylococcus aureus*

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**Abstract:** Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have increased dramatically over the last two decades. The types of infections can range from complicated skin and skin structure infections (cSSSI) to pneumonia and endocarditis. Oral antimicrobial therapy, such as trimethoprim-sulfamethoxazole, clindamycin, long-acting tetracyclines, or linezolid may provide enhanced benefit to those with uncomplicated cutaneous lesions when used in conjunction with incision and drainage in an outpatient setting. However, resistance, susceptibilities, patient-specific circumstances, and adverse effects can impact a healthcare professional's choice of antibiotics. In patients with complicated infections requiring hospitalization or parenteral treatment, vancomycin remains the drug of choice, even though increased resistance and decreased efficacy have crept into clinical practice. Linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline are alternative intravenous agents for the treatment of CA-MRSA. Investigational agents such as dalbavancin, telavancin, oritavancin, iclaprim, ceftobiprole, ceftaroline, and others may expand our therapeutic armamentarium for the treatment of infections caused by CA-MRSA in the future.

**Keywords:** community-associated methicillin-resistant *Staphylococcus aureus*, CA-MRSA, complicated skin and skin structure infections, cSSSI, Panton-Valentine leukocidin, PVL, *in vitro* activity

## Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961 soon after the introduction of methicillin, the first beta-lactamase resistant penicillin.<sup>1</sup> MRSA soon emerged as a common nosocomial organism infecting patients in hospitals and intensive care units around the world.<sup>2</sup> Prior to the 1990s, MRSA was almost exclusively a nosocomial organism. During the 1990s, MRSA began to infect patients with no known contact to healthcare organizations and who were otherwise healthy. These types of MRSA were noted to be genetically unique and soon began to be referred to as community-associated MRSA (CA-MRSA).<sup>3</sup> Understanding this complex pathogen has now become a primary focus for many practitioners as illness related to CA-MRSA can be life-threatening. Despite major medical advances, MRSA continues to cause significant disease.

## Epidemiology

CA-MRSA differs from healthcare-associated MRSA (HA-MRSA) genetically and epidemiologically. Methicillin resistance is mediated by the *mecA* gene which resides on the staphylococcal cassette chromosome *mec* (SCC*mec*).

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encodes for the penicillin-binding protein 2a (PBP2a) resulting in the inability of methicillin to bind to *S. aureus*.<sup>4</sup> CA-MRSA strains predominantly carry SCCmec type IV; however, SCCmec type V has also been identified in these strains.<sup>3</sup> These SCCmec genes are generally smaller than those genes found in HA-MRSA strains allowing for more rapid spread. In addition, these genes only confer resistance to methicillin and other beta-lactams while maintaining susceptibility to narrow-spectrum antibiotics such as tetracyclines, trimethoprim-sulfamethoxazole (TMP-SMX), and clindamycin. CA-MRSA, like HA-MRSA, remains susceptible to vancomycin, linezolid, daptomycin, and quinupristin/dalfopristin (Q/D).<sup>3,5</sup> One distinct feature of CA-MRSA is its ability to carry the gene encoding for Panton-Valentine leukocidin (PVL), a deadly exotoxin. This exotoxin is the key feature associated with CA-MRSA that causes necrotizing infections of the soft tissue as well as necrotizing pneumonias.<sup>2,6</sup> CA-MRSA did not originate from the hospital setting. Rather, it appears as though methicillin-susceptible *S. aureus* (MSSA) acquired the SCCmec gene producing a new genetic variant with two distinct clones occurring in the United States, USA300 and USA400. USA300 more frequently contains PVL genes and is now considered a major cause of necrotizing soft tissue infections.<sup>2,3</sup> The Centers for Disease Control and Prevention (CDC) define CA-MRSA infections as those seen in people who meet the following criteria:<sup>7</sup>

- Diagnosis of MRSA made in the outpatient setting or by a positive culture for MRSA within 48 hours of admission to the hospital.
- No medical history of MRSA infection or colonization.
- No medical history in the past year of:
  - Hospitalization
  - Admission to a nursing home, skilled nursing facility, or hospice
  - Dialysis
  - Surgery
- No permanent indwelling catheters or medical devices that pass through the skin into the body.

One important development with CA-MRSA is the observation of these strains among patients in the healthcare setting. Because most patients acquire CA-MRSA from the community and because these infections can be quite serious, many may require hospitalization which can potentially transmit these strains to other inpatients.<sup>8</sup> A review of 352 patients within the same institution with HA-MRSA found that CA-MRSA had become the most common cause of HA-MRSA. When MRSA

strains were phenotyped, it was noted that the SCCmec IV gene increased from 17% to 56% in a 5-year period.<sup>9</sup>

## Clinical presentation and risk factors

Skin and skin structures are the predominant sites of infection of CA-MRSA, furuncles being the most common type reported. CA-MRSA can also cause cellulitis, deep tissue abscesses, and in more serious cases, necrotizing fasciitis and osteomyelitis. CA-MRSA may be associated with localized necrosis caused by the PVL gene. Often, patients experience sudden onset of a raised red lesion with central necrosis resembling a spider bite.<sup>10</sup> This can be confusing to both patients and physicians especially in areas of the United States where spider bites leading to cellulitis are uncommon. Presentations of this sort may be indicative of CA-MRSA infection as necrosis is a common feature of CA-MRSA both in skin and skin structure infections (SSSI) and lung infections. Pneumonia associated with PVL-producing CA-MRSA generally occurs as a necrotizing pneumonia with a high mortality rate.<sup>11</sup> More cases of CA-MRSA necrotizing pneumonia have been seen in young, otherwise healthy children and adults.<sup>3</sup> CA-MRSA necrotizing pneumonias are often seen following or concomitantly with an influenza-like illness. Patients often present with hemoptysis and a rapid onset of respiratory decompensation. In addition, patients appear septic with symptoms of hypotension, tachycardia, tachypnea, fever, and may often develop leukopenia.<sup>12</sup>

