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## Epidemiology and Virulence of Community-Associated MRSA

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### Abstract

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) emerged unexpectedly in the 1990s and is now a problem worldwide. CA-MRSA is epidemic in the United States and is the most common cause of community-associated bacterial infections. Here, we provide a basic overview of CA-MRSA epidemiology and discuss molecules that contribute to the enhanced virulence phenotype of this pathogen.

### Introduction

*Staphylococcus aureus* is the leading cause of bacterial infections in the United States and is a significant human health problem in most developed countries (1,2). *S. aureus* is also a commensal microorganism that typically colonizes the anterior nares of 30% of the human population, and colonization has been associated with a greater risk of infection with the same strain (3,4). In addition to being a common cause of human infections, *S. aureus* is widely known for its ability to acquire resistance to antibiotics, most notably  $\beta$ -lactam antibiotics, such as penicillin and methicillin.

Methicillin-resistant *S. aureus* (MRSA) emerged in hospitals in the 1960s (5) and is now a leading cause of healthcare-associated infections worldwide. It is important to note that hospital- or healthcare-associated MRSA (HA-MRSA) infections occur in individuals with risk factors for infection, e.g., those that have had surgery or are

immunocompromised. By comparison, community-associated MRSA (CA-MRSA) infections, which were first documented in the 1990s, occur in otherwise healthy individuals without such risk factors. For example, CA-MRSA outbreaks have occurred among seemingly healthy groups of children (6,7), prisoners (8,9), participants on sports teams (10-12), and military personnel (8,13). CA-MRSA infections typically manifest as skin and soft tissue infections (14,15); however, the pathogen can cause life-threatening infections, including osteomyelitis, necrotizing pneumonia, and fatal sepsis (16-21).

### Antibiotic Resistance

Penicillin resistance in *S. aureus* is conferred by beta-lactamase (penicillinase), which degrades penicillin. Penicillin-resistant *S. aureus* (PRSA) became widespread by the 1950s, after which time the antibiotic was no longer an effective agent for treatment of *S. aureus* infections. Currently, 90 to 95% of all *S. aureus* isolates are resistant to penicillin. Methicillin, a penicillinase-resistant structural homologue of penicillin, was developed by Beecham Laboratories in 1959 as a therapeutic agent for PRSA infections. Like peni-

cillin, methicillin inhibits cell wall biosynthesis. MRSA emerged within 2 years after the introduction of methicillin (22) and has since spread worldwide. It is endemic in hospitals in Canada, Europe, the U.S., and many other developed countries. In the U.S., the mortality rate for the pathogen has surpassed that of any other single infectious agent, including HIV (23). Resistance to methicillin and analogs is conferred by PBP2a, an altered penicillin binding protein that has a low affinity for methicillin, thus preventing its incorporation into the cell wall (reviewed by Chambers [24]). PBP2a is encoded by the *mecA* gene of the staphylococcal cassette chromosome *mec* (SCC*mec*), a mobile genetic element (MGE) described in more detail below.

Although CA-MRSA isolates can be resistant to multiple antibiotics (25), most are susceptible to agents other than  $\beta$ -lactam antibiotics. Current

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### In This Issue

#### Epidemiology and Virulence of Community-Associated MRSA

..... 153

therapeutic antibiotics for CA-MRSA include clindamycin, daptomycin, linezolid, minocycline and doxycycline (long-acting tetracyclines), trimethoprim-sulfamethoxazole, and vancomycin (or teicoplanin where available) (26-28). Development of new antibiotics, such as ceftobiprole (29), dalbavancin (30), oritavancin (31), telavancin (32), and tigecycline (33), all reviewed by Stryjewski and Chambers (34), should result in potential alternatives for the treatment of CA-MRSA infections.

