

# Community-Associated Meticillin-Resistant *Staphylococcus aureus* Infections

## Epidemiology, Recognition and Management

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### Abstract

Meticillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of infection, particularly in hospitalized patients and those with significant healthcare exposure. In recent years, epidemic community-associated MRSA

(CA-MRSA) infections occurring in patients without healthcare risk factors have become more frequent. The most common manifestation of CA-MRSA infection is skin and soft tissue infection, although necrotizing pneumonia, sepsis and osteoarticular infections can occur. CA-MRSA strains have become endemic in many communities and are genetically distinct from previously identified MRSA strains. CA-MRSA may be more capable colonizers of humans and more virulent than other *S. aureus* strains. Specific mechanisms of pathogenicity have not been elucidated, but several factors have been proposed as responsible for the virulence of CA-MRSA, including the Panton-Valentine leukocidin, phenol-soluble modulins and type I arginine catabolic mobile element. The movement of CA-MRSA strains into the nosocomial setting limits the utility of using clinical risk factors alone to designate community- or healthcare-associated status. Identification of unique genetic characteristics and genotyping are valuable tools for MRSA epidemiological studies. Although the optimum pharmacological therapy for CA-MRSA infections has not been determined, many CA-MRSA strains remain broadly susceptible to several non- $\beta$ -lactam antibacterial agents. Empirical antibacterial therapy should include an MRSA-active agent, particularly in areas where CA-MRSA is endemic.

The widespread emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in recent years highlights the impact of resistant bacterial infections on healthcare and society. MRSA has particularly been an important cause of infection in critically ill patients and in some settings is more common than methicillin-susceptible *S. aureus* (MSSA).<sup>[1]</sup> *S. aureus* infections are estimated to have a significant cost to healthcare,<sup>[2]</sup> and MRSA additionally has been an important cause of both morbidity and mortality in the US.<sup>[3]</sup>

In addition to its role in nosocomial infections, MRSA has become a common cause of infections in healthy patient populations that lack traditional risk factors for MRSA exposure. The MRSA strains responsible for these infections have been found to be epidemiologically and genetically unique from nosocomial MRSA strains and are now designated as community-associated MRSA (CA-MRSA). CA-MRSA may be both more capable colonizers of humans and more virulent than other *S. aureus* strains as evidenced by the rapidity with which it has become endemic in many parts of the world. Indeed, CA-MRSA is the most frequent cause of cutaneous infections in some communities, as well as an important

cause of invasive infections such as pneumonia and sepsis. CA-MRSA strains continue to spread into new niches and are now common in some hospitals and responsible for causing nosocomial infections such as bacteraemia and surgical site infections.

This article discusses the epidemiology, unique genetic characteristics, virulence and pathogenesis of CA-MRSA. Pharmacological and non-pharmacological therapies for CA-MRSA are reviewed. The term 'community-associated' is used in this discussion, but is synonymous with the terms 'community-acquired' and 'community-onset', both of which are also present in the literature. Published literature from 1950 through to December 2008 was reviewed via the PubMed search engine using the primary search terms 'methicillin-resistant staphylococcus aureus', 'community-associated methicillin-resistant staphylococcus aureus', 'CA-MRSA' and 'HA-MRSA'. Individual antibacterials were also searched via PubMed and additional articles were obtained from the reference sections of source articles identified via PubMed. Finally, information on CA-MRSA management was also obtained from the US Centers for Disease Control and Prevention website (<http://www.cdc.gov>).

## 1. Epidemiology of Community-Associated Meticillin-Resistant *Staphylococcus aureus* (CA-MRSA)

MRSA was first identified in the early 1960s,<sup>[4]</sup> became an increasingly common hospital pathogen in the 1980s and is now a major pathogen in most hospitals, particularly in the critical-care setting. In contrast to penicillin resistance, which is common in both nosocomial and community strains of *S. aureus*, MRSA was considered to be an exclusively nosocomial pathogen. Patients who developed MRSA infections typically had the following risk factors: (i) surgery, dialysis, hospitalization or residence in a long-term care facility within the prior year; (ii) indwelling percutaneous devices such as central venous catheters or feeding tubes; (iii) an MRSA infection identified more than 48 hours after hospital admission; or (iv) had previously had MRSA cultured.<sup>[5]</sup> MRSA cultured from patients with any of these risk factors are now clinically designated as health-care-associated MRSA (HA-MRSA) to distinguish it from CA-MRSA, which is cultured from patients without any of these clinical risk factors. Before the widespread appearance of CA-MRSA strains, outbreaks of MRSA infections occurring in patients lacking the traditional risk factors were occasionally reported.<sup>[6,7]</sup> Phenotypically, HA-MRSA is often resistant to several antibacterial classes in addition to the  $\beta$ -lactam agents.

Early reports of CA-MRSA came from Western Australia.<sup>[8]</sup> Twenty-five MRSA isolates cultured between 1989 and 1991 were collected, with 18 representing infections and the remainder representing colonization. None of the patients had been hospitalized outside of the region in the previous 12 months. Of note, MRSA had not become established in the local hospitals and thus acquisition of MRSA in these patients was not felt to be nosocomial. Molecular genotyping revealed that the majority of these MRSA isolates were identical and were noted to be susceptible to chloramphenicol, gentamicin and trimethoprim, antibacterials to which nosocomial MRSA strains in Australia typically exhibited resistance.

By the late 1990s, reports of MRSA infections occurring in children in North America were

described in a Children's Hospital in Chicago,<sup>[9]</sup> as well as four cases of rapidly fatal infection in four children from the Midwestern US.<sup>[10]</sup> Subsequently, outbreaks were noted among incarcerated adults,<sup>[11-13]</sup> Alaska natives,<sup>[14]</sup> athletes<sup>[15-17]</sup> and military recruits.<sup>[18]</sup> Common to many of these outbreaks was the frequent presentation of patients with a soft-tissue infection, absence of traditional MRSA risk factors, genetic relatedness of the infecting MRSA strains and susceptibility of the bacteria to many non- $\beta$ -lactam antibacterials. Given the epidemiological differences from nosocomial strains of MRSA, a distinction was made between CA- and HA-MRSA. Following recognition of epidemiologically related outbreaks of CA-MRSA infection, non-outbreak infections have been reported from North America, Central and South America, Europe, Australia and Asia.<sup>[19-30]</sup>

### 1.1 Colonization

The prevalence of nasal colonization with MRSA appears to be increasing in the US. Based on data collected as part of the National Health and Nutrition Examination Survey, overall MRSA nasal colonization has increased from 0.9% (95% CI 0.5, 1.4) in 2001–2 to 1.5% (95% CI 1.2, 1.8) in 2002–4.<sup>[31,32]</sup> The proportion of MRSA strains identified genetically as CA-MRSA also increased from 8.1% (95% CI 1.1, 25.3) to 19.7% (95% CI 12.4, 28.8). It is possible these data may underestimate MRSA colonization, as other anatomical sites may also be important sites of colonization exclusive of the nares.<sup>[33-35]</sup>

Asymptomatic colonization with MRSA is a risk factor for subsequent infection with the colonizing strain.<sup>[36-38]</sup> The risk of developing a subsequent infection may be increased if colonized with CA-MRSA versus MSSA. An observational study of 812 military recruits noted nasal colonization with CA-MRSA in 3% compared with 28% colonized with MSSA, but 38% of the CA-MRSA-colonized individuals developed soft-tissue infections compared with 3% of MSSA colonized individuals (relative risk 10.7; 95% CI 4.6, 25.2;  $p < 0.01$ ).<sup>[39]</sup> Whether CA-MRSA strains are more likely to colonize and cause

subsequent infection than HA-MRSA or MSSA strains remains unanswered, although the endemicity and volume of CA-MRSA infections seem to suggest these strains may be more 'fit' and virulent than other *S. aureus* strains.