CA-MRSA has been reported to cause serious outbreaks of infections in certain populations including personnel in competitive team sports, Alaskan natives, Native Americans, correctional facility inmates, children, and military personnel.<sup>13</sup> Transmission of CA-MRSA is predominantly through direct contact with an infected person. However, data from CA-MRSA outbreaks indicate that fomites, or inanimate objects, can also facilitate the spread of CA-MRSA.<sup>14</sup> One notable incident occurred in 2003 when 8 MRSA infections developed in 5 professional football players. The MRSA clone was identified as a PVL-containing CA-MRSA which appeared to have been transmitted via close contact with infected abrasions and equipment.<sup>15</sup>

Risk factors for the acquisition of CA-MRSA are difficult to identify. It seems evident that close physical contact plays an important role; however, beyond that there are few well-designed studies that analyze risk factors.<sup>16</sup> Risk factors that most healthcare professionals agree on are listed in Table 1.<sup>2,3,16,17</sup>

**Table 1** Risk factors for infection with community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)<sup>2,3,16,17</sup>


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Children < 2 years old
Children attending daycare centers
Injection drug users
Military personnel
Inmates
Homeless persons
Those in crowded living conditions
Household contact with a person known to be colonized and/or infected with MRSA
Men who have sex with men
HIV-infected persons
Athletes of contact sports
Adults ≥ 65 years old
Poor personal hygiene
History of colonization or recent infection with CA-MRSA
Recent influenza-like illness or pneumonia
African Americans
Pacific Islanders
Native Americans

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### *In vitro* activity

The assessment of *in vitro* activity of a given compound against select clinically significant pathogens has always been an early component in the development of new antimicrobials. Once the *in vitro* activity has been well defined, additional drug-specific data follow including basic pharmacokinetic parameters, human safety data, and ultimately, human outcome data. Specific to *S. aureus*, and more specifically MRSA, the differentiation into CA-MRSA and HA-MRSA subsets is a relatively new concept. Consequently, *in vitro* data for MRSA is not often subdivided into CA-MRSA or HA-MRSA. For the assessment of *in vitro* activity of various drugs against CA-MRSA, data are currently limited but accumulating. While it is unclear whether the genotypic identification of a given strain is clinically significant once susceptibility testing has been performed, it is clear that the susceptibility patterns differ based on the origin of the strain.

Use of the term CA-MRSA with regard to *in vitro* susceptibilities in contemporary literature generally refers to one of two issues. First, it may refer to strains which are consistent with the CDC definition as previously described.<sup>7</sup> Alternatively, the strain may have been genotyped and specifically identified to be a community-associated strain (ie, USA300, USA400, etc). For the purpose of this review, either determination has been considered sufficient to access *in vitro* activity. The *in vitro* activities of several antimicrobial agents

have been evaluated against CA-MRSA and are summarized in Table 2. Included in this table are enteral and parenteral agents, both traditional and contemporary, which are commonly associated in the treatment of CA-MRSA infections.

### Treatment options

Current guidelines recommend incision and drainage of uncomplicated-SSSI caused by CA-MRSA.<sup>18</sup> Many patients can be treated with surgical drainage; however, antimicrobial therapy may provide additional benefits to the patient.<sup>19</sup> Factors that may persuade a clinician to incorporate antimicrobial therapy into the treatment plan include: presence of cellulitis, swift enhancement of the SSSI, systemic illness, immunocompromised patient, age of the patient, abscess location that is difficult to access, and inappropriate response to the initial incision and drainage.<sup>20</sup> Multiple non-beta-lactam oral antibiotics are available for outpatient therapy including: TMP-SMX, clindamycin, long-acting tetracyclines, and linezolid.

### Enteral treatment options

#### Trimethoprim-sulfamethoxazole (TMP-SMX)

TMP-SMX (Septra®; King Pharmaceuticals, Bristol, TN, USA) is not approved by the Food and Drug Administration (FDA) for the treatment of staphylococcal infections.<sup>21</sup> However, TMP-SMX has shown *in vitro* bactericidal properties against strains of CA-MRSA.<sup>22</sup> The evidence to support the efficacy of TMP-SMX came from a randomized, controlled clinical trial comparing it with vancomycin in intravenous drug abusers with various *S. aureus* infections, including bacteremia, endocarditis, osteomyelitis, and SSSI. Vancomycin demonstrated superiority in the *S. aureus* treatment arm; however, the authors concluded that TMP-SMX is a viable treatment option in select cases of MRSA.<sup>23</sup> In another study conducted in an ambulatory clinic, the increased use of TMP-SMX correlated with improved clinical outcomes in patients with SSSI.<sup>24</sup> While data are lacking, TMP-SMX is widely used in clinical practice.

#### Clindamycin

Clindamycin (Cleocin®; Pfizer, Inc, New York, NY, USA) is another common antibiotic used to treat CA-MRSA.<sup>25</sup> It has a potential protective effect against toxins, including the PVL toxin.<sup>26</sup> There is a potential for resistance with high-inoculum infections via efflux or ribosomal alterations. A disk diffusion antibiotic assay (D-test) identifies inducible clindamycin

**Table 2** *In vitro* activity of select antimicrobial agents against community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)

