Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA): molecular background, virulence, and relevance for public health

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**Abstract:** *Staphylococcus aureus* and coagulase-negative *Staphylococcus* (CoNS) are frequently found in nosocomial environments as the main pathogen in several infections. In 1961, reports of nosocomial *S. aureus* resistant to methicillin, the drug of choice against penicillin-resistant strains, required new alternatives and vancomycin started being used to treat infections caused by methicillin-resistant *S. aureus* (MRSA). Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) was first reported in 1990 affecting patients without risk factors for infection with MRSA of hospital origin. MRSA of community origin harbor the genes responsible for the synthesis of Panton-Valentine leukocidin (PVL), a toxin associated with skin and soft tissue infections and that carries the staphylococcal cassette chromosome *mec* (SCCmec) type IV. CA-MRSA emergence has caused great impact on the worldwide medical community since the presence of this pathogen in patients without risk factors represents a high risk to public health.

**Key words:** methicillin-resistant *Staphylococcus aureus*, meca gene, oxacillin, Panton-Valentine leukocidin, drug resistance, epidemiology.

**INTRODUCTION**

*Staphylococcus aureus* belongs to the family Staphylococcaceae and the genus *Staphylococcus* with 45 species, of which 17 can be isolated from human samples. *Staphylococcus aureus* is the most important species and can be found in both healthy and immunocompromised individuals (1, 2).

The genus *Staphylococcus* is divided into two groups known as coagulase-positive, represented by *Staphylococcus aureus*, *S. intermedius*, *S. hyicus*, *S. schleiferi* subsp. *schleiferi*, *S. lutrae* and *S. delphini*, and coagulase-negative, represented by the remaining species (3). Both groups can cause infections to humans and the main species are: *S. aureus*, *S. epidermidis*, *S. saprophyticus*, *S. haemolyticus*, *S. hominis*, *S. warneri*, *S. capitis*, *S. saccarolyticus*, *S. lugdunensis*, *S. cohnii*, *S. xylosus*, *S. simulans*, *S. auricularis*, *S. caprae* and *S. schleiferi* (4, 5).

Humans are the main source of this genus, which can be found in the skin, throat, intestine and nose without causing damage to the host. In hospitals, asymptomatic hosts can disseminate *S. aureus* to immunocompromised patients (2). Since they are ubiquitous, these bacteria can cause several types of infections such as: necrotizing pneumonia, skin and soft tissue infections, bacteremia, as well as food poisoning through enterotoxin production (2, 6-9).

Staphylococcal infections used to be treated with penicillin, which was introduced in 1940; two years later, however, penicillinase-producing strains arose in the hospitals, becoming resistant to penicillin (10). Soon after, the same occurred with the community strains, requiring the use of...
alternative antibiotics to treat infections caused by *S. aureus* (11).

In the late 1950s in Europe, resistant *Staphylococcus* spp. of community and nosocomial origin showed penicillin resistance rates of 70 and 90%, respectively (10). This finding led to the search for alternative drugs and in 1959 6-aminopenicillanic acid was shown to cause a change in the precursor of penicillin, protecting the β-lactam ring. Methicillin is a semi-synthetic penicillin (oxacillin is the other member of this antimicrobial class, commonly used in Brazil) that showed resistance to the action of β-lactamase. However, both drugs were efficient for a short period, since in 1961 the first strains resistant to the semi-synthetic penicillin emerged. These new strains were named MRSA (methicillin-resistant *Staphylococcus aureus*) and were so far exclusive of hospitals (10, 12).

In 1990, infections by *S. aureus* in individuals without risk factors for acquiring hospital-acquired MRSA (HA-MRSA) were first reported, and the strains isolated from the community were then called community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) to differentiate from HA-MRSA (10). The former infections are distinct from the latter because CA-MRSA are generally resistant to β-lactam antibiotics only and may carry the gene for the synthesis of Panton-Valentine Leukocidin (PVL), responsible for tissue invasion before skin infections (13).