### 1.2 High-Risk Populations for CA-MRSA Infection

Various populations have been suggested as being at increased risk for developing CA-MRSA infections based on published reports of outbreaks in specific populations (table I). However, as CA-MRSA strains have become endemic in many parts of the world, it appears that almost any person can develop CA-MRSA infections. Nonetheless, certain populations may be at increased risk for infection because of inherent host factors or behaviours that enhance the transmission of CA-MRSA or the development of infection. Transmission of CA-MRSA between individuals is likely to be facilitated by crowded living conditions,<sup>[11-13,18]</sup> activities that involve skin-to-skin contact,<sup>[15-17]</sup> poor hygiene practices<sup>[40]</sup> and sharing of contaminated household items.<sup>[16]</sup> In addition, men who have sex with men,<sup>[41]</sup> some indigenous populations<sup>[14,42]</sup> and individuals who have recently received antibacterials<sup>[43]</sup> have been noted to have a higher incidence of CA-MRSA infection. Infection is more likely to occur if host defences against bacterial infections are diminished: shaving or skin abrasions, immature/compromised immune systems and loss of protective respiratory tract epithelium (as can occur following influenza infection). In communities where CA-MRSA is not yet endemic, outbreaks of infection in these

previously recognized at-risk populations might herald future endemicity.

### 1.3 CA-MRSA Strains are Distinct from Healthcare-Associated MRSA

In addition to the epidemiological differences, CA- and HA-MRSA strains have been found to be both phenotypically and genotypically distinct (table II). Molecular typing methods have identified a small number of *S. aureus* strains that comprise the majority of CA-MRSA. Pulsed-field gel electrophoresis (PFGE), a commonly used method to determine bacterial strain relatedness, is an important epidemiological tool. A classification scheme categorizing isolates as USA100–USA1200 is used to describe MRSA by PFGE analysis. The most common CA-MRSA genotypes include USA300 or USA400,<sup>[44]</sup> but also include USA1000 and USA1100.<sup>[45]</sup> Common HA-MRSA genotypes include USA100, USA200 and USA500.<sup>[44]</sup> The Midwest strain MW2 that caused the epidemic infections in children<sup>[10]</sup> is classified as USA400, and the pandemic clone of MRSA found throughout the US and Europe is classified as USA300. One particular strain of MRSA USA300, termed USA300-0114, is especially common in many outbreaks and surveillance studies.

Multi-locus sequence typing analysis is also useful for describing clones of CA-MRSA. Common CA-MRSA sequence types include ST1, which includes MW2, and the early Australian strains,<sup>[8,10]</sup> ST30, ST59, ST80 and ST8, which includes the pandemic USA300 strain.<sup>[44]</sup>

As noted in early reports of CA-MRSA outbreaks, the isolates exhibit susceptibility to many

**Table I.** Groups at risk for community-associated methicillin-resistant *Staphylococcus aureus* infection and associated risk factors

Population or group	Possible risk factors	References
Inmates/prisoners	Crowded living conditions, close contact	11-13
Men who have sex with men	Close contact	41
Athletes	Close contact, skin abrasions, sharing of equipment	15-17
Military recruits	Crowded living conditions, skin abrasions	18
Native Americans, Alaska natives	Close contact, crowded living conditions	14,42
Children	Close contact, skin abrasions	9,10
Methamphetamine users	Poor skin hygiene	40

**Table II.** Overview of general characteristics of community- and healthcare-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA and HA-MRSA)<sup>[5,14,21,46-57]</sup>

Characteristic	CA-MRSA	HA-MRSA
Common manifestations	SSTI, necrotizing pneumonia	Nosocomial bacteraemia, pneumonia, wound infections
Antibacterial susceptibility	Frequently susceptible to non- $\beta$ -lactam antibacterials, low prevalence of iMLS <sub>B</sub> resistance	Broad resistance to non- $\beta$ -lactam antibacterials, iMLS <sub>B</sub> resistance common
SCCmec type	IV, V	I, II, III
Accessory gene regulator type	<i>agr</i> III	<i>agr</i> I, II
Genotype (PFGE)	USA300, USA400, USA1000 USA1100	USA100, USA200, USA500, USA600, USA800
Sequence type (MLST)	ST1, ST8, ST30, ST59, ST80	ST5, ST36, ST45
Virulence genes/factors	<i>pvl</i> , <i>sea</i> , <i>seb</i> , <i>sec</i> , <i>seh</i> and type I ACME common; higher expression of PSM; more rapid <i>in vitro</i> growth	<i>pvl</i> uncommon, type I ACME absent

**ACME** = arginine catabolic mobile element; **iMLS<sub>B</sub>** = inducible macrolide-lincosamide-streptogramin B; **MLST** = multi-locus sequence typing; **PFGE** = pulsed-field gel electrophoresis; **PSM** =  $\alpha$ -type phenol-soluble modulins; **SCC** = staphylococcal cassette chromosome; **SSTI** = skin and soft tissue infection.

non- $\beta$ -lactam antibacterials. In a prospective survey of MRSA in Minnesota, USA, CA-MRSA strains were significantly more susceptible than HA-MRSA strains to several antibacterials: ciprofloxacin (79% vs 16%), clindamycin (83% vs 21%), erythromycin (44% vs 9%) and gentamicin (94% vs 80%).<sup>[5]</sup> In addition, CA-MRSA was more likely to be susceptible to the combination of ciprofloxacin, clindamycin, gentamicin and cotrimoxazole (trimethoprim/sulfamethoxazole) [odds ratio 5.88; 95% CI 4.86, 6.64]. Multidrug-resistant MRSA USA300 (resistance to tetracycline, macrolides, lincosamides, streptogramin B and mupirocin) has been described in clinical isolates from San Francisco, CA, and Boston, MA, USA.<sup>[41,58,59]</sup> Multidrug resistance in many of these isolates is conferred by a conjugative plasmid, pUSA03, which has the potential to gain additional antibacterial resistance genes.<sup>[58]</sup>

CA-MRSA strains have been noted to exhibit more rapid growth than HA-MRSA strains, with CA-MRSA mean doubling time of 28.79 minutes compared with 38.81 minutes for HA-MRSA strains ( $p < 0.0001$ ).<sup>[60]</sup> This more rapid growth has been hypothesized to allow CA-MRSA to outcompete slower growing strains of *S. aureus*.

