

Not Community-Associated Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA)! A Clinician's Guide to Community MRSA - Its Evolving Antimicrobial Resistance and Implications for Therapy

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There is significant diversity in methicillin-resistant *Staphylococcus aureus* (MRSA) clones arising in the community worldwide, with considerable geographical differences in typical antimicrobial resistance profiles. Many community clones of MRSA have a non-multidrug resistant antimicrobial profile, providing increased options for empirical and directed therapy of infections caused by these strains. However, the recent description of increasing non- β lactam resistance in community clones of MRSA, especially USA300, provides a timely warning for clinicians making decisions about therapy for patients potentially infected with these strains. Continued monitoring of global epidemiology and emerging drug resistance data is critical for the effective management of these infections.

Antibiotic resistance has long been a problem with *Staphylococcus aureus*. In particular, methicillin-resistant *S. aureus* (MRSA) rapidly emerged in hospitals after the introduction of methicillin [1]. Although initially a hospital-associated problem, MRSA is well described in patients with no contact with the hospital environment; these isolates have been termed community-associated MRSA or “CA-MRSA”. This phenomenon was first described in patients from the remote Kimberley region in Western Australia in the early 1990s and has subsequently been reported worldwide [2–5]. Although hospital-associated MRSA clones are often

multidrug resistant, many of these newer MRSA clones have retained susceptibility to non- β lactam antibiotics, such as macrolides, tetracyclines, quinolones, lincosamides, and trimethoprim-sulfamethoxazole, providing increased options for the treatment of infections caused by these strains. However, recent evolving resistance in these MRSA clones, such as in USA300, threatens the use of some of these agents [6]. This review will describe the global epidemiology of MRSA, with specific emphasis on these newer clones arising in the community; discuss regional data on evolving antibiotic resistance patterns; and the implications for treatment of MRSA infection. Of note, there is potential selection bias in describing community MRSA epidemiology, with some regions more likely to detect, characterize, and report these strains compared with others.

DEFINING CA-MRSA: THE FIRST HURDLE

Currently, there is no single definition that can reliably distinguish community MRSA from traditional hospital-associated MRSA. The term “CA-MRSA” has been

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Table 1. Examples of Definitions Used for Community-Associated Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA)

Reference	Patient Population	Resistance Phenotype	Genotype
Centers for Disease Control and Prevention [9]	Diagnosis of MRSA in the outpatient setting or by positive culture within 48 hours of hospital admission. No history of MRSA infection or colonization. No history in the past year of: (1) Hospitalization (2) Admission to a nursing home, skilled nursing facility, or hospice (3) Dialysis (4) Surgery No permanent indwelling catheters or medical devices that pass through the skin into the body	Not defined	Not defined
Herold et al. [3]	Isolate from a specimen obtained within 72 hours of hospital admission. No identified risks including: (1) Hospitalization (2) Previous hospitalization or antimicrobial therapy within past 6 months (3) History of endotracheal intubation, underlying chronic disorder, presence of an indwelling venous or urinary catheter, a history of any surgical procedure (4) Notation in the medical record of a household contact with an identified risk factor	Not defined	Not defined
Vandenesch et al. [5]	Positive culture within 48 hours after hospital admission No risk factors for nosocomial acquisition, including no hospitalizations or nursing home residence in the year before admission	Generally susceptible to most of antibiotics tested apart from β lactams	Novel smaller variant of SCC <i>mec</i> (for example SCC <i>mec</i> IV). <i>lukSF-PV</i> gene locus positive
O'Brien et al. [10]	Isolates from people who have had little or no contact with health care facilities or workers	Non multiresistant: Strains resistant to <3 of the following non- β lactams: GEN, ERY, TET, TMP, RIF, FA, CIP, MUP	SCC <i>mec</i> IV Multiple clones described based on MLST

NOTE. CIP ciprofloxacin; ERY, erythromycin; FA, fusidic acid; GEN, gentamicin; MLST, multi-locus sequence type; MUP, mupirocin; RIF, rifampin; TET, tetracycline; TMP, trimethoprim.

used interchangeably to describe the source of the infection, the antibiotic phenotype, and the genotype of the organism, resulting in considerable confusion in defining the problem. Community MRSA clones usually cause community-onset infection and are usually non-multidrug resistant. Frequently, they carry SCC*mec* allotypes IV and V and also the *lukSF-PV* genes, which encode Pantone-Valentine leukocidin (PVL), a leukotoxin that may be associated with more severe disease presentations [1, 7]. However, there are exceptions to all these rules [8]. Although the Centers for Disease Control and Prevention (CDC) definition of CA-MRSA is the most widely accepted [9], there are varying definitions as to what constitutes community MRSA (Table 1). To add to the potential confusion, the evolving nature of MRSA resistance and epidemiology means that many of the listed definitions can become inaccurate and obsolete. To complicate matters further, a number of different molecular typing methods have been used to identify community MRSA clones, including multilocus sequence typing, pulsed field gel electrophoresis, and *spa* typing [1]. For the purposes of this review, we will avoid the term “CA-MRSA”, but have included clones that are described in the literature as representing community MRSA. We will use multilocus sequence typing

and SCC*mec* typing to describe MRSA clones. For example, ST8-MRSA-IV indicates that a *S. aureus* isolate is MLS type 8, methicillin resistant and contains SCC*mec*IV. This standard nomenclature is unambiguous and allows for comparison of results between laboratories. Other typing nomenclature is included only if there is widespread use of these terms.