To be considered a case of CA-MRSA, the infection must be in patients who: have no previous history of MRSA infection; show MRSA-positive culture during the first 48 hours of hospitalization; have no history of hospitalization during the last 12 months or admission to a nursing home; and have no history of dialysis, surgery, or any previous invasive treatment (12).

The transmission occurs due contact between the susceptible individual and the asymptomatic carrier. CA-MRSA dissemination is reported to be frequent among homosexuals; soldiers; athletes; illicit injecting drug users; prisoners; people with compromised skin and mucosa; poor hygiene habits and postpartum mastitis; descendants of native North American populations; and children due to their contact with contaminated nasal secretions (13, 14).

CA-MRSA isolates are associated with skin and soft tissue infections since they reach both surface and deeper tissues, into which they penetrate by rupturing natural barriers (15). The main characteristics of these infections are similar to those caused by methicillin-susceptible *S. aureus* (MSSA) (3).

CA-MRSA infection outbreaks are increasing worldwide among all age groups. Several countries have reported its presence as emerging pathogen, including the United States, Australia, New Zealand, Samoa, as well as European countries and South America (Brazil, Uruguay and Colombia) (16).

In Brazil, there are several reports of confirmed cases of this pathogen in the community involving cases of boils, metastatic infections leading to serious complications and pneumonias (17-20).

Despite all those reports the real prevalence and incidence of CA-MRSA remains unknown. Some reports reveal that the prevalence in three centers in the United States were variable, ranging from 9 to 20% and, from these, 77% had skin and soft tissue infections (21).

There are no data about the prevalence of SCC 

**SCC mec IV** in Brazilian communities, but Reinert et al. (22) characterized through pulsed-field gel electrophoresis (PFGE) a culture collection recovered between 1995 and 1999. The results showed that the predominant profile (80%) corresponded to the Brazilian endemic clone (BEC). Three of 50 selected samples carried the cassette type IVc and the multilocus sequence typing (MLST) was different among them: ST3, ST5 and ST88. Even though the study was performed with hospital samples, these data showed that **SCC mec IV** has long been present in Brazil and must have passed unnoticed in the laboratory practice. These strains must be detected both in community and in the hospital to better elucidate their epidemiology and control their dissemination (22).

MRSA dissemination among the members of one same family was reported in a study involving ten families. Strains with PFGE ST8 (USA 300), ST59 (USA 1000) and ST80 and PVL-positive were found in that study (23). They can cause serious pulmonary infections since their symptoms are similar to those of pneumonia in children; thus, it is important to consider MRSA infection, especially when there is a previous report (23).

Risk factors for acquiring MRSA must be evaluated due to its wide dissemination. In
places that provide great proximity among individuals, the risk of \textit{S. aureus} infection is higher. Studies carried out with people who keep close contact have shown that poor hygiene habits are an important factor in the acquisition of \textit{Staphylococcus aureus}. In addition, younger and obese individuals have higher tendency to colonization by MRSA. Objects of common use (such as soaps) and the environment are related to outbreaks of infections by this pathogen (24).

There is transmission between humans and animals of CA-MRSA of pathogenic multiresistant strains which can carry genes for PVL production (25, 26).

CA-MRSA colonization is different between adults and children as to the resistance profile of non-β-lactam antibiotics; it is more common for multi-sensitive strains to colonize or affect children. In addition, the antibiotics used for children may differ from those prescribed for adults, providing thus a different selective pressure in the community. CA-MRSA resistance to gentamicin, tetracycline, ciprofloxacin, clindamycin and erythromycin is more frequent in adults than in children (27).