## CA-MRSA Emergence

CA-MRSA infections were first described in small outbreaks in western Australia (35). Curiously, these infections occurred in individuals without recent hospital admittance or prolonged antibiotic use. Many of the patients lived in sparsely populated areas, such as the Kimberly region of western Australia and the Northern Territory, and several were in the aboriginal population (35). Genotypic analyses by pulsed-field gel electrophoresis (PFGE) revealed that CA-MRSA isolates were distinct from HA-MRSA recovered from eastern Australia (35). Within a decade, CA-MRSA had spread throughout Australia and subsequently to other countries.

In the late 1990s, Herold et al. (36) reported a relative increase in the number of CA-MRSA infections identified at Chicago Children's Hospital among children without identified risk factors for disease. The following year, the Centers for Disease Control and Prevention reported four cases of fatal CA-MRSA pneumonia in children from North Dakota and Minnesota that occurred from 1997 to 1999 (19). These infections were caused by a PFGE type USA400 (also multilocus sequence type 1 [MLST1, or ST1]) strain known as MW2 (37,38). Thus, the first wave of CA-MRSA infections in the U.S. was caused by USA400 strains. A study

**Table 1. SCCmec elements<sup>a</sup>**

SCCmec	Size (kb)	Typical	MDR <sup>b</sup>	<i>ccr</i>	<i>mec</i>
SCCmecI	34.3	HA-MRSA	No	<i>ccrAB1</i>	Class B
SCCmecII <sup>c</sup>	53.0	HA-MRSA	Yes	<i>ccrAB2</i>	Class A
SCCmecIII <sup>c</sup>	66.9 <sup>d</sup>	HA-MRSA	Yes	<i>ccrAB3</i>	Class A
SCCmecIV <sup>c</sup>	20.9-24.3	CA-MRSA	No	<i>ccrAB2</i>	Class B
SCCmecV	28	CA-MRSA	No	<i>ccrC</i>	Class C
SCCmecVI	20.9	HA-MRSA	No	<i>ccrAB4</i>	Class B
SCCmecVII	35.9	CA-MRSA	No	<i>ccrC2</i>	Class C

<sup>a</sup>Based on references 75, 77, 78, 118-120.

<sup>b</sup>MDR, multidrug resistant.

<sup>c</sup>These SCCmec types have multiple isoforms that are distinguished using PCR analysis.

<sup>d</sup>The size of SCCmecIII includes SCCmercury (121).

of MRSA isolates from east-central Saskatchewan, Canada, collected from 1999 to 2002 indicated that the organisms were also USA400 strains and indistinguishable from those recovered from CA-MRSA infections in the U.S. (39). Although USA400 remains a significant cause of CA-MRSA infections in North America, especially in Canada (40), a strain known as USA300 (MLST8, or simply ST8; see below for a description of classification schemes) now causes the vast majority of community-associated bacterial infections in the U.S. (1,41,42). Notably, USA300 was isolated from more than 50% of infections presenting to emergency departments in the U.S. in August 2004 (1).

By comparison, CA-MRSA infections have not reached the same proportions in Europe, in which the overall prevalence of Panton-Valentine leukocidin (PVL)-positive CA-MRSA is estimated at 1 to 3% (43-45). In addition, there are multiple CA-MRSA clones worldwide and there is segregation of these clones based upon MLST (42,43,46-51). For example, USA300 (ST8) predominates in the U.S., but USA400 (ST1), USA1100 (ST30), and USA1000 (ST59) are also notable causes of CA-

MRSA infections. ST1 and ST30 strains are the leading causes of CA-MRSA infections in Australia/Oceania (51), whereas ST80 has been the predominant clone in Europe (43). Although segregation of these clones still exists in part (for example, ST80 is not prevalent in the U.S.), there is now a trend toward increased transcontinental transfer of some clones, including USA300 (ST8), into parts of Europe (43). Despite clear molecular differences among CA-MRSA strains, clinical manifestations of the associated infections are similar.