GLOBAL EPIDEMIOLOGY AND EMERGING RESISTANCE

The global epidemiology of community MRSA is remarkably heterogeneous (Figure 1). In some regions, a single clone dominates (eg, USA300 in the United States), whereas in other regions, multiple clones have been identified (eg, there are >100 clones described in Australia). The clinical presentation, known risk factors, and typical non- β lactam susceptibility profile are summarized in Table 2 and Figure 2.

NORTH AMERICA

Community MRSA strains circulating in the USA are pulsed field type USA300 (ST8-MRSA-IV), USA400 (ST1-MRSA-IV),

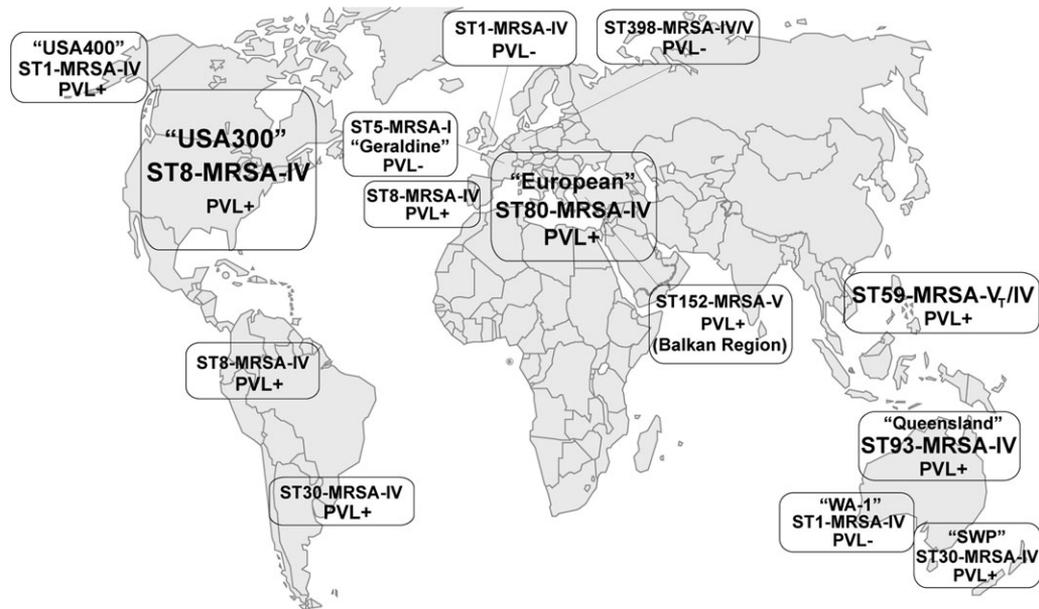


Figure 1. Global distribution of dominant community methicillin-resistant *Staphylococcus aureus* (MRSA) clones and Panton Valentine leukocidin (PVL) status.

USA1000 (ST59-MRSA-IV), and USA1100 (ST30-MRSA-IV) [29]. The dominant clones USA300 and USA400 carry *lukSF-PV*. Community MRSA was first well documented in children in the United States in the late 1990s, with infections caused by USA400 [1, 3, 15]. It is now clear that USA300 has overtaken USA400 as the epidemic clone in most of the United States, except Alaska [14, 30]. The situation in Canada is similar to that in the United States, with USA300 becoming increasingly common [31].

Resistance Profile of USA300 and USA400

The usual antibiotic susceptibility profile of USA300 and USA400 is summarized in Table 2. Of all the community MRSA clones, increasing non- β lactam resistance has been described predominately in USA300 (Figure 2). The typical antibiotic profile of USA300 is susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, and tetracycline and resistance to erythromycin and gatifloxacin [13]. The CDC recommends that isolates that test resistant to erythromycin and susceptible to clindamycin be subjected to further testing for inducible clindamycin resistance (ie, the D-test), because there have been reports of clindamycin treatment failures in this context [32]. In USA300 isolates, resistance to erythromycin was almost uniform (92.8%), whereas the clindamycin resistance rate was 6.5% (1.8% inducible) [13].

In the population of men who have sex with men in San Francisco and Boston, multidrug resistance in USA300, mediated by a large conjugative plasmid carrying genes encoding resistance to mupirocin, macrolides, and clindamycin, has been described [33, 34]. These multidrug-resistant isolates may also

harbor another plasmid that confers resistance to tetracycline (resistance rate, 63%) and may also express chromosomally encoded resistance to ciprofloxacin in up to 77% of cases [33]. Although these tetracycline-resistant isolates may appear to be susceptible to doxycycline, resistance to this agent has been induced in vitro [35]. Fortunately, susceptibility to TMP-SMX has been preserved. There has also been increasing clindamycin resistance reported in other populations, including children [36]. In the Active Bacterial Core Surveillance system study of USA300 isolates, a conjugative plasmid carrying the high-level mupirocin resistance gene and genes encoding gentamicin, TMP, and clindamycin resistance was found [12]. Rarely, there have been case reports of patients with deep-seated USA300 infections in which the isolates developed intermediate resistance to vancomycin and nonsusceptibility to daptomycin after treatment with vancomycin [37, 38]. Typically, USA400 is resistant to erythromycin and clindamycin but susceptible to other agents [14].