Genetic differences between CA- and HA-MRSA strains are numerous. Methicillin resistance is conferred by the *mecA* gene in staphylococci and is carried by the staphylococcal cassette chromosome (SCC).<sup>[61]</sup> SCC is a mobile genetic element

that appears to allow the transfer of its associated genes, in this case the *mecA* gene, between staphylococci. Three SCCmecA types, I–III, had previously been described in MRSA.<sup>[62]</sup> SCCmec types I–III have several common features, including identical chromosomal integration site, conserved genetic organization around the *mecA* gene and the presence of cassette chromosome recombinase (*ccr*) genes, which allow horizontal transfer of SCCmec. Additional antibacterial resistance genes are common in SCCmec types II and III. SCCmec type I–III range in size from 34.4 to 66.9 kb. CA-MRSA strains contain the smaller SCCmec type IV,<sup>[63,64]</sup> or less commonly, SCCmec type V (20.9–24.3 kb and 28 kb, respectively).<sup>[65]</sup> SCCmec types I, IV and V do not typically carry additional antibacterial resistance genes with the exception of *mecA*.<sup>[60]</sup> Numerous variants of SCCmec have been identified in both CA- and HA-MRSA.<sup>[66]</sup>

#### 1.4 Virulence of CA-MRSA

Virulence genes and toxins are present in CA-MRSA that are not common in other strains of MRSA. Baba and colleagues<sup>[46]</sup> found 18 unique toxins, including the superantigen staphylococcal enterotoxin H (*seh*), in the MW2 strain. Clinical MRSA isolates from Minnesota revealed that several virulence genes were significantly more common in CA-MRSA than HA-MRSA:

Panton-Valentine leukocidin (PVL) gene, and genes for staphylococcal enterotoxins A, B, C and H.<sup>[5]</sup> In addition, CA-MRSA strains are commonly accessory gene regulator (*agr*) type III, a regulatory operon that coordinates various virulence pathways whereas HA-MRSA are more likely to be *agr* I or II.<sup>[5]</sup>

Numerous genetic differences have been proposed as a potential explanation for the perceived enhanced virulence of CA-MRSA. The precise mechanisms of pathogenicity in CA-MRSA have not been determined, and debate continues on the role of specific genes and toxins. Initial attention focused on the role of the PVL toxin. The PVL gene is uncommon in traditional nosocomial *S. aureus* strains,<sup>[5,47]</sup> thus it seemed reasonable to consider this as likely to be an important virulence determinant. PVL is a bicomponent toxin produced by the *lukPV* operon that results in pore formation in leukocytes. The PVL gene is common in many clinical CA-MRSA strains and uncommon in HA-MRSA.<sup>[5,14,21,46,48,49]</sup>

Animal studies have yielded conflicting results as to the importance of *pvl*. Deletion of the *lukPV* operon in MW2 and USA300 in a murine abscess model has not been shown to reduce abscess size or bacterial density when compared with the parent MRSA strain. Similar knockout experiments in a mouse bacteraemia model also did not show differences in lethality.<sup>[50]</sup> However, in a rabbit bacteraemia model, PVL may have a modest effect in the acute phase of infection that wanes as the disease progresses and does not appear to have an effect on bacterial gene regulatory networks.<sup>[51]</sup> In a murine pneumonia model, PVL has been found both to be an important contributor to CA-MRSA virulence in one experiment<sup>[52]</sup> and non-contributory in other experiments.<sup>[53,54]</sup>

Another recently identified family of toxins in *S. aureus* that is differentially expressed in CA- and HA-MRSA strains are  $\alpha$ -type phenol-soluble modulins (PSMs). PSMs have leukocidal activity and are expressed at higher levels in CA-MRSA. CA-MRSA strains that express PSMs have been shown to be more virulent than non-PSM MRSA strains in bacteraemia and abscess mouse models.<sup>[55]</sup>

Genome sequencing of the pandemic clone USA300 revealed it has acquired the type I arginine catabolic mobile element (ACME), a pathogenicity island that may enhance bacterial fitness and survival, from *S. epidermidis*.<sup>[56,57]</sup> Type I ACME appears to be unique to the USA300 pandemic clone and is uncommon in other MRSA. Type I ACME is physically linked to *SCCmec* using the same *ccr* recombinases for mobilization and transfer.<sup>[57]</sup> Thus, the combination of antibacterial resistance conferred by *SCCmec* and the virulence of type I ACME may provide the survival advantage that has allowed USA300 to become a dominant clone of MRSA.

## 2. Manifestations of CA-MRSA Disease

### 2.1 Skin and Soft Tissue Infection

The spectrum of disease caused by CA-MRSA appears to be similar to that of other *S. aureus*, although certain manifestations are particularly common. Early reports of CA-MRSA infections described severe disease including sepsis, osteomyelitis and pneumonia. Subsequent reports established that the most common manifestation of CA-MRSA is skin and soft tissue infection (SSTI), particularly abscess or furunculosis. Many affected patients often report a history of a 'spider bite' that they believe subsequently became infected, a description that is usually describing the natural history of CA-MRSA SSTI and not an infected arthropod bite.

A surveillance study of three different communities in the US found that SSTI was the most common manifestation of CA-MRSA disease (77%), followed by wound infection (10%), urinary tract infection (4%), sinus infection (4%) and pneumonia (2%).<sup>[25]</sup> Among patients presenting to an urban medical centre with community-onset SSTI due to *S. aureus*, CA-MRSA caused 63% (244 of 389 episodes) of infections compared with 28% (110 of 389 episodes) due to MSSA.<sup>[67]</sup> Similarly, in a multicentre study, *S. aureus* was found to be the most common cause of SSTI among patients presenting to the emergency department (76%).<sup>[27]</sup> The prevalence of MRSA was 59% overall and pulsed-field type USA300

CA-MRSA accounted for 97% of all MRSA. Patients with CA-MRSA SSTIs often experience recurrent infections.<sup>[68,69]</sup>

Serious CA-MRSA soft-tissue infections have been noted to occur. In a retrospective review of MRSA wound cultures at an urban hospital in Los Angeles, CA, USA, 14 of 843 patients from the community were found to have necrotizing fasciitis, necrotizing myositis or both.<sup>[70]</sup> All of the MRSA isolates were susceptible to clindamycin, cotrimoxazole and rifampin. Molecular typing of the isolates found all were USA300, SCCmec type IV and PVL gene-positive. All of the patients described survived, suggesting that CA-MRSA may be less virulent than other organisms that cause fasciitis. Additional reports of fasciitis and myositis have since been reported, although both conditions appear to be relatively uncommon manifestations of CA-MRSA disease.<sup>[71-75]</sup> Fournier's gangrene due to CA-MRSA (PVL gene-positive) has also been reported.<sup>[76]</sup>

## 2.2 Pulmonary Infection

*S. aureus* is an important cause of nosocomial pneumonia and less commonly a cause of community-acquired pneumonia (CAP). CA-MRSA strains, particularly PVL gene-positive strains, are increasingly reported to cause CAP in both adults and children.<sup>[77-79]</sup> Francis and colleagues<sup>[78]</sup> reported four patients who developed necrotizing pneumonia due to PVL gene-positive, USA300 CA-MRSA. The patients ranged in age from 20 to 52 years and presented with cavitory lung lesions and shock. Two patients had laboratory-confirmed influenza infection and two patients had an influenza-like prodrome without confirmatory influenza testing. One patient died, the remaining three had prolonged hospitalizations with complications including shock, cavitory pneumonia, empyema, pneumothoraces and gangrene. Gonzalez and colleagues<sup>[79]</sup> described 47 children with CA-MRSA infection and abnormal pulmonary imaging. Common manifestations of pulmonary infection included pneumonia, empyema and necrotizing pneumonia. Co-infection with influenza or parainfluenza virus was noted in three patients who developed

severe necrotizing pneumonia. Metastatic pulmonary disease was present in 20 patients with osteomyelitis. Additional cases of CA-MRSA CAP associated with influenza have been reported, particularly in young, healthy patients and often presenting with severe disease.<sup>[80,81]</sup>

With the success of pneumococcal vaccines in reducing *Streptococcus pneumoniae* pneumonia, CA-MRSA is an important consideration as a cause of severe CAP, especially in the setting of concomitant influenza infection or as a metastatic complication of existing CA-MRSA infection. Empirical therapy for severe CAP should include antibacterials active against CA-MRSA.