**GENETIC FEATURES OF CA-MRSA**

Studies have been carried out into the genetic and molecular features responsible for the resistance of microorganisms to antibiotics, indicating that MRSA strains acquired and integrated in their genome the mobile element that harbors resistance genes called staphylococcal cassette chromosome mec (SCC\textit{mec}). This element harbors the gene responsible for the resistance to methicillin (\textit{mecA}) and remaining β-lactam antibiotics, as well as the genes that determine the resistance to other antibiotic classes. Strains related to community infections carry the small and lighter element, SCC\textit{mec} IV or V (21 to 25 kb), which is generally resistant to β-lactams only (28). HA-MRSA strains carry the heavier mobile elements (SCC\textit{mec} I to III) since they have genes that codify the resistance to antibiotics of several classes (29).

The mobile element SCC\textit{mec} is characterized by the presence of essential genetic elements: complexes \textit{mec} (A to E) and \textit{ccr}, junkyards (J) and 3’ extremity regions linked to the open reading frame (orf\textit{X}) (30, 31). SCC\textit{mec} is integrated to \textit{Staphylococcus} chromosome at a specific site named \textit{attBsc} and located downstream to orf\textit{X} (32). There are several types of SCC\textit{mec} (I to XI) besides the subtypes IIA to IIE, IVa to IVg, and VT (30, 33). The complex \textit{ccr} has four allotypes for \textit{ccrA} and \textit{ccrB}: \textit{ccrA1} to \textit{ccrA4}, \textit{ccrB1} to \textit{ccrB4}, and \textit{ccrC}. The allotypes of the complex SCC\textit{mec} are characterized according to the presence of certain \textit{ccr} genes (34). The genes \textit{ccrA} and \textit{ccrB} codify the recombinases of the family “invertases/resolvases”. These enzymes mediate the integration inside and outside the chromosome, promoting the cassette mobility (28).

The \textit{J} regions codify several pseudogenes that seem to have no role in bacterial metabolism and contain non-β-lactam or heavy metal resistance genes mediated by plasmids or transposons (28, 31). There are three main regions: \textit{J1}, between the right extremity and the complex \textit{ccr}; \textit{J2}, between the complexes \textit{ccr} and \textit{mec}; and \textit{J3}, between \textit{mec} and orf\textit{X}. The \textit{J1} region has been identified in SCC\textit{mec} as types II and IV. The presence or lack of resistance genes in the \textit{J3} region could be a marker to classify the SCC\textit{mec} elements (35).

SCC\textit{mec} are found in several \textit{Staphylococcus} species besides \textit{S. aureus}, including \textit{S. epidermidis}, \textit{S. haemolyticus}, \textit{S. hominis} and \textit{S. warneri} (30). SCC\textit{mec} origin is unknown and there are no reports of other bacterial genera presenting this chromosome cassette. The presence of SCC\textit{mec} type IV in \textit{S. epidermidis} colonizing healthy people suggests it is responsible to convert CA-MSSA into CA-MRSA and the transmission occurs mainly by bacteriophage transduction (36, 37).

The gene \textit{mecA} encodes for the penicillin binding protein PBP2 or PBP2a present in the outer surface of the cytoplasmic membrane (11, 38). Strains that are sensitive to traditional PBP easily bind to β-lactam antibiotics, preventing the correct formation of the cell wall. However, PBP2a has low affinity to this antimicrobial class, explaining the resistance to methicillin/oxacillin (38, 39).

The gene \textit{mecA} is regulated by the genes \textit{mecl} and \textit{mecR1}, the roles of which are analogous to those of \textit{blaI} and \textit{blaR1} in the mechanism of regulation of β-lactamase production. The precise regulation mechanism is still unknown, but basically the gene \textit{blaI} is a DNA-binding protein that suppresses the transcription of the gene β-lactamase, and \textit{blaR1} codifies for a signal transduction PBP that leads to the transcription
of the enzyme in the presence of β-lactam antimicrobials (40).

Other resistance mechanisms have been discovered in strains that lack the gene mecA, such as the β-lactamase overproduction, which is responsible for oxacillin inactivation or modified resistance (MOD-SA), mediated by different PBP types with altered affinity to this antimicrobial. Strains with this resistance pattern are called borderline (41).