EUROPE

European community MRSA is very heterogenous, and accurate description of MRSA epidemiology is made difficult by the lack of standardized surveillance, clonal diversity, and the high degree of geographical segregation of clones. Fortunately, there is relatively low prevalence of community MRSA in Europe, despite high rates of hospital-associated MRSA in many countries. Countries with the lowest incidence of MRSA infection (eg, northern European countries) are paradoxically those for which data are the most readily available and accurate. However, these data probably cannot be extrapolated to all of Europe.

Table 2. Summary of Genetic Features, Clinical Profile, and Antimicrobial Susceptibility of Dominant Global Clones of Community Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Region	Dominant MRSA clones	Frequency	Typical disease pattern	Risk factors	<i>lukSF-PV</i> pos	Typical non-β lactam susceptibility (% susceptible)										Isolate collection dates and References
						ERY	CLI	TMP/SMX	TET	FQ	VAN	RIF	FA	AG	MUP	
North America	USA300 (ST8-MRSA-IV)	97% of MRSA presenting as community SSTI [4]	SSTI most common. Also reports of bacteremia, necrotizing fasciitis, severe pneumonia including post influenza [6, 11].	Has spread to the entire population but known risk factors are: sports teams, jailed inmates, military, IVDU, MSM, children [6]	Y	NA	93**	99	91	NA	NA	NA	NA	99.2 (Gent)	97	2005-8 [12]
						1.8	93.5**	99.6	91.3	57.4 (Gati)	100	NA	NA	NA	NA	2004-7 [13]
	USA400 (ST1-MRSA-IV)	<1% of MRSA SSTI [4]. Still predominant clone in Alaska [14].	SSTI most common. Also reports of fulminant sepsis [15].	Native American [14]	Y	40	42.5**	100	NA	93.3(Cip)	100	97.5	NA	95.8 (Gent)	NA	1996, 2000, 2004-6 [14]
Europe*	ST80-MRSA-IV	<5% (Spain) to 92% (Greece) of MRSA [16]	SSTI most common. [17]. Also reports of necrotizing pneumonia [18].	Travel/migration from South Mediterranean countries [19]	Y	94.6	95.6#	NA	15.3	99.2	100	99.5	7.4	15.3(Strep), 9.4 (Kan)	100	1999-2006 [17]
						69	NA	NA	22	100	100	100	<5	<5 (Kan), >95 (Tob, Gent)	NA	F. Laurent, 2008 (unpublished data of >200 isolates)
	ST398-MRSA-IV/V	20% of all MRSA in Netherlands [20]	SSTI most common [20]. Invasive infections uncommon.	Close contact with pigs	N	77	77#	98	0	98	100	100	100	59 (Kan), 57 (Tob), 63 (Gent)	100	[21]
	ST5-MRSA-I Geraldine clone	0.54% of all <i>S. aureus</i> and 2.61% of all MRSA in France (F. Laurent, 2008, unpublished data)	SSTI, bacteremia, pneumonia, toxic shock syndrome [18]	No data	N	74	NA	NA	85	99	100	94	1	22 (Kan), 78 (Tob), 100 (Gent)	NA	F. Laurent, 2008 (unpublished data of >100 isolates)

Asia	ST59-MRSA-V _T /IV	5.8% of children colonized in Taiwan [22]. 3.2% of adults colonized in Taiwan [23]. ~13% of community onset SAB [24].	SSTI most common. Also bacteremia, musculoskeletal, bone & joint and lung and CNS involvement [24].	Children	Yes in SCCmec V _T and in isolates causing SSTI	11.6	14.3#	99.3	99.3 (Min)	100 (Cip)	100	100	NA	74.1 (Gent)	NA	2007 [23]
Australia	ST93-MRSA-IV (Queensland clone)	19% of all MRSA [25]	Skin Infection. Also reports of necrotizing pneumonia and deep musculoskeletal infection [26].	Initially isolated in the white population but has spread to the entire population.	Y	90.7	NA	NA(-data from 2006 100%)	99.3	100(Cip)	NA	100	100	100(Gent)	100	2008 [25, 27, 28]
	ST1-MRSA-IV (WA-1 clone)	13% of all MRSA [25]	Skin Infection	Initially isolated in the Aboriginal population but has spread to the entire population.	N	77.9	NA	NA (data from 2006 100%)	98.4	95.2 (Cip)	NA	96.8	71.4	98.4 (Gent)	98.4	2008 [25, 27, 28]
	ST30-MRSA-IV (SWP clone)	7% of all MRSA [25]	Skin Infection Also reports of bone and joint infection [26]	Initially isolated in the Pacific Islander population but has spread to the entire population.	Y	95.7	NA	NA (data from 2006 100%)	100	97.9 (Cip)	NA	100	100	100 (Gent)	100	2008 [25, 27, 28]

NOTE. AG, aminoglycoside; Cip, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; FQ, fluoroquinolone; FA, fusidic acid; Gati, gatifloxacin; Gent, gentamicin; Kan, kanamycin; Min, minocycline; MUP, mupirocin; NA, not available in referenced study; pos, positive; RIF, rifampicin; Strep, streptomycin; TET, tetracycline; TMP-SMX, trimethoprim-sulfamethoxazole; Tob, tobramycin; VAN, vancomycin. . *For ST8-MRSA-IV (USA300) see North America and for ST1-MRSA-IV (WA-1 clone) see Australia. ** Inducible clindamycin resistance testing was performed. #No inducible clindamycin resistance testing performed.