## Transmission

Direct contact with infected individuals is believed to be the mode of transmission of CA-MRSA (1,52) (also see [http://www.cdc.gov/ncidod/dhqp/ar\\_mrsa\\_ca.html](http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca.html)). In support of this notion, nasal colonization by CA-MRSA strains is very low (~0.4%) and contrasts with the relatively high number of infections caused by these organisms (53). For athletic teams, especially contact sports, breaks in the skin and abrasions, sharing of towels and equipment, contaminated pool water, and cosmetic shaving have been linked to CA-MRSA skin infections (52). CA-MRSA outbreaks have also occurred on Native American

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reservations (54) and among religious communities (55) where travel is limited and many routine activities are confined to a single community.

More recent MRSA clones isolated from the community are transmitted between animals and humans. For example, a strain known as ST398 (SCC*mecV* and PVL negative) was recently found in pigs and pig farmers in Europe (56) and has now been reported in the U.S. (57,58) and Canada (59). Intensive surveillance in The Netherlands indicates that the prevalence of this clone among humans was as high as 21% in 2006 and accounted for >20% of the MRSA isolates in The Netherlands (60). Antibiotic resistance is a major concern with ST398, as many traditional antibiotics (e.g., tetracycline) are given to livestock and these strains show increased resistance to these antibiotics (61). In addition to transmission between pigs and humans, Weese et al. (62) reported significant colonization of horses (4.7%) and human horse handlers/personnel (13%) with a single CA-MRSA strain in an area encompassing Ontario, Canada, and New York state. The strain is known as Canadian epidemic MRSA-5 (CMRSA-5; also ST8 and SCC*mecIV*, USA500), an organism closely related to the USA300 epidemic clone (63). Subsequent work identified CMRSA-5 (USA500) skin infections in personnel working with a foal colonized with the same strain, thereby providing strong evidence for equine-to-human transmission of CA-MRSA (64). This group of investigators identified a USA300 skin infection in a domesticated cat whose owner had a history of soft tissue infection and was colonized with USA300 (65). Therefore, in addition the primary mode of CA-MRSA transmission by human-to-human contact, that occurring between animals and humans raises yet another potential route of dissemination for the organism.

### Molecular Epidemiology and MRSA Classification Methods

Inasmuch as *S. aureus* is widespread and has significant genetic diversity, classification or typing schemes are critical for surveillance and epidemiologic study of CA-MRSA. Current molecular examination of MRSA classifies isolates into distinct categories based on DNA content. Diversity among MRSA

isolates is caused in part by acquisition of MGEs and other large chromosomal replacements (66). There is evidence that genetic recombination by large chromosomal replacements has contributed to long-term evolution of *S. aureus*, whereas clonal variation is driven by single-nucleotide polymorphisms (67). The evolution of MRSA has been relatively rapid, and there exist at least 10 major lineages or clonal complexes (based upon MLST) that have disseminated worldwide (67-70).

### Multi-Locus Sequence Typing

MLST is a bacterial classification method based on allelic variation of seven housekeeping genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpi*, and *yqiL*) in *S. aureus* (71). The discriminatory allelic profile obtained for *S. aureus* isolates is known as multi-locus sequence type (MLST or ST). *S. aureus* strains that have identity at five or more of the seven housekeeping genes based upon MLST can be grouped within a clonal complex (CC), which is determined by an algorithm named BURST (67). This classification method indexes variation that accumulates slowly and can be used to measure long periods of evolution among strains. A database for *S. aureus* contains up-to-date information on all reported STs (<http://saureus.mlst.net>). Combined with PFGE, MLST provides additional information with which to classify and differentiate isolates. For example, USA500 and USA300 are ST8 and belong to CC8; they are closely related but distinct strains. An additional level of clone differentiation can be provided by *spa* typing (72), which is now a widely used classification method, or ultimately whole-genome DNA sequencing (73).