The microorganisms that harbor SCCmec can carry toxin genes such as lukS and lukF which encode for Panton-Valentine leukocidin (PVL) (42). Leukocidin was first associated with skin and soft tissue infection by Panton and Valentine in 1932. PVL genes are obtained through the transduction of a specific phage type, phiSLT, which lyses a cell that harbors this gene and transports it to another cell. From its transcription, two exoproteins are synthesized: LukS-PV and LukF-PV. When secreted, LukS-PV links to the membrane of the polymorphonuclear (PMN) leukocyte and is dimerized with LukF-PV, alternately with the former until the heptamer is completely formed. Calcium channels are also formed, triggering the production of interleukins and inflammatory mediators. Depending on the toxin concentration, PMN lysis or apoptosis may occur. This evidences that PVL may be not directly associated with tissue necrosis but with the cytotoxic lysosomal granules released due to PMN lysis, with reactive oxygen species released from granulocytes and/or with inflammatory mediators (43).

Boyle-Vavra et al. (44) carried out a study with patients who had skin and soft tissue infections or were colonized by CA-MRSA to test the resistance to several antimicrobials and isolate the strains that harbored the gene mecA. The results showed that 94% strains recovered from infections and 85.3% strains colonizing healthy patients were resistant to three or more non-β-lactam antibiotics. SCCmec type IV was found in 34% samples from patients who had at least one risk factor for MRSA (44).

Another feature that CA-MRSA can express is the induced resistance to clindamycin, an alternative antibiotic to treat both MSSA and MRSA infections, especially in cases of toxic shock syndrome. Among positive macrolide-lincosamide-streptogramin B inducible (MLSBI) strains, an inducer promotes the synthesis of methylase by the gene erm and the subsequent methylation of 23S ribosome unit, leading the strain to express resistance to lincosamine (such as clindamycin). Phenotypically, these strains are resistant to erythromycin and susceptible to clindamycin; however, when the erythromycin disk is at 15 mm from the clindamycin disk the strains express induced resistance, forming a D zone. The presence of gene mecA itself is not a criterion for induced resistance (45).

MRSA VIRULENCE MECHANISMS

S. aureus pathogenicity depends on several determinants, such as toxin production and extracellular membrane compounds (8, 9). The molecular bases of S. aureus pathogenicity are related to the expression of broad classes of accessory genes producing cell wall compounds and extracellular proteins. The expression of these virulence factors is regulated by genes present in the operon agr (accessory gene regulator), which codifies toxin and adhesion genes (46). Enzymes like coagulase and catalase are responsible for the invasion of the immune system (9).

Staphylococcal toxins can cause toxic shock syndrome (TSS), staphylococcal scarlat (both due to the toxic shock syndrome toxin 1(TSST-1) and staphylococcal enterotoxins), scalded skin syndrome (SSSS, due to exfoliatins) and food poisoning (se's staphylococcal enterotoxins) (2, 8, 47).

Group A Streptococcus (Streptococcus pyogenes) is another bacterium frequently associated with TSS. S. pyogenes produces a toxin very similar to that synthesized by Staphylococcus aureus, differing in the infection clinical evolution. The pathogen can only be determined based on the result of the culture of a sample from the infection site (48). In addition, both pathogens have the potential to cause impetigo, cellulites and necrotizing fasciitis. There are reports of the association between Staphylococcus aureus and Streptococcus pyogenes causing non-bolus impetigo (49).

Deep skin and soft tissue infections such as boils and abscesses, besides necrotizing pneumonia, are caused by the presence of the toxin PVL produced by S. aureus. PVL-positive strains are rarely found in hospital environments associated with bacteremia (50, 51). This toxin acts by means of a synergic action between two proteins LukS-
PV and LukF-PV, which are codified by the genes in the CA-MRSA chromosome (51, 52).

In the lungs, PVL can lead to hemorrhage, extensive necrosis in the alveolar septa, and destruction of the epithelium covering the bronchi and bronchioles (28). In addition, histopathological sections showed necrotic lesions of the tracheal mucosa (50). Thus, previous studies suggested that the propensity of CA-MRSA to cause severe skin and soft tissue infections and necrotizing pneumonia is due to the gene that codifies PVL production (52).