Overall, the predominant clone in Europe is the *lukSF-PV*-positive European ST80-MRSA-IV clone. However, USA300 (ST8-MRSA-IV) has also been reported throughout the United Kingdom and Europe. In addition to this, there are 4 other significant clones: in northern Europe (the Netherlands, Germany, and Denmark), pig-associated ST398-MRSA-IV/V has been reported; in the United Kingdom, Australian WA-1 (ST1-MRSA-IV) is prevalent in some populations (intravenous drug users and homeless persons) [19, 39]; and in France, ST5-MRSA-I (Geraldine clone) has been reported. In addition, a *lukSF-PV*-positive ST152-MRSA-V clone has sporadically been reported in a number of countries [40–42]. Some of the patients infected with this strain had ties to Balkan countries, which may indicate its origins. There are many other clones described, but these are geographically limited and currently not highly prevalent.

ST80-MRSA-IV

ST80-MRSA-IV emerged in the late 1990s [43] and has been detected in the majority of European countries. In northern Europe, the clone has been implicated in a high proportion of MRSA infections, although overall prevalence of MRSA infection is low in this region [17, 19]. Conversely, in Greece, where the prevalence of MRSA infection is very high, up to 92% of all community-acquired staphylococcal infections and 24% of hospital-associated MRSA infections are due to ST80 [16, 44–46]. Of interest, many patients infected with the ST80 clone have epidemiological links to countries south of the Mediterranean (Algeria, Tunisia, Egypt, and Lebanon), indicating that ST80 may have originated from this region [19]. This clone is typically resistant to tetracycline and may demonstrate intermediate susceptibility or resistance to fusidic acid [17, 18, 44, 47]. Fluoroquinolone resistance was rare (0.8%) in Danish isolates but may be variable elsewhere [17]. There are no definitive data available on emergence of resistance to non- β lactams. At a single center in Algeria, 40% of ST80 hospital-associated MRSA infections were fluoroquinolone resistant, whereas resistance was absent in community strains of ST80 MRSA [48].

ST398-MRSA-IV/V

First described in France, the pig-associated clone ST398-MRSA-IV/V has recently emerged as a human public health problem, especially in northern Europe [49]. The clone accounts for 20% of all MRSA isolates in the Netherlands, and many other European countries have also reported sporadic isolates [19, 20, 50, 51]. The ST398 clone has been described in Canada and the United States [52, 53]. Although ST398 colonization and transmission has been reported primarily in animals, persons with occupational exposure to livestock are at higher risk of carriage, compare with the general population [50]; human-to-human transmission has been described elsewhere [20, 51]. In

addition to uniform tetracycline resistance, various resistance phenotypes were reported among subsets of isolates from pigs, including resistance to erythromycin, clindamycin, TMP, chloramphenicol, and aminoglycosides. Of note, there is almost uniform susceptibility to fluoroquinolones, fusidic acid, and mupirocin [21, 54]. Recently, a multidrug-resistant plasmid containing genes encoding resistance to streptogramin A, lincosamides, pleuromutilins, kanamycin-neomycin, tetracyclines, and TMP was described in a pig ST398 isolate [54].

ST5-MRSA-I

An atypical TSST-1 positive MRSA clone, the Geraldine ST5-MRSA-I clone, is now the most prevalent community MRSA clone in France [55] (F. Laurent, personal communication). The clone causes community-onset and hospital-acquired infections [18, 56]. All isolates are susceptible to fluoroquinolones, lincomycin, and gentamicin and are nonsusceptible to fusidic acid [18, 55]. Resistance to kanamycin, tobramycin, and erythromycin is variable.

ASIA

Only limited data are available on community MRSA epidemiology in Asia. In Taiwan, ST59-MRSA-V₇/IV is the predominant clone [23, 57]. Up to 7.3% of Taiwanese children are colonized with MRSA, and >80% of the colonizing clones are ST59 [22]. This clone is typically resistant to erythromycin, clindamycin, and occasionally, gentamicin but is susceptible to TMP-SMX, tetracyclines, and fluoroquinolones [23]. In Hong Kong, the predominant community MRSA clones are ST30-MRSA-IV and ST59-MRSA-IV/V that carry *lukSF-PV*, whereas in Singapore, the predominant clone is ST30-MRSA-IV [58, 59]. In contrast, in a community study involving children in Japanese day-care centers and kindergartens, 4.3% of participants were found to be colonized with MRSA; the majority of the colonizing clones were ST78-MRSA-IV and ST91-MRSA-IIb/IV [60].

SOUTH AMERICA

A paucity of data is available from South America. In a study conducted in Colombia, Ecuador, Peru, and Venezuela, there were significant differences in the rates of MRSA recovery among health care centers [61]. Of note, 81% of community MRSA isolates were ST8-MRSA-IV. In Uruguay, there was a large outbreak of *lukSF-PV*-positive ST30-MRSA-IV infection in jails and the community [62]. A subsequent report confirmed that ST30 is the predominant circulating strain in Uruguay [63].