Antimicrobial agent	CA-MRSA					Reference
	No. of isolates	% susceptible	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	MIC range (µg/mL)	
Clindamycin	152	100	≤0.25	≤0.25	≤0.25	Sader et al 2008 <sup>76</sup>
	157	97	na	na	na	King et al 2006 <sup>89</sup>
	127	96	na	na	na	Huang et al 2006 <sup>88</sup>
	348	93	na	na	na	Naimi et al 2001 <sup>90</sup>
	200	92	0.25	0.5	0.03 to >32	Tsuji et al 2007 <sup>91</sup>
	23	91	na	0.13	0.06–64	Johnson et al 2006 <sup>49</sup>
	1301	87	na	na	na	Fridkin et al 2005 <sup>87</sup>
	191	80.6	na	na	na	Crum et al 2006 <sup>86</sup>
	1989	34.2	>8	>8	≤0.06 to >8	Mendes et al 2008 <sup>45</sup>
Daptomycin	23	100	na	0.25	0.12–0.25	Johnson et al 2006 <sup>49</sup>
	60	100	0.25	0.25	0.12–0.5	Saravolatz et al 2007 <sup>44</sup>
	152	100	0.25	0.5	0.25–1	Sader et al 2008 <sup>76</sup>
	200	100	0.5	1	0.13–2	Tsuji et al 2007 <sup>91</sup>
Erythromycin	318	64	na	na	na	Naimi et al 2001 <sup>90</sup>
	185	20	na	na	na	Crum et al 2006 <sup>86</sup>
	1236	18	na	na	na	Fridkin et al 2005 <sup>87</sup>
	157	13	na	na	na	King et al 2006 <sup>89</sup>
	127	7	na	na	na	Huang et al 2006 <sup>88</sup>
	1989	5.7	>8	>8	≤0.06 to >8	Mendes et al 2008 <sup>45</sup>
	200	4	>16	>16	0.13 to >16	Tsuji et al 2007 <sup>91</sup>
	152	1.3	>8	>8	2 to >8	Sader et al 2008 <sup>76</sup>
23	0	na	64	2.0–64	Johnson et al 2006 <sup>49</sup>	
<b>Fluoroquinolones</b>						
Ciprofloxacin	325	93	na	na	na	Naimi et al 2001 <sup>90</sup>
	23	83	na	16	0.12–64	Johnson et al 2006 <sup>49</sup>
	861	65	na	na	na	Fridkin et al 2005 <sup>87</sup>
	127	53	na	na	na	Huang et al 2006 <sup>88</sup>
	1989	15.1	>4	>4	≤0.03 to >4	Mendes et al 2008 <sup>45</sup>
Levofloxacin	152	92.8	0.25	0.5	≤0.12 to >4	Sader et al 2008 <sup>76</sup>
	157	90	na	na	na	King et al 2006 <sup>89</sup>
	23	87	na	4	0.06–32	Johnson et al 2006 <sup>49</sup>
	1989	15.5	>4	>4	0.06 to >4	Mendes et al 2008 <sup>45</sup>
	200	12	>16	>16	0.125 to >16	Tsuji et al 2007 <sup>91</sup>
Moxifloxacin	23	96	na	1	0.03–4	Johnson et al 2006 <sup>49</sup>
Linezolid	23	100	na	2	2.0–2.0	Johnson et al 2006 <sup>49</sup>
	200	100	2	4	0.24–4	Tsuji et al 2007 <sup>91</sup>
	60	100	2	2	2	Saravolatz et al 2007 <sup>44</sup>
	152	100	2	2	1–2.0	Sader et al 2008 <sup>76</sup>
	1989	>99.9	2	2	≤0.06–16	Mendes et al 2008 <sup>45</sup>
	25	96	na	na	na	Fridkin et al 2005 <sup>87</sup>
Quinupristin–dalfopristin	60	100	0.25	0.5	0.25–1	Saravolatz et al 2007 <sup>44</sup>
	1989	>99.9	0.5	1	≤0.25–2	Mendes et al 2008 <sup>45</sup>
Rifampin	23	100	na	0.03	0.03–0.03	Johnson et al 2006 <sup>49</sup>
	127	100	na	na	na	Huang et al 2006 <sup>88</sup>

(Continued)

Table 2 (Continued)

	157	99	na	na	na	King et al 2006 <sup>89</sup>
	211	99	na	na	na	Naimi et al 2001 <sup>90</sup>
	887	98	na	na	na	Fridkin et al 2005 <sup>87</sup>
	1989	93.7	≤0.5	≤0.5	≤0.5->2	Mendes et al 2008 <sup>45</sup>
<b>Tetracyclines</b>						
Doxycycline	200	86	0.5	8	0.06->16	Tsuji et al 2007 <sup>91</sup>
Minocycline	166	100	na	na	na	Crum et al 2006 <sup>86</sup>
Tetracycline	249	95	na	na	na	Naimi et al 2001 <sup>90</sup>
	152	94.7	≤0.5	≤0.5	≤0.5->16	Sader et al 2008 <sup>76</sup>
	23	91	na	0.5	0.13-32	Johnson et al 2006 <sup>49</sup>
	1063	88	na	na	na	Fridkin et al 2005 <sup>87</sup>
	127	80	na	na	na	Huang et al 2006 <sup>88</sup>
	1989	9.1	≤2	4	≤2->8	Mendes et al 2008 <sup>45</sup>
Tigecycline	76	100	na	na	na	McAlesse et al 2005 <sup>60</sup>
	1989	98.2-100	≤0.12	0.5	≤0.12-0.5	Mendes et al 2008 <sup>45</sup>
Trimethoprim-sulfamethoxazole	23	100	na	0.06/1.19	0.03/0.59-0.5/9.5	Johnson et al 2006 <sup>49</sup>
	152	100	≤0.25	≤0.25	≤0.25	Sader et al 2008 <sup>76</sup>
	157	100	na	na	na	King et al 2006 <sup>89</sup>
	127	100	na	na	na	Huang et al 2006 <sup>88</sup>
	186	98.3	na	na	na	Crum et al 2006 <sup>86</sup>
	60	98	0.06/1.19	0.5/9.5	0.03/32-0.59/608	Saravolatz et al 2007 <sup>44</sup>
	342	97	na	na	na	Naimi et al 2001 <sup>90</sup>
	1218	97	na	na	na	Fridkin et al 2005 <sup>87</sup>
	200	92	0.25	1	0.03->8	Tsuji et al 2007 <sup>91</sup>
	1989	91.1	≤0.5	≤0.5	≤0.5->2	Mendes et al 2008 <sup>45</sup>
Vancomycin <sup>a</sup>	23	100	na	0.5	0.25-0.5	Johnson et al 2006 <sup>49</sup>
	1989	100	1	1	0.25-4	Mendes et al 2008 <sup>45</sup>
	60	100	0.5	0.5	0.25-1	Saravolatz et al 2007 <sup>44</sup>
	152	100	1	1	0.5-2	Sader et al 2008 <sup>76</sup>
	157	100	na	na	na	King et al 2006 <sup>89</sup>
	1345	100	na	na	na	Fridkin et al 2005 <sup>87</sup>
	127	100	na	na	na	Huang et al 2006 <sup>88</sup>
	343	100	na	na	na	Naimi et al 2001 <sup>90</sup>
	200	100	2	2	0.5-2	Tsuji et al 2007 <sup>91</sup>

<sup>a</sup>Not all vancomycin data are reflective of Clinical and Laboratory Standards Institute breakpoint changes made in 2006 specific to *Staphylococcus aureus* and may overestimate susceptibility.