### Pulsed-Field Gel Electrophoresis

The CDC established a national MRSA database based upon PFGE profiles of genomic DNA digested with the endonuclease *SmaI* (37). The distinct banding pattern of the DNA segments for each strain provides segregation into specific PFGE or "USA" types (37). For example, in the U.S., CA-MRSA strains are predominantly USA300 and USA400 and, to a lesser extent, USA1000 or USA1100 (37). This classification method is appropriate for the evaluation of the recent evolution among strains and can be used to inves-

tigate outbreaks of *S. aureus* infections. PFGE is more discriminatory than MLST (37) but cannot distinguish unique clones within the same PFGE (USA) type. Also, many MRSA isolates from animals are not typeable by PFGE, because DNA is methylated at cytosine residues and thus not digested by *SmaI* (74).

### SCC*mec* Typing

In addition to *mecA*, SCC*mec* also contains the cassette chromosome recombinase (*ccr*) genes, which encode the enzymes responsible for excising and mobilizing SCC*mec* from genomic DNA. There are several different isoforms of *ccr* and *mecA* genes, and the organization of these genes in part dictates specific SCC*mec* types (SCC*mecI* to -VII) (Table 1) (75-79). The genetic diversity of MRSA and the breadth of SCC*mec* subtypes provide strong support to the idea that acquisition of SCC*mec* by *S. aureus* has occurred multiple times by horizontal gene transfer (80-82). CA-MRSA strains are typically SCC*mecIV*, -V and -VII, whereas HA-MRSA isolates are usually SCC*mecII* or -III. Studies in vitro indicate that strains containing SCC*mecIV* (i.e., CA-MRSA) have higher growth rates than strains containing the larger SCC*mecI* to -III elements (83,84). Therefore, this attribute may contribute to the success of CA-MRSA. SCC*mec* typing is often used in conjunction with MLST in an international nomenclature for MRSA that has been accepted by the International Union of Microbiological Societies subcommittee on *S. aureus* typing. For example, USA300 is ST8 and SCC*mecIV* and thus ST8-MRSA-IV.

Collectively, these typing methods are critical for identifying strains, tracking outbreaks, and monitoring the evolution of *S. aureus*. The continued improvement and expansion of these methods, as well as the development of new diagnostic methods, will ensure that newly emerging *S. aureus* clones are identified quickly and that appropriate therapeutic approaches can be implemented.

### CA-MRSA Strains in the Health Care Setting

Given the high prevalence of USA300 CA-MRSA infections in the U.S. over the past several years, one might predict that this strain would eventually become a significant cause of infections in health

care settings. Indeed, USA300 is now a notable cause of MRSA infections in hospitals (42,85-87). For instance, Liu et al. (42) reported that USA300 was isolated from 43.4% of all hospital-onset MRSA infections in San Francisco, CA, thereby replacing ST5 strains (USA100) as the leading cause of disease in this setting. Consistent with these findings, recent studies by Seybold et al. (86) found that USA300 and USA500 account for 34% and 36% of health care-associated bloodstream infections versus 29% caused by USA100, a traditional HA-MRSA strain. Mathematical modeling predicts that CA-MRSA will ultimately replace traditional HA-MRSA strains as the predominant MRSA isolates recovered from healthcare-associated infections (88). The vector for transmission of CA-MRSA into the hospital may be those individuals who are infected with MRSA and then transport the pathogen into the hospital setting. Many European hospitals have stringent surveillance programs and have aggressively treated individuals colonized with MRSA to limit the introduction of MRSA into hospitals and prevent spread to hospital patients. Although successful termination of a community *S. aureus* outbreak by decolonization has been reported for a relatively small group of individuals (89) and for athletic teams (12), such an approach might be difficult for a large metropolitan area.

### Pathogenesis and Virulence

*S. aureus* has numerous cell surface proteins and secreted toxins that contribute to virulence by promoting evasion of the host innate immune system (reviewed in reference 90). Polymorphonuclear leukocytes (PMNs) or neutrophils are the most prominent component of the cellular innate host defense against bacterial infection in humans, and as such, CA-MRSA pathogenesis is dictated to a significant extent by the outcome of interaction of the pathogen with neutrophils.