## 2.3 Osteoarticular Infections

Acute, haematogenous CA-MRSA osteoarticular infections are more frequently reported in children<sup>[79,82-85]</sup> than in adults.<sup>[86,87]</sup> Osteoarticular infection may be complicated by subperiosteal abscess, myositis and bursitis. Metastatic infection including pneumonia and bacteraemia are frequently associated with osteoarticular infection. Interestingly, several reports have noted an association between CA-MRSA osteomyelitis and development of venous thrombosis.<sup>[84,88]</sup>

## 2.4 Other Infections

A variety of other manifestations of CA-MRSA infection have been reported. Infective endocarditis due to SCCmec type IV<sup>[89]</sup> and USA300 genotype MRSA has been described.<sup>[90]</sup> Sepsis can complicate virtually any manifestation of CA-MRSA disease, particularly pneumonia and osteomyelitis.<sup>[10,78,91]</sup> Sepsis presenting with purpura fulminans<sup>[92]</sup> and associated with Waterhouse-Friderichsen syndrome<sup>[93]</sup> have also been reported. Uncommon manifestations of CA-MRSA infection include meningitis,<sup>[94]</sup> cavernous sinus thrombosis,<sup>[95]</sup> puerperal mastitis<sup>[96,97]</sup> and ophthalmic infections.<sup>[98]</sup>

# 3. Defining CA-MRSA

The presence or absence of clinical risk factors for MRSA has been the basis of clinical definitions for CA- and HA-MRSA, and broad non- $\beta$ -lactam

antibacterial susceptibility is generally believed to be consistent with CA-MRSA. Initially, CA-MRSA strains were almost exclusively found in the outpatient setting. More recently, CA-MRSA strains have been increasingly isolated from hospitalized patients<sup>[96,99-105]</sup> and have caused infections that are generally considered to be healthcare related such as prosthetic joint infections<sup>[106]</sup> and surgical site infections.<sup>[107]</sup> Several studies suggest that community strains of MRSA are replacing or adding to the traditional nosocomial strains of MRSA in many populations.<sup>[108-110]</sup>

Defining CA- and HA-MRSA on clinical risk factors alone is becoming less useful as these strains intermingle within the healthcare setting. Antibacterial susceptibility phenotypes may still be useful to distinguish between some CA- and HA-MRSA strains, although increasing antibacterial resistance has been noted in some CA-MRSA isolates.<sup>[41]</sup> Epidemiological investigations may require molecular genotyping methods and identification of various marker genes (e.g. *SCCmec* type, virulence/toxin genes) in addition to clinical data to fully characterize MRSA isolates. Strict definitions for CA- and HA-MRSA should be used whenever possible, and could include molecular genotype assignment, *SCCmec* type, and the presence or absence of various genes such as PVL, type I ACME and *agr* type.

#### 4. Treatment of CA-MRSA Infections

Optimum management of CA-MRSA infections has not been determined. Current strategies include a combination of pharmacological and non-pharmacological interventions. In patients with recurrent infections, attempts to decolonize CA-MRSA are also frequently attempted, although the long-term benefit of this strategy remains unclear.

Many CA-MRSA are susceptible to several non- $\beta$ -lactam antibacterial classes, providing clinicians with several outpatient options (table III). Frequently, older antibacterials such as clindamycin, doxycycline and cotrimoxazole are prescribed for the treatment of CA-MRSA infections, despite a lack of specific MRSA indications for these drugs. For more serious infections,

vancomycin remains the standard of care for most patients who require intravenous therapy. Other alternatives include daptomycin, tigecycline and quinupristin/dalfopristin. In addition, linezolid is available in both oral and intravenous formulations. Ceftobiprole is currently under review for approval and may be another intravenous option in the near future. It is unclear if the newer antibacterials necessarily represent an efficacy advantage over older options and each has unique limitations to consider.

##### 4.1 Tetracyclines

Tetracyclines, particularly doxycycline and minocycline, have been used for many years clinically as treatment of *S. aureus* infections, especially SSTIs. At present, there have been no well designed clinical trial data published describing the efficacy of tetracyclines for the treatment of MRSA infections. One recent case series describes 24 patients with serious tetracycline-susceptible MRSA infections who were treated with either doxycycline or minocycline.<sup>[120]</sup> The types of infection in this series were complicated SSTI (16 patients), osteomyelitis or septic arthritis (five patients), urinary tract infection (two patients) and bacteraemia (one patient). Thirteen (54%) patients received doxycycline and clinical cure was achieved in 83% of patients. The authors reviewed published literature describing patients with *S. aureus* (both MSSA and MRSA) infections treated with tetracyclines and found 85 patients from nine studies. The overall cure rate in this group was 85%. Tetracyclines remain an option for the treatment of uncomplicated CA-MRSA SSTIs, but are generally not recommended for the treatment of invasive infections.

##### 4.2 Clindamycin

The emergence of CA-MRSA has renewed the empirical use of clindamycin, particularly for SSTIs. Clindamycin is a lincosamide that inhibits protein synthesis by binding to the bacterial 50S ribosomal subunit and has activity against several clinically important Gram-positive bacteria, including staphylococci, streptococci and anaerobes.



**Table III.** Antibacterials for the treatment of community-associated methicillin-resistant *Staphylococcus aureus* infections

Agent	Usual dosages	Adverse effects	Comments
Ceftibiprole <sup>[111]</sup>	500 mg IV q8h	Nausea, diarrhoea, vomiting	Not yet widely available
Clindamycin <sup>[112]</sup>	300–600 mg PO q6h 300–900 mg IV q8h	Nausea, diarrhoea, <i>Clostridium difficile</i> -associated disease	iMLS <sub>B</sub> resistance may reduce activity
Daptomycin <sup>[113]</sup>	4–6 mg/kg IV q12h	Rhabdomyolysis, myopathy	6 mg/kg IV indicated for bacteraemia; do not use to treat pneumonia
Doxycycline <sup>[114]</sup>	100 mg PO or IV q12h	Nausea, hypersensitivity to sunlight	Contraindicated in pregnancy, children aged <8 y; activity against GAS is unknown
Linezolid <sup>[115]</sup>	600 mg PO or IV q12h	Nausea, pancytopenia if used >2 wk, optic neuritis, lactic acidosis, potential for serotonin syndrome	Not recommended for the treatment of bacteraemia
Quinupristin/dalfopristin <sup>[116]</sup>	7.5 mg/kg IV q12h	Myalgias, arthralgias, infusion site inflammation	iMLS <sub>B</sub> resistance may reduce activity
Tigecycline <sup>[117]</sup>	100 mg IV once, then 50 mg IV q12h	Nausea, vomiting	Treatment of bacteraemia not recommended because of low serum concentration
Cotrimoxazole <sup>[118]</sup> (trimethoprim/ sulfamethoxazole)	160 mg PO q12h 2.5 mg/kg IV q12h	Rash, including Stevens-Johnson syndrome, cytopenias	Activity against GAS is unknown; not for use in infants aged <2 mo or during third trimester of pregnancy
Vancomycin <sup>[119]</sup>	15–20 mg/kg q8 to q12h	'Redman' syndrome, nephrotoxicity at higher doses, neutropenia, thrombocytopenia	Requires monitoring of trough concentrations when treating serious infection

**GAS**=group A streptococci; **iMLS<sub>B</sub>**=inducible macrolide-lincosamide-streptogramin B; **IV**=intravenous; **PO**=oral; **qxh**=every x hours.