The sequencing of a strain named MW2, from CA-MRSA, revealed the presence of genes responsible for specific virulence factors such as the toxin PVL and the staphylococcal enterotoxins H \((\text{seh})\) and C \((\text{sec})\) (52).

**CHARACTERIZATION OF CA-MRSA STRAINS**

Multiplex polymerase chain reaction (M-PCR) and new protocols have proposed rapid, cheap and practical typing for the differentiation of CA-MRSA clones. Some techniques are capable of differentiating clone USA 300 from clone USA 400, besides detecting the gene that determines the resistance to oxacillin, \(\text{mec}A\), the target gene of 16S RNA which differentiates *Staphylococcus* from other bacteria, the gene \(\text{nuc}\), specific for *S. aureus*, PVL genes and other specific genes (32). M-PCR also allows the detection of genes that encode for the toxins and the chromosomal cassettes responsible for the resistance to antimicrobials in a rapid and reliable manner, compared to other methods (53).

Multilocus sequence typing (MLST) is widely used for typing genes that encode for essential proteins defining each species based on the sequence of fragments from the seven loci of the essential genes. There are no identical profiles due to the different combinations for each gene, and the matching profiles are considered members of one same clone. This technique can be used to study evolutionary and population biology of these bacteria (54).

Strains isolated in the United States were classified as pulsed-field types (PFT) USA 300, USA 400, USA 500, USA 600, USA 700, USA 100 and USA 800, USA 900, USA 1000 and USA 1100 (55). It is estimated that most CA-MRSA show the genetic profile USA 300, US A400, USA 1000 and USA 1100, of which USA 300 predominates among community isolates. On the other hand, USA 100, USA 200 and USA 500 are frequently associated with nosocomial infections and most of them show multiresistance at the chromosomal cassette type II (13).

For MRSA typing, PCR and PFGE-based techniques such as ribotyping and plasmid typing have been widely used with successful results. The high genetic similarity among these microorganisms requires the use of more than one method to obtain an accurate characterization (56).

The \(\text{spa}\) typing method is a sequencing technique used to characterize the polymorphic region X in the protein A gene \((\text{spa})\), which has a certain number of repeated regions of 24 bp flanked by well conserved regions. This typing, based on the sequence of one locus, is a practical and rapid method of low cost which also has lower error probability compared to PFGE and MLST techniques and can be applied in local and global epidemiological studies due to the micro and macro variations present simultaneously in the X region. In CA-MRSA, the following \(\text{spa}\) types can be found: t008, t019, t021, t044, t131, and t216 (57).

**RESISTANCE TO VANCOMYCIN**

After the emergence of CA-MRSA strains there have been reports of strains resistant to other antibiotics such as mupirocin, quinolones, clindamycin and tetracycline. One of the main community strains, USA 300, showed plasmid-mediated resistance to tetracycline, mupirocin and clindamycin (55).

Another concern nowadays is the emergence of resistance to the antibiotic of choice for MRSA treatment, vancomycin. There are few drugs left to treat MRSA infections and vancomycin is one of them. Reports of resistance and low sensitivity to this antibiotic in nosocomial environments are common worldwide (5).

The first case of reduced susceptibility to vancomycin was reported by Hiramatsu (58), in Japan, in a pediatric patient who had positive culture for MRSA and was treated with glycopeptides. Phenotypic analyses have shown that the minimum inhibitory concentration (MIC) for this strain was 8 mg/L in the microdilution test, and molecular analyses have resulted negative for the presence of the genes...
vanA or vanB. The strain Mu50, recovered from this patient, is the first S. aureus strain showing such a level of vancomycin resistance (58).