### Evasion of killing by human neutrophils

The ability of prominent CA-MRSA strains (e.g., USA300 and USA400) to cause disease in otherwise healthy individuals suggests that these organisms have enhanced capacity to circumvent killing by neutrophils. USA300 and USA400 are rapidly ingested by PMNs

in vitro (91). Despite normal neutrophil activation, there is significant survival of ingested *S. aureus*, albeit survival is varied depending upon the strain (91). Compared with the representative HA-MRSA strains COL (early MRSA isolate) and MRSA252 (one of the most abundant hospital MRSA clones in the United Kingdom and U.S.), USA300 and USA400 have enhanced capacity to survive after phagocytosis and ultimately to cause PMN lysis (91). Differences in survival among these strains are not likely to be attributable to differential abilities of the organisms to moderate the effects of neutrophil microbicides, as this ability appears comparable among the strains (92). In accordance with the in vitro results using human neutrophils, USA300 and USA400 are more virulent in mouse models of skin infection and sepsis than COL or MRSA252. Significant effort has been directed to understanding the basis for the enhanced virulence of CA-MRSA. Some of the notable findings are summarized below.

### PVL

PVL is a two-component leukotoxin that has been epidemiologically linked to CA-MRSA infections (38,93). In addition, the leukotoxin is associated with rare CA-*S. aureus* necrotizing pneumonia (19,94,95). PVL subunits are encoded by *lukS-PV* and *lukF-PV* present within prophage elements, and the protein subunits assemble as pore-forming structures on the surfaces of myeloid cells. Although PVL has long been known to be a potential virulence factor (96), its contribution to CA-MRSA virulence and pathogenesis, if any, remains unknown. First, early studies with purified PVL demonstrated that injection of high concentrations of PVL (up to 10 mg PVL/kg body weight) into mice or rabbits failed to adversely affect animal health (97,98). In addition, other two-component leukotoxins with significant homology and/or identity to PVL (e.g., gamma-hemolysin) are present in most *S. aureus* strains, whereas PVL is present in very few clinical isolates overall (typically 5% or less) (45,99). Finally, the most recent epidemiological studies indicate that not all CA-MRSA strains contain the genes encoding PVL. For example, O'Brien et al. (100) showed that there was no definitive correlation between SCCmecIV and PVL

in Australian CA-MRSA isolates, and a recent study in Ireland (48) showed that less than 7% of CA-MRSA isolates in Ireland harbored PVL. Additionally, the spread of CA-MRSA in Korea is attributable to two PVL-negative clones (101), and PVL-negative USA400 strains are a prevalent cause of CA-MRSA infections in Canada (40). Collectively, these data provide indirect evidence that PVL cannot explain the spread of CA-MRSA.

Several recent studies using mouse and rat infection models, which include skin infection, sepsis, and pneumonia models, found no difference in virulence between USA300 and USA400 wild-type and isogenic PVL-negative mutant strains (102-105). Consistent with these results, survival rates of USA300 and USA400 wild-type and PVL-negative strains following phagocytosis by human neutrophils were comparable, and each strain caused similar levels of host cell lysis after uptake (102). However, not all studies concur, and therein lies the basis for much of the current debate over the role of PVL in CA-MRSA pathogenesis. In contrast to the findings of Bubeck Wardenburg et al. (103,104) and Montgomery et al. (105), Labandeira-Rey et al. (106) reported that PVL promoted *S. aureus* necrotizing pneumonia in a mouse model, and this finding was linked to a putative gene regulatory role for PVL. Follow-up studies by Diep et al. (107) revealed that PVL had no role in gene regulation in USA300 or USA400 strains but contributed transiently to colonization of the kidneys in a rabbit bacteremia model. Villaruz et al. (108) then demonstrated that the reported gene regulatory role of PVL in the studies of Labandeira-Rey et al. was due to an unintended mutation in the *S. aureus* global gene regulator *agr*. More recent studies by Brown et al. (109), using the same strains and animal infections models as Bubeck Wardenburg et al. (104), reported a difference in virulence between USA300 wild-type and PVL-negative strains in a mouse model of pneumonia and skin infection. The reason for the difference in these similar models is unclear, but in the aggregate the data suggest PVL has either a very limited contribution to CA-MRSA virulence or none at all.