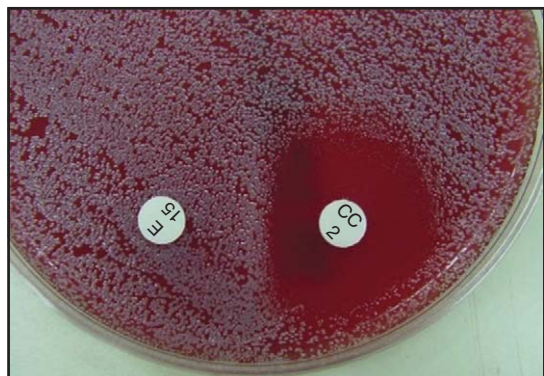
Resistance to clindamycin can be constitutive or inducible, and is related to methylation of the ribosomal binding site. *S. aureus* with inducible macrolide-lincosamide-streptogramin B (iMLS<sub>B</sub>) resistance will phenotypically be resistant to erythromycin and susceptible to clindamycin. Detection of iMLS<sub>B</sub> resistance can be performed using the double-disk diffusion test (D-zone test), in which an erythromycin disk will induce clindamycin resistance (see figure 1).<sup>[121]</sup> *S. aureus* that express iMLS<sub>B</sub> have an increased rate of spontaneous mutation to constitutive resistance (erythromycin and clindamycin resistant), which may become apparent during therapy with clindamycin.

Prevalence of iMLS<sub>B</sub> resistance appears to be more common in HA-MRSA than CA-MRSA strains. A single-centre characterized 308 MRSA isolates between 2004 and 2006. Inducible clindamycin resistance was present in 8.4% of 102 CA-MRSA and 50% of 115 HA-MRSA isolates ( $p \leq 0.001$ ).<sup>[104]</sup> The prevalence of iMLS<sub>B</sub> resistance in clinically defined CA-MRSA was noted to decrease in one community from 93% in

1999 to 7% in 2002.<sup>[122]</sup> The decline in the prevalence of iMLS<sub>B</sub> resistance was associated with the emergence of MRSA strains consistent with USA300 genotype and is likely to represent a clonal shift as USA300 CA-MRSA became endemic in that community.

Expression of iMLS<sub>B</sub> resistance associated with clinical failure of clindamycin has been reported, as have cases of patients who were successfully treated with clindamycin despite infection with iMLS<sub>B</sub> MRSA strains.<sup>[123–128]</sup> *In vitro* and *in vivo* experiments in a neutropenic mouse thigh abscess model suggest clindamycin activity against iMLS<sub>B</sub> CA-MRSA strains is partially impacted by inoculum size, exerting only bacteriostatic activity and selection for resistant bacteria when higher inoculum of bacteria is present.<sup>[129]</sup> In non-inducible CA-MRSA, clindamycin maintained bactericidal activity at higher bacterial inoculum.

Evaluation for the presence of iMLS<sub>B</sub> resistance by the D-zone test is recommended for all MRSA isolates exhibiting the erythromycin-resistant, clindamycin-susceptible phenotype. Alternatives to clindamycin should be considered



**Fig. 1.** Double-disk diffusion (D-zone) test for identification of inducible macrolide-lincosamide-streptogramin B (iMLS<sub>B</sub>) resistance. An erythromycin disc (E) and clindamycin disc (CC) are placed on sheep blood agar streaked with *Staphylococcus aureus*. Note the blunted zone of growth inhibition in the region between the two discs, forming a zone of clearing in the shape of the letter 'D'. This represents a positive D-zone test, indicating the presence of iMLS<sub>B</sub> resistance.

for the treatment of MRSA infections that express iMLS<sub>B</sub>, particularly if there is a large burden of infection, as in the setting of undrained abscesses or osteomyelitis.

#### 4.3 Cotrimoxazole

Folate antagonists have been used for the treatment of staphylococcal infections for decades. Although largely replaced with  $\beta$ -lactam agents or vancomycin in the past, the emergence of CA-MRSA has led to renewed interest in the off-label use of folate antagonists for the treatment of *S. aureus* infections. The combination of trimethoprim and sulfamethoxazole blocks folate biosynthesis, necessary for thymidine biosynthesis, by inhibition of two different enzymes. Sulfonamides inhibit dihydropteroate synthase and are bacteriostatic; trimethoprim inhibits tetrahydrofolate reductase. The combination of trimethoprim and sulfamethoxazole is bactericidal.<sup>[130,131]</sup>

Resistance to cotrimoxazole can occur if there are mutations in both target enzymes and can be spread horizontally by plasmids encoding the altered genes encoding resistance.<sup>[132]</sup> Addition of exogenous thymidine can also reverse the antistaphylococcal effects of folate antagonists.

Injured tissue and inflammatory cells release DNA, which *S. aureus* thermonuclease utilizes to release thymidine.<sup>[133,134]</sup> Susceptibility of CA-MRSA to cotrimoxazole remains high with 91.1% of isolates from the SENTRY Antimicrobial Surveillance Program susceptible.<sup>[135]</sup>

Despite the widespread use of cotrimoxazole for MRSA infection, it does not have a specific US FDA approved indication for the treatment of *S. aureus* infections. Only one randomized, prospective trial studying the efficacy of cotrimoxazole has been published. In this study, cotrimoxazole was compared with vancomycin for the treatment of *S. aureus* (MSSA and MRSA) infections in injection drug users.<sup>[130]</sup> Infection was caused by MRSA in 46% of patients and 64% of patients were bacteraemic, including some with endocarditis, and SSTIs were noted in 32%. Overall efficacy was 86% (95% CI 76, 96) for cotrimoxazole and 98% (95% CI 94, 100) for vancomycin. No statistically significant differences were noted between the treatment groups in terms of duration of fever, bacteraemia or positive wound cultures in the MRSA infected patients. All treatment failures occurred in patients with MSSA infections.

More recent evaluations of the efficacy of cotrimoxazole for the treatment of SSTIs are more likely to have included CA-MRSA strains, although no study to date has specifically reported efficacy in CA-MRSA strains. One urban ambulatory clinic noted an increase in MRSA SSTIs starting in 2002 that subsequently became more common than MSSA SSTIs by 2005.<sup>[136]</sup> During the same period of time, empirical cotrimoxazole use and clinical resolution of *S. aureus* SSTIs was noted, although this may have been affected by a concurrent increase in the number of patients who had incision and drainage procedures of their infection, which some authors have suggested as possibly having a greater impact on resolution of uncomplicated SSTIs than antibacterial choice.

Despite the lack of efficacy data for the treatment of CA-MRSA specifically, cotrimoxazole has become a common empirical agent for patients with suspected MRSA SSTI as it is convenient and generally well tolerated. An important

disadvantage of cotrimoxazole is its reduced activity against group A streptococci precluding its use if streptococcal infection is suspected, and an alternative agent such as clindamycin may be more appropriate for its broader Gram-positive spectrum of activity.