The first report of resistance to vancomycin in the United States was described by Sievert et al. (59). The patient was treated with several antimicrobials, including vancomycin, and developed a blood infection caused by MRSA due to the hemodialysis catheter. The patient received vancomycin, rifampicin and required the removal of the infected device. A sample culture of the catheter revealed oxacillin- and vancomycin-resistant S. aureus. One week later, vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) were isolated. Surveillance cultures did not recover VRSA from the patient, who responded well to the treatment with trimethoprim/sulfamethoxazole. Molecular analyses revealed the presence of the gene vanA of enterococci, which explains the resistance to glycopeptides, and the gene meca (59).

Cases of vancomycin-intermediate resistant (VISA) and heteroresistant S. aureus (hVISA) are increasingly common in healthcare centers where MRSA infections are treated with vancomycin (26, 60, 61).

Kim et al. (61) reported vancomycin-resistant strains presenting changes in the cell wall due to the selective pressure caused by the prolonged use of vancomycin to control MRSA infections (61). On the other hand, *in vitro* studies indicated that the resistance of the gene vanA can be transferred from vancomycin-resistant *Enterococcus* to S. aureus strains (59).

Resistance detection is controversial to some researchers, who state that the disk diffusion method may not be effective to detect resistance to glycopeptides, specially vancomycin (61, 62). Biofilms are easily formed by these microorganisms, requiring the removal of catheters in case the infection persists. *S. aureus* and coagulase-negative *Staphylococcus* resistant to oxacillin are present in the microbiota found in biofilms from catheters (5).

In San Francisco, USA, a patient with several successive complications was diagnosed with MRSA initially susceptible to trimethoprim/sulfamethoxazole. A more accurate study was carried out proving that the strain belonged to PFGE USA 300-0114 of community origin and had intermediate resistance to vancomycin. This strain is closely related to skin and soft tissue infections besides pneumonia. The United States surveillance in San Francisco shows an explosive increase in infections caused by CA-MRSA USA300, capable of replacing other strains (63).

Adhikari et al. (64) studied strains from clinical isolates as to the deletion of gene meca induced by the use of vancomycin. Forty-nine strains were cultured in tryptic soy broth (TSB), which contained 6 mg/L vancomycin, and were stored at 37°C. There was a decrease in the incubation time of plates to 1 or 2 days of growth. Five of 49 samples showed reduced susceptibility to oxacillin, of which four kept the gene meca and one strain, Vr6-1126a, lost this gene. Lines of this strain that had MIC above 4 mg/L for vancomycin completely deleted the gene meca. The deletion of this gene is related to increased vancomycin resistance, deletion of regions Smal-G to Smal-I in SCCmec, and phenotypic pleiotropic changes (64).

**CONCLUDING REMARKS**

The emergence of methicillin-resistant *Staphylococcus aureus* in the community as the main agent of severe skin and soft tissue infections constitutes a concern since oxacillin would be the drug of choice to treat infections caused by microorganisms resistant to other antibiotics.

Several techniques can be used to identify resistance to oxacillin; however, PCR still remains the safest and most effective technique. Besides PCR, other techniques allow the typing of more than one genetic feature of CA-MRSA, detailing the existing toxins and differentiating the clones involved in outbreaks. These techniques help the epidemiologist to find the correct measures to control the dissemination of this pathogen.

The emergence of CA-MRSA strains showing low susceptibility to vancomycin is alarming and may impair the treatment. Several studies are being made in order to determine the prevalence, risk factors and also elucidating the real importance of CA-MRSA in the clinical practice and for public health. Educational resources that are available on the Center for Disease Control and Prevention (CDC) inform people how to prevent and control MRSA skin and soft tissue infections (65). This initiative is really valuable especially when applied seriously in the community. It should be taking into consideration in many countries where CA-MRSA spread in not under control.
The lack of the prevalence and incidence data worldwide reveals the importance of a surveillance system in this field. Studies that are being currently developed will clarify the role and the prevalence of CA-MRSA, which can be useful for management in public health. Despite all those information, more studies are required to know the real prevalence and incidence of CA-MRSA in Brazil and worldwide.

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