### Arginine Catabolic Mobile Element

Type I arginine catabolic mobile ele-

ment (ACME) is a 31-kb DNA segment identified by Diep et al. (25) and has been epidemiologically linked to USA300 (110). ACME is inserted into *orfX* and is juxtaposed to *SCCmec* (25). ACME encodes an arginine deiminase pathway (*arcABCD* cluster) and an oligopeptide permease operon (*opp-3*) that have been proposed to contribute to virulence. Compared with the wild-type USA300 strain, an isogenic ACME deletion mutant had decreased capacity for dissemination to major organs in a rabbit bacteremia model (110). This finding is intriguing, because ACME may provide an explanation in part for the observed enhanced transmissibility and fitness of the epidemic USA300 clone. By comparison, Montgomery et al. (111) found no difference in virulence between isogenic ACME positive and -negative USA300 strains in rat models of pneumonia and skin infection. Thus, further studies are needed to delineate the role of ACME in CA-MRSA transmission.

### Alpha hemolysin

Alpha hemolysin (Hla) is a well-studied secreted cytolytic toxin of *S. aureus*. Hla is lethal in animals and has been linked to human deaths (112). Although the role of Hla in the virulence of *S. aureus* has been studied previously in animal infection models (113,114), its role in CA-MRSA pathogenesis was unknown until recently. Using USA300 and USA400 wild-type and isogenic Hla-negative mutant strains, Bubeck-Wardenburg et al. (103) demonstrated that Hla is essential for pathogenesis in a mouse model of CA-MRSA pneumonia. Subsequent studies (115) by the same group indicated that immunization against Hla protects animals from lethal pneumonia. Thus, it is clear that Hla is a major determinant in the pathogenesis of *S. aureus* pneumonia, and as such, the molecule is a potential vaccine candidate. In more recent studies, Bartlett et al. (116) reported that Hla promotes *S. aureus* pneumonia by facilitating the generation of CXC chemokine gradients that ultimately recruit neutrophils in to the lung. These studies provide strong support to the idea that pathogenesis of severe pneumonia is due at least in part to damage caused by host neutrophils rather than *S. aureus* or *S. aureus* molecules per se.

### Alpha-type phenol-soluble modulins

*S. aureus* alpha-type phenol-soluble modulins (PSMa) are short amphipathic alpha helical peptides (~20 amino acids) that have the ability to recruit, activate, and destroy leukocytes (117). Using wild-type and isogenic USA300 and USA400 PSMa-negative strains, Wang et al. (117) demonstrated that PSMa peptides contribute significantly to virulence in mouse models of skin infection and sepsis (bacteremia). Compared with HA-MRSA strains, these peptides are expressed at much higher levels in CA-MRSA strains and thus contribute significantly to the enhanced virulence phenotype of CA-MRSA strains (63,117). Based upon studies by Li et al. (63), a major difference between CA- and HA-MRSA strains is in the level of PSM gene and protein expression rather than the presence or absence of the genes. This observation has important implications for our understanding of CA-MRSA pathogenesis, as it suggests the role played by MGEs in virulence is more limited than previously thought.

### Conclusions

CA-MRSA has been a human health problem in the U.S. for more than a decade and is currently the most frequent cause of community-associated bacterial infections. Although progress has been made, more work is needed to better understand the success of epidemic *S. aureus*. The advent of new technologies, such as high-throughput whole-genome sequencing, will likely facilitate a better understanding of *S. aureus* outbreaks such as those caused by CA-MRSA.

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