**Abbreviation:** na, not available.

resistance in erythromycin-resistant, clindamycin-susceptible *S. aureus* isolates.<sup>27</sup> While the rate of resistance to clindamycin continues to be low in CA-MRSA, the frequency of inducible resistance is variable and unknown.<sup>28</sup> Therefore, if confirmatory D-testing is not available, clindamycin should not be used to treat erythromycin-resistant CA-MRSA.

## Tetracyclines

Doxycycline (Vibramycin<sup>®</sup>; Pfizer, Inc, New York, NY, USA) and minocycline (Minocin<sup>®</sup>; Wyeth Pharmaceuticals,

Philadelphia, PA, USA) can also be effective in treating CA-MRSA SSSI.<sup>29,30</sup> Although there are limited published data, the long-acting tetracyclines appear to be good treatment options in most tetracycline-susceptible MRSA SSSI.<sup>31</sup> Most laboratories in the United States test *S. aureus* for susceptibility to tetracycline (Sumycin<sup>®</sup>; Par Pharmaceuticals, Spring Valley, NY, USA) and not doxycycline or minocycline.<sup>32</sup> The use of tetracycline as a surrogate may overestimate the prevalence of resistance to doxycycline or minocycline since there are two different



genes that confer resistance, *tetM* and *tetK*. *TetK* confers resistance to tetracycline, while *tetM* confers resistance to all agents in the class. *TetK* has been the predominant gene associated with resistant isolates of MRSA in the community, which points towards the continued use and effectiveness of doxycycline and minocycline.<sup>33</sup>

## Linezolid

Linezolid (Zyvox®; Pfizer, Inc, New York, NY, USA) may be a reasonable alternative following failure of treatment or allergic reactions.<sup>34</sup> It is a bacteriostatic antimicrobial approved to treat MRSA complicated-SSSI (cSSSI). Controlled trials with linezolid versus vancomycin determined them to be comparable in treatment of MRSA cSSSI.<sup>35</sup> Though resistance to linezolid is rare, the possibility of resistance has emerged with its increased use.<sup>36</sup> Similar to clindamycin, linezolid also suppresses the PVL toxin in CA-MRSA. This may prove beneficial in severe human infections with necrosis.<sup>37</sup>

## Other antimicrobials

Rifampin (Rifadin®; Sanofi-Aventis, Bridgewater, NJ, USA) should never be used as a single agent for the treatment of MRSA SSSI because of the rapid resistance that can develop in *S. aureus*.<sup>38,39</sup> Rifampin can be used in combination with other antimicrobial agents for potential eradication enhancement, but there is lack of evidence through studies, available for the benefit.<sup>40</sup>

Due to the relative ease of *S. aureus* in developing resistance with fluoroquinolone usage, they cannot be recommended for use in MRSA SSSI. The fluoroquinolones can cause chromosomal mutations in genes encoding the subunits of the drugs' target enzymes, DNA gyrase and topoisomerase IV.<sup>41</sup>

## Parenteral treatment options

Several parenteral agents are currently available for the treatment of serious infections caused by MRSA, regardless of the strain, which include vancomycin (or teicoplanin), Q/D, linezolid, daptomycin, and tigecycline (Table 4). While vancomycin has long been used for the treatment of MRSA, increasing resistance has begun to limit its use in contemporary clinical practice.<sup>85</sup> Vancomycin has long been considered the "gold standard" for the treatment of MRSA, but recent reports of treatment failures are causing concern.<sup>42</sup> Since the emergence of CA-MRSA, limited attention has been directed toward the efficacy of vancomycin due to the availability of multiple new

compounds. Of the remaining parenteral agents, linezolid is the only agent with an oral formulation and has been previously discussed.

## Quinupristin/dalfopristin (Q/D)

Q/D (Synercid®; Monarch Pharmaceuticals, Bristol, TN, USA) is a semisynthetic streptogramin antibiotic with a potent gram-positive spectrum of activity, including CA-MRSA.<sup>43-45</sup> Prospective randomized controlled trials support its use for the treatment of bacteremia caused by vancomycin-resistant *Enterococcus faecium* and for cSSSI caused by MSSA or *Streptococcus pyogenes*.<sup>43,46,47</sup> Despite previously demonstrated *in vitro* activity, Q/D lacks an indication in MRSA infections because this pathogen was not isolated in sufficient quantity to be evaluated. Historically the use of Q/D has been limited due to the high incidence of adverse reactions. Use is generally reserved for patients in whom conventional therapy is not tolerated or is otherwise contraindicated.

## Daptomycin

Daptomycin (Cubicin®; Cubist Pharmaceuticals, Lexington, MA, USA) is a lipoglycopeptide antibiotic with a potent *in vitro* gram-positive spectrum of activity, specifically with rapid bactericidal action against MRSA.<sup>48</sup> Additional *in vitro* data have also demonstrated the activity of daptomycin against CA-MRSA.<sup>44,49</sup> However, some data suggest a relationship between decreased susceptibility of vancomycin to MRSA and a decreased susceptibility of daptomycin to MRSA.<sup>50-53</sup> Randomized controlled trials support the use of daptomycin for the treatment of cSSSI due to susceptible strains of gram-positive pathogens, and for the treatment of bacteremia and right-sided endocarditis caused by *S. aureus*.<sup>54,55</sup> MRSA was the pathogen identified at baseline in 9.3% (n = 40) of daptomycin-treated patients in the cSSSI trials and 37.4% (n = 45) in the right-sided endocarditis trial.<sup>54,55</sup> The MRSA strains in these trials were not differentiated into HA-MRSA or CA-MRSA. Outcomes were found to be similar between daptomycin and comparator for infections caused by MRSA. Prospective outcome data, however, are lacking for the treatment of CA-MRSA infections specifically. A retrospective evaluation assessed the use of daptomycin for the treatment of community-phenotype-MRSA (CP-MRSA) infections, defined by the authors as MRSA with susceptibility to both clindamycin and TMP-SMX.<sup>56</sup> All other phenotypes were classified by the authors as other-phenotype-MRSA (OP-MRSA). Of the 352 patients included in this evaluation, 100 were classified

**Table 3** Antimicrobials recommended for outpatient treatment of suspected methicillin-resistant (MRSA) skin and skin structure infections

Selection of empiric therapy should be guided by local susceptibility and modified based on results of culture and susceptibility testing. The duration of therapy for most SSSI is 7–10 days, but may vary depending upon the severity of infection and clinical response. Some infections may require a more prolonged treatment course.