AUSTRALIA AND OCEANIA

The first report of community MRSA infection in Australia and Oceania was due to isolates from the remote Kimberley region of

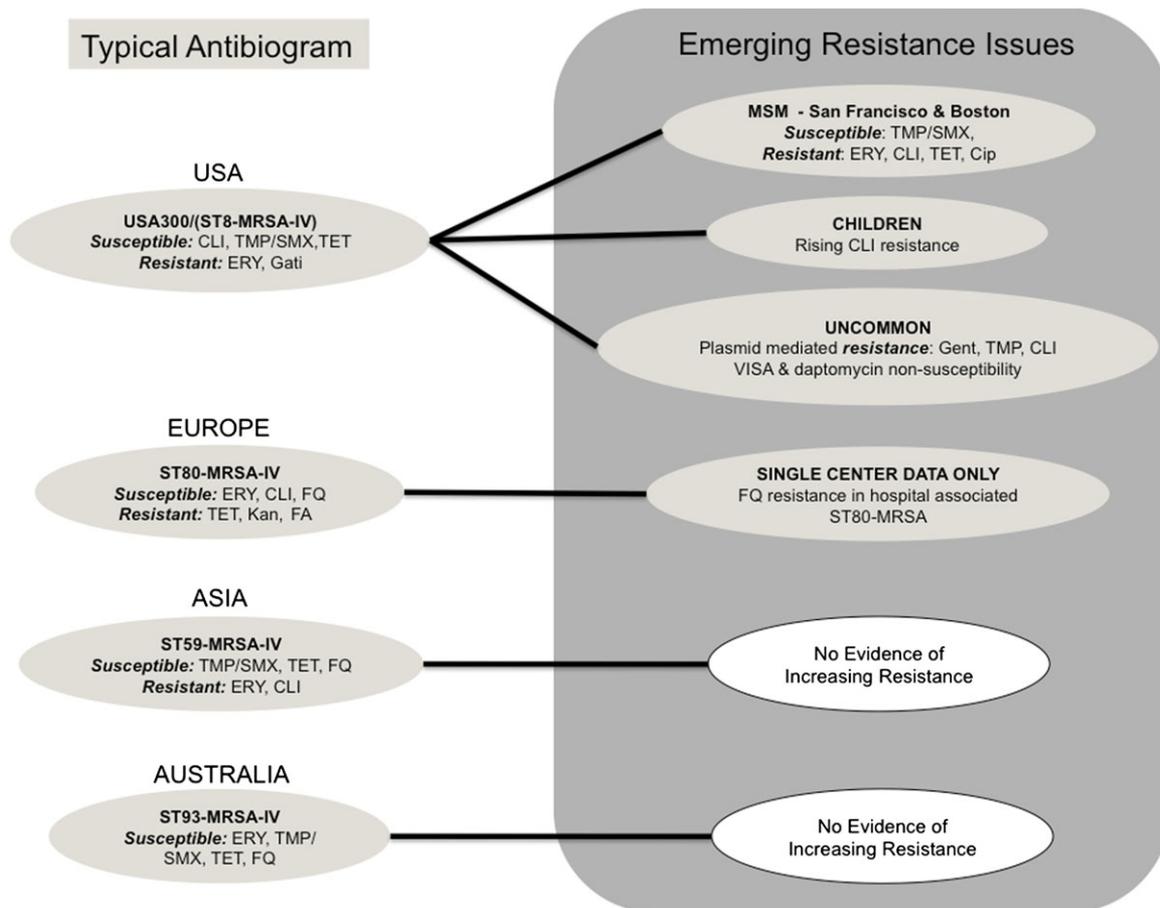


Figure 2. Summary of typical antimicrobial resistance profile of dominant global clones of community methicillin-resistant *Staphylococcus aureus* (MRSA) and emerging resistance issues. CLI, clindamycin; ERY, erythromycin; FA, fusidic acid; FQ, fluoroquinolone; Gati, gatifloxacin; Gen, gentamicin; Kan, kanamycin; MSM, men who have sex with men; TET, tetracycline; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus*

Western Australia (*lukSF-PV*-negative ST8-MRSA-IV) [2]. The most frequent clone in this region is currently ST1-MRSA-IV (WA-1), which is also generally *lukSF-PV* negative [64]. Rates of colonization and infection with MRSA in remote Australian Aboriginal communities are very high [65], and recently, a novel clone, ST75-MRSA-IV, was found to predominate in this population in northern Australia [66]. In the late 1990s, MRSA skin infections caused by the South West Pacific (SWP, ST30-MRSA-IV, *lukSF-PV* positive) strain were observed in eastern Australia [64]. This is also the dominant clone in New Zealand [67]. Subsequently, a unique Australian clone was described (Queensland clone, ST93-MRSA-IV, *lukSF-PV* positive) [64]. The 3 major Australian clones have spread across the continent, and ST93-MRSA-IV is now the most prevalent Australian clone (Figure 1) [25]. Biennial surveys from the Australian Group on Antimicrobial Resistance have revealed an increase in the prevalence of community MRSA from 4.7% (in 2000) to 11.1% (in 2006), as a proportion of community *S. aureus* infections [25, 27, 68]. ST93-MRSA-IV is typically uniformly susceptible to non- β lactams [25, 28]. Susceptibility patterns for ST1-MRSA-

IV and ST30-MRSA-IV are shown in Table 2. Comparison of isolates from the 2000 and 2008 Australian Group on Antimicrobial Resistance surveys revealed no significant increase in antimicrobial resistance.