#### 4.4 Vancomycin

Vancomycin has been the preferred therapy for serious MRSA infections and is generally well tolerated with a low incidence of adverse effects. Despite its long history as the 'gold standard' of MRSA therapy, some data suggest that glycopeptide susceptibility may be decreasing and clinical failures of vancomycin therapy are increasing. Based on a growing body of evidence suggesting reduced vancomycin efficacy in treating isolates with borderline susceptible minimum inhibitory concentrations (MICs), the vancomycin susceptibility breakpoints were reduced in 2006.<sup>[137]</sup> The vancomycin breakpoints were lowered from  $\leq 4$  to  $\leq 2$   $\mu\text{g/mL}$  for 'susceptible', from 8–16 to 4–8  $\mu\text{g/mL}$  for 'intermediate' and from  $\geq 32$  to  $\geq 16$   $\mu\text{g/mL}$  for 'resistant'. Vancomycin is not recommended for the treatment of vancomycin-resistant *S. aureus* or vancomycin-intermediate *S. aureus* (VISA).

Evaluation of a large collection of *S. aureus* strains between 1997 and 2003 did not show increasing vancomycin MICs and isolates with vancomycin MIC  $> 2$   $\mu\text{g/mL}$  were uncommon.<sup>[138]</sup> In contrast, evaluation of *S. aureus* from single centres have shown significant increases in vancomycin MICs over time.<sup>[139,140]</sup> It is important to note that, although the vancomycin MICs increased over time, they still remained within the susceptible range for *S. aureus*. The differences in changes in vancomycin MIC may be related to the local vancomycin usage, with higher use associated with increased vancomycin MICs.

The significance of high-susceptible range vancomycin MICs is unclear, although as the MIC increases, the frequency of heteroresistant VISA (hVISA) strains also increases.<sup>[141]</sup> hVISA strains appear to be susceptible to vancomycin on routine susceptibility testing, but may harbour

subpopulations of VISA that may be selected for by vancomycin treatment.

Several studies suggest that vancomycin efficacy may be reduced when treating MRSA infections with vancomycin MICs in the high-susceptible range.<sup>[142–145]</sup> Two studies with different designs have noted vancomycin MIC of 1.5  $\mu\text{g/mL}$ <sup>[145]</sup> and 2.0  $\mu\text{g/mL}$ <sup>[142]</sup> are predictors of clinical failure and mortality, respectively. All of the published studies have important limitations including retrospective study design for many of the studies, absence of specific vancomycin administration information and trough concentrations, inclusion of study populations that may be biased towards failure by previous extensive vancomycin failure and absence of information regarding non-pharmacological treatment strategies (e.g. central venous catheter removal, surgical interventions) that could affect infection outcomes. Further prospective studies are needed to define the role of vancomycin in the treatment of high-susceptible MIC *S. aureus*.

Although vancomycin heteroresistant USA300 MRSA strains have been identified, most CA-MRSA strains remain highly susceptible.<sup>[146,147]</sup> Monitoring of vancomycin trough concentrations, treatment response and changes in vancomycin MIC should be performed in patients with invasive CA- and HA-MRSA infections. High-dose vancomycin therapy has been suggested by some (maintaining vancomycin target trough concentrations of 15–20  $\mu\text{g/mL}$ ), although nephrotoxicity may be more common in this dose administration strategy.<sup>[148]</sup> Rising vancomycin MICs may indicate the presence of hVISA strains and alternative therapy should be considered in these situations, especially if clinical response is unsatisfactory.

#### 4.5 Daptomycin

Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against almost all Gram-positive cocci including MRSA. Although the precise mechanism of action has not been elucidated, daptomycin is hypothesized to cause membrane depolarization via calcium-dependent insertion into the bacterial membrane.<sup>[149]</sup>

Evaluation of large collections of MRSA indicated all MRSA tested were susceptible to daptomycin with a MIC at which 90% of bacteria are inhibited (MIC<sub>90</sub>) of 0.5 µg/mL.<sup>[150,151]</sup> Decreasing susceptibility to daptomycin has been reported to occur in clinical *S. aureus* isolates both in patients with and without prior exposure to daptomycin.<sup>[152-156]</sup> hVISA may have an increased daptomycin MIC value, probably as a consequence of a thickened cell wall. Although vancomycin and daptomycin have different mechanisms of action, both mechanisms are directly related to the bacterial cell wall and the increased thickness may provide a physical barrier that limits the drug binding and activity. Decreasing susceptibility to daptomycin was reported in a USA300, PVL-positive CA-MRSA isolate from a patient with aortic valve endocarditis.<sup>[157]</sup>

Daptomycin is approved for the treatment of complicated SSTIs (including MRSA), *S. aureus* (MSSA and MRSA) bacteraemia and right-sided endocarditis based on prospective, randomized clinical trials using vancomycin or antistaphylococcal penicillins as comparators.<sup>[158,159]</sup> In both the SSTI and bacteraemia trials, daptomycin was found to be noninferior to the comparator regimen. In the bacteraemia trial, low success rates were noted among patients with left-sided endocarditis in both the daptomycin and standard therapy groups (11.1% vs 22.2%, respectively).

Observational studies have described the efficacy of daptomycin for a variety of infections including osteomyelitis,<sup>[160,161]</sup> septic arthritis<sup>[162]</sup> and prosthetic joint infections<sup>[163]</sup> with varying degrees of success. At present, no prospective clinical trials have been performed to thoroughly evaluate the efficacy of daptomycin for the treatment of osteoarticular infections.

Daptomycin is not recommended for the treatment of pneumonia. In a phase III clinical trial for the treatment of CAP, daptomycin failed to achieve non-inferiority to ceftriaxone (79% vs 87% efficacy).<sup>[164]</sup> *In vitro* experiments have shown that pulmonary surfactant interacts directly with daptomycin and inhibits its antibacterial activity. Daptomycin irreversibly inserts into surfactant lipid aggregates.<sup>[164]</sup> Surfactant is not likely to be present in quantities to affect

daptomycin activity in pulmonary abscesses and thus daptomycin may still be active in patients with tricuspid endocarditis complicated by pulmonary abscesses.

Daptomycin is generally well tolerated with a low incidence of renal dysfunction noted in the bacteraemia trial.<sup>[159]</sup> Elevation of creatine kinase (CK) with or without muscle pain has been noted in patients on daptomycin therapy. Among 534 patients with complicated SSTI receiving daptomycin 4 mg/kg, 0.2% reported myopathy.<sup>[158]</sup> In the bacteraemia trial (using daptomycin 6 mg/kg), elevation of CK to >500 IU/L was more common in the daptomycin arm than the standard therapy arm (9.5% vs 1.5%; *p*=0.02). CK levels normalized either with discontinuation of daptomycin or after completion of therapy. It is recommended that daptomycin-treated patients have CK levels monitored at baseline and weekly thereafter, and that the use of other drugs that may similarly increase CK or cause myopathy (e.g. HMG-CoA reductase inhibitors) is suspended. CK levels >1000 IU/L associated with unexplained myopathy or asymptomatic patients with CK levels ≥5 to 10 times the upper limit of normal (ULN) should have daptomycin discontinued.

#### 4.6 Linezolid

Linezolid is a bacteriostatic, synthetic oxazolidinone that inhibits protein synthesis at the 50S ribosome and is active *in vitro* against *S. aureus* including MRSA, penicillin-resistant *S. pneumoniae* and vancomycin-resistant enterococci. Linezolid is available in both intravenous and oral formulations, and is approved in the US for the treatment of complicated SSTIs and nosocomial pneumonia caused by susceptible bacteria.

Patients with nosocomial pneumonia treated with linezolid were noted to have a significantly higher clinical cure rate than patients treated with vancomycin plus aztreonam in double-blind clinical trials (59% vs 36%, respectively; *p*<0.01).<sup>[165]</sup> Low cure rates in the vancomycin treatment arm suggest subtherapeutic vancomycin administration may have occurred as trough concentrations were not measured in these trials.