Antimicrobial	Adult dose	Pediatric dose	Considerations
Clindamycin <sup>1</sup>	300–450 mg PO QID	10–20 mg/kg PO per DAY divided into 3–4 doses per day; not to exceed adult dose.	See below <sup>1</sup>
Doxycycline or minocycline <sup>2</sup>	100 mg PO BID	Do not use in children < 8 years old. Age ≥ 8 years old: 4 mg/kg PO per DAY divided BID; not to exceed adult dose.	Chelated by divalent cations. Separate from iron, calcium, and multivitamins. May make skin more sensitive to sunlight, sunburn may result. Do not use if pregnant or breastfeeding.
Linezolid <sup>3</sup>	600 mg PO BID	Age > 7 days–11 years old: 10 mg/kg PO per DOSE given every 8 hours; not to exceed 1200 mg daily. Age ≥ 12 years old: 600 mg PO BID.	Low-tyramine diet required. Avoid concomitant MAO-I or SSRI agents due to potential for serotonin syndrome. Monitor CBC with prolonged courses (potential for leukopenia, thrombocytopenia). Monitor for peripheral neuropathy.
Rifampin <sup>4</sup>	300 mg PO BID	15–20 mg/kg PO per DAY divided BID; not to exceed 600 mg daily.	NUMEROUS CYP450 drug–drug interactions. INR should be closely followed (for rapid decrease) in patients on warfarin. Causes bodily fluids (urine, sweat, etc.) to turn orange/red while on therapy.
Trimethoprim–sulfamethoxazole <sup>2</sup>	1–2 DS tablets (160 mg TMP/800 mg SMX per tab) PO BID. May consider dose increase for morbidly obese patients (8–10 mg/kg TMP per DAY divided BID–TID, maximum dose 2 DS tablets TID).	Base dose on TMP. Age ≥ 2 months: 8–2 mg/kg TMP (40–60 mg/kg SMX) PO per DAY divided BID; not to exceed adult dose.	Dose adjustment required in renal dysfunction. Significant drug interaction with warfarin; INR should be closely followed for rapid increase. Avoid in patients with G6PD deficiency. May make skin more sensitive to sunlight, sunburn may result.

<sup>1</sup>Clindamycin resistance is becoming increasingly prevalent. Pay close attention to the patient's culture and sensitivity reports when considering Clindamycin use. Clindamycin should not be used if isolate is erythromycin resistant or if "inducible resistance" is present (D-test).

<sup>2</sup>For cellulitis of unknown cause where Group A *Streptococcus* may be a concern, clindamycin in combination with doxycycline/minocycline provides additional coverage for both organisms. Adjunctive clindamycin therapy may also be useful in toxigenic *Staphylococci*/*Streptococci* infections.

<sup>3</sup>Due to significant drug interactions and expense, infectious disease consultation is recommended when considering linezolid.

<sup>4</sup>Rifampin must always be used in combination with another antibiotic.

**Notes:** Outpatient use of fluoroquinolones or macrolides is NOT RECOMMENDED for routine treatment of MRSA. Resistance to fluoroquinolones can develop rapidly on therapy, so these agents should not be routinely used even if the isolate is reported to be susceptible. Consider a consultation with an infectious disease physician before prescribing.

**Abbreviations:** SSSI, skin and skin structure infections; MAO-I, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; CBC, complete blood count; INR, international normalized ratio; G6PD, glucose-6-phosphate dehydrogenase.

as CP-MRSA and 252 as OP-MRSA. The CP-MRSA group tended to be younger with fewer underlying diseases. Success rate, time to clinical response, and duration of therapy were similar in both groups, prompting the authors to conclude that daptomycin was equally efficacious for the treatment of CP-MRSA or OP-MRSA infections in this select group of patients. However, these data cannot necessarily be extrapolated to all patient populations.

## Tigecycline

Tigecycline (Tygacil®; Wyeth Pharmaceuticals, Philadelphia, PA, USA), the first glycylglycyl antibiotic, has a broad range

of *in vitro* activity against most gram-positive (including MRSA), most gram-negative, and anaerobic bacteria.<sup>57</sup> Mendes and colleagues evaluated tigecycline against 1989 human isolates of CA-MRSA collected from the SENTRY Antimicrobial Surveillance Program, 94.7% of which were PVL positive.<sup>45</sup> Tigecycline was active against 98.2% of the strains tested, similar to the susceptibility rates for vancomycin, teicoplanin, Q/D and linezolid. Randomized controlled clinical trials have demonstrated its safety and efficacy for the treatment of cSSSI and complicated intra-abdominal infections (cIAI).<sup>58,59</sup> While MRSA has been included in the FDA approval for its association to cSSSI, it is lacking

**Table 4** Parenteral agents for the treatment of severe community-associated methicillin-resistant *Staphylococcus aureus* infections<sup>34,43,48,57,85</sup>

Drug	Drug class	Indication	Dose (Intravenous)	Considerations
Daptomycin	Lipoglycopeptide	cSSSI, bacteremia with right-sided infective endocarditis	4–6 mg/kg (actual body weight) every 24 hours	Dose adjust to every 48 hours if CrCl < 30 mL/min. Monitor CPK.
Linezolid	Oxazolidinone	uSSSI, cSSSI, CAP including concurrent bacteremia, NP	600 mg every 12 hours	Low-tyramine diet required. Avoid concomitant MAO-I or SSRI agents due to potential for serotonin syndrome. Monitor CBC with prolonged courses (potential for leukopenia, thrombocytopenia). Monitor for peripheral neuropathy.
Quinupristin–dalfopristin	Streptogramin	Bacteremia, cSSSI	7.5 mg/kg (actual body weight) every 8–12 hours	Monitor LFTs. Use often limited by high incidence of arthralgias and myalgias.
Tigecycline	Glycylcycline	cSSSI, cIAI	100 mg once, then 50 mg every 12 hours	Does not achieve optimal concentrations in blood or urine as highly distributed to the tissues.
Vancomycin	Glycopeptide	Severe gram-positive infections	15 mg/kg every 12 hours	Dose adjust in renal dysfunction. Monitor levels and SCr.