TREATMENT OF COMMUNITY MRSA INFECTION

Skin and Soft-Tissue Infection (SSTI)

Empirical antibiotic treatment should be guided by local antimicrobial resistance patterns, when possible, and specimens should be obtained for culture and susceptibility testing. A proposed treatment algorithm is shown in Figure 3. Some authorities have suggested that a change in empirical antibiotic therapy is warranted after the prevalence of community MRSA infection exceeds 10%–15%, although there are no specific data to support this figure [69]. Many focal MRSA SSTIs in the immunocompetent host will be adequately treated with incision and drainage alone, and this is encouraged [70]. The role of antibiotic therapy in addition to

incision and drainage is controversial [71, 72]. In 2 randomized controlled studies comparing TMP-SMX with placebo, there was no difference in failure rates between the 2 treatment arms [73, 74]. TMP-SMX may decrease the risk of development of new lesions in the short term; however, the significance of this is unclear. In the context of severe disease, rapid progression, signs of systemic illness, and significant comorbidities or when incision and drainage is not possible or ineffective, systemic antimicrobial therapy should be used [32].

There have been no large randomized studies comparing frequently used oral agents for community MRSA [7]. Observational studies have reported good outcomes with clindamycin

[3, 75], TMP-SMX [76], and doxycycline-minocycline [77, 78] for treatment of SSTI. Although combination antibiotic therapy has been recommended by some authorities [79], it may incur additive adverse drug reactions, and we do not recommend combination therapy for skin infection. In addition, topical fusidic acid and mupirocin therapy should be avoided because of the risk of inducing resistance [80, 81]. Linezolid is not generally recommended for the treatment of uncomplicated SSTI because of potential toxicity and high cost.

Invasive Infections

For severe community MRSA infection, vancomycin remains the treatment of choice [7, 82]. Although there are some

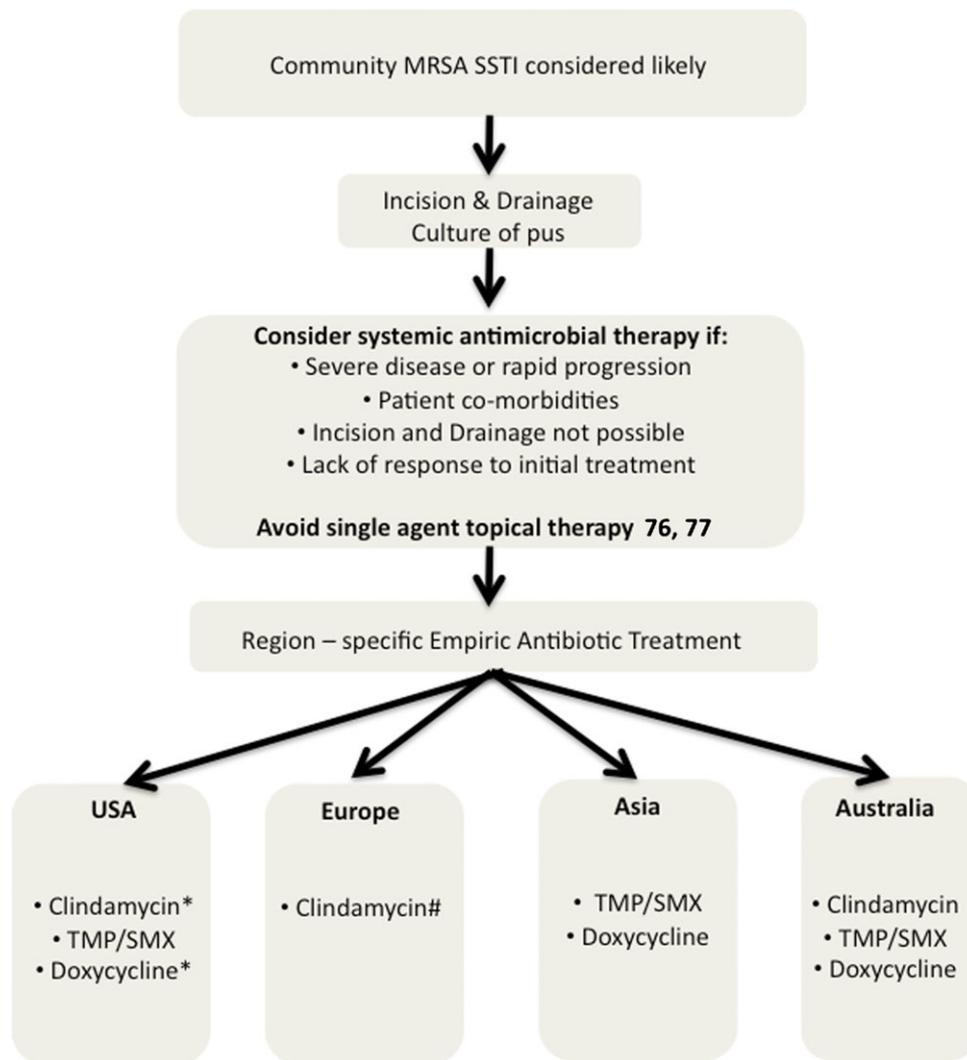


Figure 3. Treatment algorithm for empirical therapy of skin and soft-tissue infections (SSTIs) potentially caused by community methicillin-resistant *Staphylococcus aureus* (MRSA). For severe invasive disease potentially caused by community MRSA. MSM, men who have sex with men; TMP-SMX, trimethoprim-sulfamethoxazole. *Consider use of alternative agent in MSM population in San Francisco & Boston [34]. #Possible alternative agents to clindamycin include rifampicin and fusidic acid. These agents should not be used as single agents because of the risk of development of resistance. However, combination therapy may incur additive adverse drug reactions. Whether antibiotic therapy is necessary for uncomplicated skin infection should therefore be considered.