Linezolid is hypothesized to achieve higher lung tissue concentrations than vancomycin,<sup>[166-168]</sup> and thus may have an advantage over vancomycin for the treatment of pneumonia, although a recent clinical trial found that early microbiological response was similar in patients with MRSA ventilator-associated pneumonia who were treated with linezolid versus vancomycin.<sup>[169]</sup> Linezolid has not been evaluated specifically for the treatment of CA-MRSA necrotizing pneumonia, although it remains as an important option because it may reduce toxin production in *S. aureus* in addition to its antibacterial effects.<sup>[170]</sup>

Although a retrospective review of linezolid clinical trials shows patients with bacteraemia had similar outcomes to comparator drugs,<sup>[171]</sup> the role of linezolid for the treatment of *S. aureus* bacteraemia remains unclear. An open-label, randomized clinical trial comparing linezolid with vancomycin for the treatment of catheter-associated bloodstream infections was terminated early because of higher mortality in the linezolid arm.<sup>[172]</sup> The mortality difference was seen in patients with Gram-negative, mixed Gram-positive/Gram-negative infections, or no infection, and not in patients with Gram-positive infections alone. *Post hoc* analysis showed that treatment for infection with Gram-negative pathogens may have been inadequate in more than half of the deaths. Nonetheless, given the limited data available and bacteriostatic mode of action of linezolid, alternative agents should be considered for the treatment of bacteraemia.

The most common adverse reactions to linezolid include nausea, vomiting and diarrhoea. Significant limiting adverse effects include reversible thrombocytopenia,<sup>[173]</sup> serotonin toxicity,<sup>[174,175]</sup> peripheral neuropathy,<sup>[176]</sup> optic neuritis<sup>[177]</sup> and lactic acidosis.<sup>[178]</sup> Patients who receive >2 weeks of linezolid therapy should have weekly monitoring for myelosuppression. The ability of linezolid to cause serotonin syndrome is related to its weak non-selective inhibition of monoamine oxidase. Drugs with serotonergic activity (e.g. serotonin reuptake inhibitors, monoamine oxidase inhibitors, pethidine [meperidine], bupropion) should not be used concomitantly with linezolid.

#### 4.7 Quinupristin/Dalfopristin

Quinupristin/dalfopristin is a combination streptogramin agent that is approved for the treatment of SSTIs due to MSSA and streptococci, and for the treatment of vancomycin-resistant *Enterococcus faecium* bacteraemia. Individually, quinupristin (a group B streptogramin) and dalfopristin (a group A streptogramin) are bacteriostatic, but the combination of quinupristin/dalfopristin is bactericidal against *S. aureus* via inhibition of protein synthesis by interfering with different components of 23S RNA in the 50S subunit of the bacterial ribosome. Resistance to quinupristin/dalfopristin is conferred by the *MLS<sub>B</sub>* methylation mechanism previously described (section 4.2). Constitutive resistance confers resistance to quinupristin; however, synergy with streptogramin A agents may be retained,<sup>[179]</sup> although the activity may become bacteriostatic. Among *S. aureus* strains exhibiting *iMLS<sub>B</sub>* resistance, quinupristin remains active, as it is not an inducer of the methylase.

Quinupristin/dalfopristin has been studied for the treatment of MRSA infections in an open-label, emergency-use programme.<sup>[180]</sup> Patients with documented MRSA infections and who were either not responding to or intolerant of other MRSA active antibacterials were included in this study. Overall successful treatment was noted in 66.7% of patients who were clinically and bacteriologically evaluable, but this was largely driven by success in treating osteoarticular infections and SSTIs. Therapy failed in two patients with endocarditis. The *MLS<sub>B</sub>* resistance phenotype (susceptible, constitutive or inducible resistance) did not appear to affect the response to therapy. Use of quinupristin/dalfopristin has been limited by its significant adverse effects including infusion site pain, arthralgias and myalgias, which can be severe enough to lead to discontinuation of therapy.<sup>[181]</sup>

#### 4.8 Tigecycline

Tigecycline is a semisynthetic glycylcycline that has an expanded broad-spectrum antibacterial with activity against Gram-positive, Gram-negative, anaerobic and various atypical pathogens.

Although derived from minocycline, an altered 9-t-butylglycylamido side chain confers a broader spectrum of activity and allows tigecycline to overcome tetracycline resistance. Tigecycline has *in vitro* activity against several drug-resistant pathogens including MRSA, VISA, vancomycin-resistant enterococci and many extended-spectrum  $\beta$ -lactamase Gram-negative bacteria. Tigecycline has limited or no activity against *Pseudomonas* spp. and reduced activity against *Proteus mirabilis*.

Glycycyclines are bacteriostatic and exhibit activity by binding to bacterial 30S ribosomal subunit, preventing protein synthesis. Steric hindrance produced by the large substituent at position 9 allows tigecycline to overcome the major mechanisms of tetracycline resistance: active efflux of the drug out of the bacterial cell and ribosomal protection.<sup>[182]</sup> Tigecycline MIC values against MRSA are generally low, ranging from  $\leq 0.06$  to  $2 \mu\text{g/mL}$ .<sup>[183]</sup> Among 1989 clinical isolates of CA-MRSA from North America, tigecycline was active against 98.2% of strains at the susceptibility breakpoint of  $\leq 0.5 \mu\text{g/mL}$ , the remaining 1.8% had an MIC of  $1.0 \mu\text{g/mL}$ .<sup>[135]</sup> The majority of these strains were SCCmec type IV, PVL-positive MRSA (94.7%) and 88.4% were PFGE genotype USA300-0114.

The pharmacokinetic and pharmacodynamic properties of tigecycline have been well described elsewhere.<sup>[184]</sup> It is important to note that tigecycline is extensively distributed in tissues and there is a rapid decline in plasma concentration during the first 2 hours after administration.<sup>[184]</sup> Based on its relatively low plasma concentration, tigecycline should be used with caution in patients with suspected or proven bacteraemia.

Tigecycline is approved in the US for the treatment of complicated SSTI, including MRSA, and for complicated intra-abdominal infections (including MSSA but not MRSA infection). Tigecycline was noninferior to the combination of vancomycin and aztreonam for the treatment of complicated SSTIs in pooled data from two phase III, double-blind studies.<sup>[185]</sup> Nausea and vomiting were the most common adverse effects reported in the clinical trials. Later evaluation of the MRSA strains from all of the tigecycline registrational studies found that 76 of 173 (44%)

isolates had at least one genetic feature associated with CA-MRSA.<sup>[186]</sup>

#### 4.9 Ceftobiprole

Ceftobiprole is a broad-spectrum cephalosporin that retains activity against MRSA by tightly binding to penicillin-binding protein 2a, the major determinant of methicillin resistance in staphylococci. Ceftobiprole is administered intravenously and appears to have a low potential to select for resistance. Prolonged serial passage in the presence of subinhibitory concentrations of ceftobiprole failed to select for clones with MIC values  $>4$  times the parent strains, with a maximum MIC of  $8 \mu\text{g/mL}$  in only one of ten strains tested.<sup>[187]</sup>

A randomized, double-blind trial comparing ceftobiprole with vancomycin plus ceftazidime for the treatment of complicated SSTI showed noninferiority of ceftobiprole monotherapy.<sup>[111]</sup> Infection due to MRSA was present in 22% and 18% of the ceftobiprole and comparator arms, respectively, with the majority of the remainder of infections due to MSSA, Enterobacteriaceae, *P. aeruginosa* and streptococci. Among MRSA-infected patients, PVL-positive strains were present in 92% and 84% of ceftobiprole and comparator arms, respectively. *In vitro* susceptibility testing of SCCmec type IV CA-MRSA isolates found all isolates were susceptible to ceftobiprole with MIC<sub>50</sub> and MIC<sub>90</sub> values of 1 and  $2 \mu\text{g/mL}$ , respectively.<sup>[188]</sup> Ceftobiprole has been approved for the treatment of complicated SSTI including diabetic foot infections in Canada and Switzerland, and is currently under review for approval by regulatory authorities in the US, EU and Australia.