**Abbreviations:** cSSSI, complicated skin and skin structure infections; uSSSI, uncomplicated skin and skin structure infections; CAP, community-acquired pneumonia; NP, nosocomial pneumonia; cIAI, complicated intra-abdominal infections; SCr, serum creatinine; LFTs, liver function tests; MAO-I, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; CBC, complete blood count; CrCl, creatinine clearance; CPK, creatine phosphokinase.

for cIAI due to a small sample size in the registration trials, similar to Q/D. A retrospective evaluation of the 173 MRSA isolates obtained from these phase III trials, 85% of which were from the cSSSI trial, found that 76 isolates had characteristics consistent with known CA-MRSA on the basis of genotyping and the presence of both PVL-encoding locus and SCCmec type IV.<sup>60</sup> All strains demonstrated *in vitro* susceptibility to tigecycline.

## Drugs under investigation

Multiple antimicrobial agents with potent *in vitro* MRSA activity are currently in development. These agents are summarized in Table 5 with regard to drug name, route of administration, dose, indication for which it is under evaluation, and phase of development at this point of time. Drug classes currently in clinical use with additional drugs in development include glycopeptides, oxazolidinones, and a dihydrofolate reductase inhibitor. In addition, for the first time ever, beta-lactam antibiotics which possess MRSA activity, specifically new cephalosporins and carbapenems, are being developed.

## Glycopeptides

Adding to vancomycin and teicoplanin of the glycopeptide drug class, dalbavancin, telavancin, and oritavancin are currently in the developmental stage. Dalbavancin is a semisynthetic lipoglycopeptide with a long half-life allowing for once-weekly dosing.<sup>61</sup> Building on a successful phase II trial evaluating dalbavancin versus standard-of-care, a phase III trial evaluated dalbavancin versus linezolid for the treatment of cSSSI.<sup>62,63</sup> MRSA was identified in 51% of patients from whom a pathogen was isolated at baseline. Dalbavancin was well tolerated and efficacy was found to be noninferior. A phase II trial for bacteremia has yielded similar results.<sup>64</sup> In an *in vitro* evaluation of 329 pathogens associated with diabetic foot infections (DFIs), susceptibility to dalbavancin was compared with other antimicrobial agents.<sup>65</sup> Of these 329 pathogens, 60 were MRSA, with an estimated 50% suspected CA-MRSA. Though this was not confirmed via pulse field gel electrophoresis (PFGE), >50% of the suspected CA-MRSA isolates were resistant to clindamycin with an MIC > 8 µg/mL. The authors observed that dalbavancin was more active than vancomycin, daptomycin, and linezolid



against MRSA. They concluded that the *in vitro* data, coupled with dalbavancin outcome data (versus linezolid for the treatment of SSSI, including DFI), indicate that it may provide an advantage to patients with DFI in emergency departments, inpatient settings, and outpatient settings.

Telavancin, another lipoglycopeptide, possesses potent MRSA activity.<sup>66</sup> An *in vitro* evaluation tested telavancin against 60 strains of CA-MRSA (as defined by the CDC).<sup>44</sup> Thirty-two (54%) of the 60 CA-MRSA strains were identified via PFGE to be the USA300 strain which harbors PVL genes. Telavancin demonstrated bactericidal activity against all 60 CA-MRSA isolates, including all USA300 strains. A phase III study found telavancin to be safe and at least as effective as vancomycin for the treatment of cSSSI caused by gram-positive organisms, including MRSA.<sup>67</sup> Many of the MRSA isolates were SCCmec type IV and PVL positive.<sup>68</sup>

Oritavancin, another semisynthetic lipoglycopeptide with MRSA activity, has a long half-life allowing for less frequent dosing compared to contemporary glycopeptides.<sup>69</sup> Two phase III trials have been completed evaluating oritavancin versus comparator for the treatment of cSSSI.<sup>70,71</sup>

Although these data are as yet unpublished, favorable results have been reported in abstract form and a new drug application (NDA) was submitted to the FDA in early 2008 for the treatment of cSSSI. Additional data specific to CA-MRSA are lacking.

## Oxazolidinones

Several oxazolidinones are currently in development. While multiple compounds are under investigation, most are in pre-clinical development stage and have not yet been named beyond their chemical number. AZD2563, for example, has demonstrated *in vitro* activity similar to linezolid against gram-positive pathogens, including MRSA.<sup>72</sup> Additional oxazolidinones have been evaluated by McKee and colleagues, but they are far from clinical development.<sup>73</sup>

## Dihydrofolate reductase inhibitor

Iclaprim, a dihydrofolate reductase inhibitor similar to trimethoprim, is currently being evaluated as an intravenous formulation for the treatment of cSSSI in phase III trials.