Table 3. Summary of Randomized Controlled Trials of Vancomycin versus Linezolid, Daptomycin, or Tigecycline for the Treatment of Severe Staphylococcal Infection in Adults^a

Comparator	Disease	Study Type	Number of Patients	Outcomes	Proportion MRSA	Comment	Reference
Linezolid	Nosocomial Pneumonia	Randomized, Double Blind	203	Equivalence		Results of MRSA infected patients subsequently combined with Wunderink <i>et al</i> 2003 [83]. Posthoc analysis of 160/1019 MRSA patients - mortality benefit and better clinical cure rate with linezolid compared to vancomycin. The validity of the post-hoc analysis has been questioned [84, 85].	[86, 87]
	Nosocomial Pneumonia	Randomized, Double Blind	623	Equivalence		See above	[83, 87]
	Hospitalized patients (skin infection, pneumonia, urinary tract infection)	Randomized, Open Labeled	460	Equivalent	53% <i>S. aureus</i> . Of these, 93% MRSA		[88]
	Febrile Neutropenia	Randomized, Double Blind	488	Equivalence	1.5% MRSA		[89]
	Nosocomial pneumonia, skin infection, septicemia	Randomized, Open Labeled	151	No difference in clinical success rates. End of treatment microbiological eradication rates higher in linezolid group but no difference at follow up.	69% MRSA		[90]
	Ventilator associated pneumonia	Randomized, Open Labeled	149	No statistically significant difference	34% MRSA		[91]
Daptomycin	Catheter related blood stream infection and skin infection	Randomized, Open Labeled	726	Linezolid non inferior	12% MRSA		[92]
	<i>S. aureus</i> Septicemia and Endocarditis	Randomized, Open Labeled	235	Daptomycin non inferior	38%	Subgroup analysis of MRSA infected patients – suggestion of better outcomes with daptomycin treated patients	[93, 94]
Tigecycline	Hospitalized patients with MRSA and VRE (skin infection and intraabdominal infection)	Randomized, Double Blind	156 (MRSA group)	Not powered for statistical comparison between groups but cure rates similar	100% of MRSA group		[95]
	Secondary Bacteremia	Pooled results from 7 Randomized Double Blind trial and 1 open labeled noncomparative trial	170	No significant difference between treatment groups	5.9%	Post-hoc pooled results from 8 different studies with heterogenous design. Hence, comparator agent against tigecycline were varied but the comparator was vancomycin for the 10 patients with MRSA	[96]

^a Studies which are primarily skin infection studies have been excluded

Table 4. Community Methicillin-Resistant *Staphylococcus aureus* (MRSA) Decolonization Studies

Reference	Study Goal	Study Type	No. Participants	Study Site	MRSA Clone	Regimen	Outcome
Bartels et al. [108]	Outbreak termination	Observational	23	Community, Denmark	ST30-MRSA-IV	Standard therapy: whole-body wash and hair wash in 4% chlorhexidine once daily, combined with mupirocin nasal intment 2% three times daily for 5 days. If ineffective, chlorhexidine washing was prolonged to 10 days, combined with a 5 day regime of mupirocin. Some throat carriers received rifampicin plus fusidic acid or clindamycin alone or clindamycin plus fusidic acid or clarithromycin plus fusidic acid.	Colonization eradicated in all patients. No skin infections occurred.
Campbell et al. [109]	Outbreak termination	Observational	206	Military camp, USA	ST8 MRSA, lukSF-PV positive	Nasal mupirocin and body wash with an antimicrobial skin cleanser on three separate occasions. Barracks routinely disinfected with 5% bleach.	Termination of outbreak
Longtin et al. [110]	Outbreak termination	Observational	45	Community, Switzerland	Multiple clones	Twice-daily nasal mupirocin and daily 4% chlorhexidine showers for 10 days. Frequent linen changes and the use of dedicated personal hygiene products	39/45 No clinical relapse and no MRSA isolated. 6/45 remained MRSA positive.