#### 4.10 Other Agents and Combination Therapy

Many CA-MRSA strains show susceptibility to fluoroquinolone agents.<sup>[5,104]</sup> Despite the *in vitro* susceptibility, fluoroquinolones are not recommended as therapy for suspected or proven MRSA infections because of concerns about the acquisition of resistance during therapy.<sup>[189,190]</sup> Rifampin is active against many CA-MRSA isolates, but is not recommended as monotherapy

for the treatment of *S. aureus* infections because of the rapid emergence of resistance that can occur during therapy.<sup>[191]</sup> Combination therapy of rifampin with other anti-staphylococcal agents, particularly tetracyclines and cotrimoxazole, has been used for the treatment of CA-MRSA, although there are limited data supporting this practice.<sup>[192]</sup>

#### 4.11 Investigational Agents

Several investigational agents for the treatment of MRSA infections have completed phase II or III studies and may potentially be available pending approval. Dalbavancin is a semisynthetic glycopeptide that has the unique characteristic of having a long half-life allowing for once-weekly administration.<sup>[193]</sup> The dose administration regimen is 1000 mg intravenously on day 1, then 500 mg intravenously on day 8. It inhibits cell-wall synthesis and exhibits concentration-dependent bactericidal activity. In a phase II study comparing dalbavancin to twice-daily linezolid therapy for 14 days, MRSA eradication was similar in the two groups (91% of dalbavancin recipients and 89% of linezolid recipients). However, clinical cure was not specifically reported.<sup>[194]</sup> An open-label, phase II study of catheter-related Gram-positive bacteria bloodstream infections showed dalbavancin was superior to vancomycin in curing infection (87% vs 50%;  $p < 0.05$ ), although the number of patients with MRSA infection was small.<sup>[195]</sup>

Telavancin is a rapidly bactericidal lipoglycopeptide that exhibits activity through inhibition of cell-wall synthesis and membrane depolarization.<sup>[196]</sup> It has a long half-life of 7–9 hours allowing once-daily administration using 7.5–10 mg/kg/day. Telavancin has completed phase III studies with vancomycin as the comparator in patients with SSTI.<sup>[197]</sup> In these studies, MRSA caused a significant number of infections and most of these isolates were SCCmec type IV and PVL positive.<sup>[198]</sup> Telavancin therapy led to cure in 90.6% of patients versus 86.4% of vancomycin-treated patients. It is currently under review by regulatory authorities in the US.

Oritavancin is a semisynthetic glycopeptide that has completed phase III studies of efficacy in the treatment of complicated SSTI, although complete clinical details of these studies are not yet available.<sup>[199,200]</sup> Favourable outcomes were noted in the oritavancin-treated patients compared with those who received vancomycin followed by cephalexin. Oritavancin appears to exhibit a dual mode of action to inhibit cell-wall synthesis,<sup>[201]</sup> and has been shown to demonstrate activity against vancomycin-resistant staphylococci and enterococci.<sup>[202]</sup>

Other agents that are under study include the broad-spectrum cephalosporin ceftaroline and the diaminopyrimidine dihydrofolate reductase inhibitor iclaprim. Both agents have activity against MRSA and clinical studies are ongoing.<sup>[203–208]</sup>

#### 4.12 Non-Pharmacological Therapy of CA-MRSA Infections

Data from epidemiological studies<sup>[25,27,209]</sup> and randomized trials<sup>[210,211]</sup> have noted cure of uncomplicated CA-MRSA SSTIs following incision and drainage despite the use of non-MRSA active antibacterial. Incision and drainage is recommended for any suspected uncomplicated cutaneous abscess and may be sufficient without systemic antibacterial therapy.<sup>[212,213]</sup> Systemic antibacterial therapy is warranted in addition to incision and drainage if surrounding cellulitis or fever is present.<sup>[212,213]</sup>

The importance of removing intravascular catheters or implanted prosthetic devices whenever possible cannot be overstated if these devices are potentially contaminated with *S. aureus*. Even in the presence of appropriate antibacterial therapy, infection can persist on artificial devices and lead to prolonged infection or treatment failure.

#### 4.13 Clinical Approach to Diagnosis and Therapy of CA-MRSA Infections

The ideal approach to management of CA-MRSA infection has not been determined, but current expert opinion suggests a combination of medical and surgical therapy based on the extent of infection.<sup>[214,215]</sup> CA-MRSA should be

considered as a cause of infection in patients presenting with disease consistent with frequently described manifestations, particularly SSTIs (especially if there is a description of 'spider bite'), fasciitis and myositis, necrotizing pneumonia and haematogenous osteoarticular infections. Culture data should be obtained whenever possible to guide antibacterial therapy, particularly if there is little response to empirical therapy. Incision and drainage of furuncles or carbuncles should be performed and may be sufficient therapy alone without antibacterial therapy for uncomplicated soft-tissue infections. Empirical antibacterial therapy with an MRSA-active agent is recommended if cellulitis is present in addition to abscess or if the patient is immunocompromised, has severe local infection or does not improve after incision and drainage.<sup>[215]</sup> Complicated SSTIs and suspected invasive CA-MRSA infection may require initial therapy with intravenous agents. The choice of antibacterial agent should be dictated by the type and severity of infection, patient factors (e.g. allergies, concomitant medications), potential drug adverse effects, cost and availability, and culture susceptibilities if available.

## 5. Decolonization of CA-MRSA

Decolonization of *S. aureus* carriage is often attempted to prevent recurrent CA-MRSA infection. Numerous strategies have been proposed, but the most common include the use of nasal mupirocin to eradicate nasal carriage, topical chlorhexidine gluconate to eradicate other cutaneous skin carriage and occasionally systemic antibacterial agents. The efficacy of these various strategies in preventing recurrent CA-MRSA infections has not been evaluated, but can be an adjunct to environmental hygiene and cleaning.<sup>[214]</sup> Colonization has been suggested to play a lesser role in the spread of CA-MRSA than person-to-person transmission and contaminated fomites, thus limiting the impact of decolonization.<sup>[216]</sup> Consultation with an infectious diseases expert is recommended when considering decolonization strategies for patients with recurrent CA-MRSA infections.

## 6. Conclusions

The rapid emergence and spread of CA-MRSA highlights the difficulty of treating drug-resistant bacteria combined with an apparently more virulent strain. Initial reports of CA-MRSA infections represented focal outbreaks in specific populations, but current data indicate that CA-MRSA is now endemic in many regions of the world. In communities where CA-MRSA is endemic, empirical therapy for common manifestations of CA-MRSA disease, particularly SSTIs, should include MRSA active antibacterials. Clinical trials are needed to determine the optimal antibacterial therapy for CA-MRSA infections as well as the role of decolonization in preventing recurrent infections. In addition, further basic research into the virulence mechanisms of CA-MRSA strains may yield targets for non-pharmacological therapies.

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