**Table 5** Investigational agents with *in vitro* activity against methicillin-resistant *Staphylococcus aureus*

Drug	Route	Dose	Indication under evaluation	Phase
<b>Carbapenem</b>				
Multiple in early development	na	na	na	pre-clinical
<b>Cephalosporin</b>				
Ceftopibiprole	iv	500 mg every 12 hours	cSSSI	III
Ceftaroline	iv	500 mg every 12 hours	cSSSI	III
<b>Dihydrofolate reductase inhibitor</b>				
Iclaprim	iv	0.8 mg/kg every 24 hours	cSSSI	III
	iv	na	HAP (VAP and HCAP)	II
	iv to enteral switch	na	cSSSI	II
<b>Oxazolidinone</b>				
Multiple in early development	na	na	na	pre-clinical
<b>Synthetic glycopeptide</b>				
Dalbavancin	iv	1000 mg on day 1, 500 mg on day 8	cSSSI	III
	iv	1000 mg on day 1, 500 mg on day 8	bloodstream	II
Ortivancin	iv	200 mg every 24 hours	cSSSI	III
Telavancin	iv	10 mg/kg every 24 hours	cSSSI	III

**Abbreviations:** iv, intravenous; cSSSI, complicated skin and skinstructure infections; HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia; HCAP, healthcare-associated pneumonia; na, not applicable.

Positive outcomes have resulted in the submission of a NDA to the FDA., though the FDA has denied its approval. Iclaprim is currently under review in Europe and Canada. An intravenous-to-oral switch of iclaprim for the treatment of cSSSI is under evaluation in a phase II trial. Additionally, intravenous iclaprim for the treatment of hospital-acquired pneumonia, including both ventilator-associated pneumonia and healthcare-associated pneumonia is under evaluation in a phase III trial. Data specific to CA-MRSA are lacking.

## Cephalosporins

Traditionally, cephalosporins have lacked activity against MRSA. Recently this changed with the introduction of ceftobiprole and ceftaroline which have a high affinity for PBP2a, and therefore exhibit good *in vitro* activity against MRSA, including CA-MRSA.<sup>74–76</sup> When tested against 152 strains of well-characterized CA-MRSA, the MIC<sub>50</sub> and MIC<sub>90</sub> for ceftobiprole were 0.5 and 0.5 µg/mL, respectively, with a range of 0.25–1 µg/mL. Breakpoints have not yet been established and consequently these results are up for interpretation. Both ceftaroline and ceftobiprole are currently under investigation for safety and efficacy of the treatment of cSSSI; a NDA has since been filed with the FDA for ceftobiprole.

## Carbapenems

Similar to the aforementioned cephalosporins, some investigational carbapenems have demonstrated *in vitro* activity against MRSA. Specifically, ME1036 has demonstrated activity against CA-MRSA.<sup>76</sup> When tested against 152 strains of well-characterized CA-MRSA, the MIC<sub>50</sub> and MIC<sub>90</sub> were 0.12 and 0.25 µg/mL, respectively, with a range of 0.06–0.5 µg/mL. This, and other carbapenems with MRSA activity, are in the early stages of clinical development and may not reach market for several years. A review by Lo and colleagues has examined these agents in more detail.<sup>77</sup>

## Complementary/alternative medicine

Tea tree oil (TTO) has been evaluated as a potential agent for both MRSA decolonization and treatment. It is available in many forms and is widely used in cosmetic preparations. Concentrations of TTO and product integrity are often variable since it is not a regulated drug.

Several studies have evaluated the *in vitro* activity of TTO versus MRSA and many have shown promise, including one study indicating that TTO may be of benefit for eradication of MRSA biofilms.<sup>78</sup> Translating *in vitro* data to clinical practice has yielded less consistent results. A study by Dryden

and colleagues evaluated TTO for MRSA eradication in hospitalized patients.<sup>79</sup> A standard 5-day regimen of mupirocin 2% nasal ointment, chlorhexidine gluconate 4% skin cleanser and silver sulfadiazine 1% cream was compared to 10% tea tree cream and 5% tea tree body wash. Results indicated that mupirocin was significantly more effective at eradicating MRSA nasal carriage compared to TTO, 78% and 41% clearance, respectively.

A study by McMahon and colleagues investigated whether the effect of sub-lethal challenge with TTO impacted the antibiotic resistance profiles of significant human pathogens.<sup>80</sup> The authors note that TTO products often contain variable concentrations, and previously available data had not evaluated the impact of inappropriate or sublethal TTO concentrations. With respect to the MRSA strains used in the study, TTO caused an increased (2-fold or greater) MIC value for 7 out of 10 antibiotics tested.

In summary, before TTO is widely accepted as a standard-of-care for treating MRSA or for MRSA decolonization, further clinical trial data are needed. If providers recommend TTO for treatment of CA-MRSA, it should be in conjunction with one of the traditional therapies previously discussed in this article.

## Resistance

As discussed, most of the USA300 isolates are resistant to beta-lactam and macrolide antibiotics. Given that there are often other oral agents to treat most CA-MRSA strains, the question of development of resistance to these (doxycycline, minocycline, clindamycin, TMP-SMX) drugs is of concern. An epidemiologic study evaluated 123 USA300 isolates collected in an ambulatory health center in Boston, Massachusetts.<sup>81</sup> Of all the isolates, 83% had PFGE revealing either USA300–0114 (58% of total isolates) or USA300–0247 (24% of total isolates). There were 12 multidrug-resistant (MDR) isolates reported, all of which contained the *tetK* and *ermC* genes. Of the USA300–0114 isolates (n = 73), 72 (99%) were resistant to erythromycin, 36 (49%) were resistant to clindamycin and 10 (14%) were resistant to doxycycline. Two of the strains showed multidrug resistance to erythromycin, levofloxacin, clindamycin and tetracycline. Of the USA 300–0247 isolates (n = 29), 26 (90%) were resistant to erythromycin, 22 (76%) were resistant to clindamycin and 21 (72%) were resistant to tetracycline. Sixteen of the strains showed multidrug resistance to erythromycin, levofloxacin, clindamycin and tetracycline. Twelve isolates were tested for mupirocin susceptibility, and all were mupirocin resistant with MIC ≥ 128 µg/mL. The authors note that their resistance rates were considerably