Urth et al. [111]	Outbreak termination	Observational	79(26 households)	Community, Denmark	ST80-MRSA-IV	<p>From 1997-1999: Daily body and hair wash with 4% chlorhexidine and twice daily nasal 1% chlorhexidine gel for 21 days. Daily change of towels and clothes, a laundry temperature above 90°C, and extensive cleaning of the home. This regimen was not successful.</p> <p>From 2000: Daily shower using the chlorhexidine detergent and nasal 2% mupirocin for 5 days. Daily changing of towels, regular cleaning of the house, and changing of clothes and bed linens on days 1 and 5.</p>	20/26 households compliant with regimen. Decolonization successful in 19/20 compliant households.
Romano et al. [112]	Outbreak termination	Observational	107 each year, for 3 years	Football team	Not stated but likely USA300	<p>All infected cases received incision and drainage, and antibiotic therapy (doxycycline and rifampicin). All MRSA nasal carriers received topical mupirocin and oral rifampicin for 10 days. Hexachlorophene body wash. Extensive environmental decontamination including increasing laundering water temperatures to 60°C, disinfection of surfaces and use of disposable towels. Education of staff</p>	Termination of outbreak. Carriers subjected to decolonization procedures were demonstrated to have eradication of colonization at 4 weeks.

								and players including use of alcohol-based sanitizers, covering of open wounds, restriction of whirlpool use.
Nguyen et al. [113]	Outbreak termination	Observational	107		Football team	USA300	Hexachlorophene body wash. Single use towels.	Termination of outbreak.
Ellis et al. [105]	Prevention of first SSTI and new colonization and infection in close contacts who were non-carriers	Cluster randomized, double-blind, placebo-controlled	134		Military camp, USA	USA300	Investigator administered nasal 2% mupirocin or placebo twice daily for 5 days.	7.7% placebo group developed infections vs. 10.6% mupirocin group (difference not statistically significant). MRSA decolonization did not prevent new colonization. No mupirocin resistance was found in this study.
Rahimian et al. [114]	Prevention of recurrent SSTIs	Retrospective	19		Single center, USA	Not stated	Nasal mupirocin – mean duration 9.5 days	No difference in recurrent infections

concerns regarding the efficacy of this agent, none of the newer US Food and Drug Administration–approved anti-staphylococcal antibiotics have been shown to be clearly superior to vancomycin in randomized controlled trials of severe staphylococcal disease (Table 3) [82]. A community MRSA prevalence threshold as low as 5%–10% may be appropriate for use of empirical vancomycin therapy in severe, life-threatening infections. Some authorities have recommended the administration of an exotoxin-reducing agent for severe MRSA infections for which *lukSF-PV* is detected (eg, necrotizing pneumonia) [79]. In vitro studies have shown that linezolid, clindamycin, rifampicin, and fusidic acid suppress exotoxin production [97, 98]. However, there are no data to support the use of vancomycin in combination with these antibiotics [99]. There have been some reports of adjunctive intravenous gammaglobulin use for the treatment of severe *lukSF-PV*–positive community MRSA infection; the rationale for this is that anti-PVL antibodies in intravenous gammaglobulin may protect against cytotoxic effects of PVL [100, 101]. However, the role of adjunctive intravenous gammaglobulin therefore remains unclear [102].

DECOLONIZATION AND ERADICATION OF COMMUNITY MRSA

Although intranasal mupirocin therapy significantly reduces the rate of postoperative *S. aureus* infection among surgical patients who are *S. aureus* carriers [103, 104], some authors have criticized the recommendation to eradicate community MRSA carriage, because it has been largely extrapolated from the hospital-associated *S. aureus* experience [30]. Furthermore, there is concern that indiscriminate use of mupirocin will lead to increased resistance [81]. Although mupirocin resistance associated with short-term use of mupirocin is rare [105], the use of mupirocin may select for mupirocin resistance conferred by large conjugative plasmids in USA300 [12]. These plasmids also carry *ermC*, which encodes resistance to macrolides, lincosamides, and streptogramins [34] and genes that encode resistance to TMP and gentamicin [12, 106]. Resistance to triclosan and chlorhexidine has not yet been reported in community MRSA isolates [107].

The reports of decolonization in community MRSA are heterogeneous and inconclusive in their findings. In these case reports, the goal of decolonization is usually to terminate an outbreak, and interventions may include topical mupirocin; body washes with topical antiseptics, such as triclosan and chlorhexidine; extensive environmental decontamination; and in some contexts, systemic antibiotics. A standardized definition of success is lacking in the literature. A summary of some of these studies is included in Table 4. In terms of nasal mupirocin decolonization for the purpose of prevention of first-time SSTIs

in community MRSA–colonized individuals (USA300) and for the prevention of new colonization and/or infection in close contacts who are noncarriers, the findings from a randomized clinical trial showed no benefit from mupirocin [105]. USA300 significantly colonizes nonnasal sites, such as the inguinal region, and this may explain the lack of efficacy of a decolonization regimen consisting of only nasal mupirocin [115]. This predilection for nonnasal sites may not be shared by other community MRSA clones, because it is thought that the arginine catabolic mobile element or ACME element contributes to skin colonization, and this is generally not present in other community MRSA clones. There are no prospective studies assessing the use of decolonization for the prevention of recurrent SSTIs. Therefore, it is not currently clear how and when community MRSA decolonization should be attempted.

CONCLUSION

The global epidemiology of community MRSA is very heterogeneous, with important geographical differences in the predominant clones and the overall frequency with which these clones are isolated. The most common clinical syndrome for all community MRSA remains SSTI, although more invasive disease has been described. The acquisition of additional antimicrobial resistance by ST8-MRSA-IV (USA300) provides a warning for other regions where other clones predominate. Accurate drug resistance surveillance is crucial to recognize emerging resistance trends and to guide empirical antibiotic selection.

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