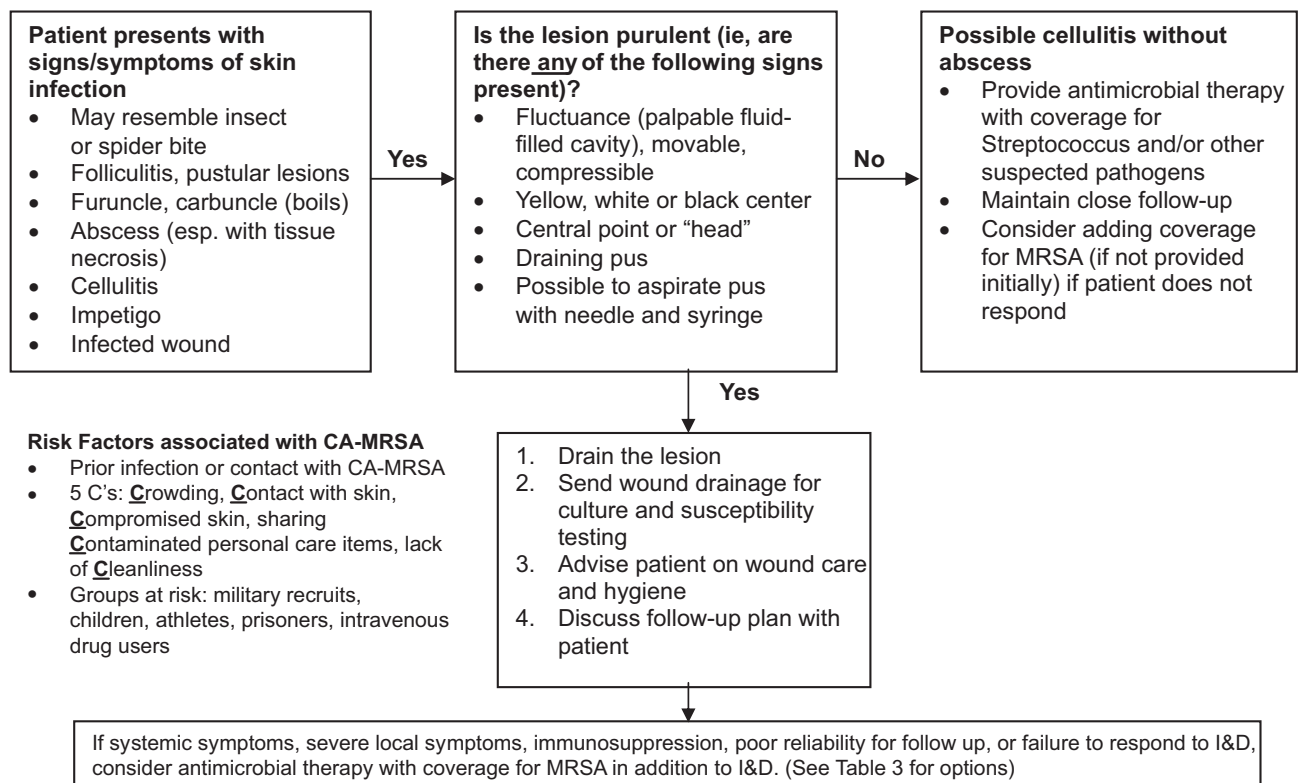
higher than other reported data as well as compared to the local health network.

A second retrospective study describes a USA300 strain that exhibits plasmid-mediated resistance to erythromycin, clindamycin and mupirocin.<sup>82</sup> This retrospective study aimed to determine the incidence of an MDR MRSA clone (USA300) in San Francisco and risk factors associated with it. Based on an analysis from nine medical centers, the annual incidence of USA300 infection in San Francisco was estimated to be 275 cases per 100 000 persons (95% CI, 256–295 cases per 100 000 persons). With respect to USA300 infections containing a MDR conjugative plasmid, the annual incidence was 26 per 100 000 persons (95% CI, 16–36 cases per 100 000 persons). When eight zip codes were pooled, the incidence rose to 59 cases per 100 000 persons (95% CI, 36–82 cases per 100 000 persons). The other 18 zip codes evaluated only had incidence or 4 per 100 000 persons (95% CI, 0–8 cases per 100 000 persons). A single zip code had 25.7% of male same-sex couples, and incidence of MDR USA300 was 170 cases per 100 000 persons (95% CI, 41–299 cases per 100 000 persons). The authors conclude that men who have sex with men may be at higher risk for infection with MDR USA300.

Data such as these reflect the need for astute monitoring of local epidemiologic patterns for CA-MRSA isolates.

## Outpatient treatment approach

The treatment approach for CA-MRSA infections is variable based upon severity and site of infection. As discussed previously in this article, the majority of CA-MRSA infections are cutaneous infections and many may be managed on an outpatient basis. While the general consensus is that minor infections can be managed by incision and drainage (I&D) alone, many practitioners are opting to also treat with oral antimicrobials when MRSA diagnosis is confirmed by culture. A study by Moran and colleagues evaluated CA-MRSA patients presenting to the Emergency Department.<sup>83</sup> Approximately 20% of patients underwent I&D alone, 10% were treated with antibiotics alone, and 66% received both I&D and antibiotic therapy. The 2005 Infectious Diseases Society of America Practice Guideline for the Diagnosis and Management of Skin and Soft-Tissue Infections recommends that if the infection involves inflammation of the surrounding tissue or has manifested in systemic symptoms, I&D with concomitant antimicrobial therapy.<sup>84</sup> Figure 1 summarizes a



**Figure 1** Outpatient management of suspected community-associated methicillin-resistant *Staphylococcus aureus* skin and skin structure infections.

Adapted from Aurora Health Care MRSA Clinical Guidelines 2008. Kathryn Leonhardt, MD, MPH, Editor.

**Abbreviations:** I&D, incision and drainage; MRSA, methicillin-resistant *S. aureus*; CA-MRSA, community-associated MRSA.

possible treatment approach for the outpatient management of suspected CA-MRSA SSSI.

## Conclusions

Although the changing epidemiology of MRSA has become better understood in recent years, the impact, both in and out of the hospital, still require further research and investigation. Understanding how to treat and prevent CA-MRSA is critical. Risk factors, optimal treatment, and infection prevention strategies need to be better defined and economic outcomes need to be measured. The most effective intervention appears to be prevention although this is one of the most difficult. As clinicians and patients become more educated about CA-MRSA and its spread, common practices will likely require modification.

## Disclosures

The authors report no conflicts of interest in this work.

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