COMMUNITY-ACQUIRED METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS

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ABSTRACT
Methicillin resistant *S. aureus* (MRSA) has emerged as an important pathogen first in hospitals and then in the community. Community-acquired MRSA (CA-MRSA) has recently emerged as a significant pathogen, mainly causing skin and soft tissue infections in immunocompetent individuals residing in the community. It may also cause serious infections such as pneumonia. Person to person spread of CA-MRSA occurs mainly due to overcrowding, skin to skin contact, compromised skin integrity, sharing contaminated materials and poor hygiene. Possession of staphylococcal cassette chromosome mec type IV (SCCmec IV) encoding for mecA gene, susceptibility to non β-lactam antibiotics and a *pvl* gene encoding Panton-Valentine Leukocidin (PVL) primarily distinguish CA-MRSA from healthcare-associated MRSA. In addition to PVL, CA-MRSA produces many other virulence factors which play important role in its pathogenicity.

**Key words:** Community-acquired MRSA, Panton-Valentine Leukocidin, Staphylococcal cassette chromosome mec IV

INTRODUCTION
*Staphylococcus aureus* continues to be an important pathogen due to its versatility of diseases caused, virulence factors and drug resistance. Methicillin resistant *S. aureus* (MRSA) emerged in the 1960s, making *S. aureus* resistant to many antibiotics. MRSA is a significant pathogen causing both health care-associated (HA-MRSA) and community-acquired (CA-MRSA) infections. HA-MRSA has been a serious problem in hospitals and health care facilities worldwide including India. In the 1990s, MRSA, which was once confined to hospital setting was seen to affect immunocompetent people with no health care risk factors such as athletes and other sportsmen. CA-MRSA then gained importance as a serious threat following the death of 4 children in North Dakota and Minnesota with severe CA-MRSA infection.

In the recent years, there have been increasing reports of CA-MRSA from various parts of the world. Initially, it was believed that CA-MRSA emerged from HA-MRSA since clonal relation was seen among them. However, with epidemiological and molecular profiling, it was observed that CA-MRSA are different from HA-MRSA in terms of risk factors associated, drug susceptibility pattern, virulence factors and molecular properties. Comparison of CA-MRSA and HA-MRSA is shown in Table 1.

DEFINITION
According to CDC, CA-MRSA is defined based on the following criteria.

- 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 following history in the previous year.
1. Hospitalization/Admission to a nursing home, skilled nursing facility or hospice
2. Dialysis
3. Surgery
   * No permanent indwelling catheters or medical devices that pass through the skin into the body.

CA-MRSA is usually susceptible to trimethoprim / sulfamethoxazole, clindamycin and gentamicin, possess staphylococcal cassette chromosome mec(SCCmec) type IV and Panton-Valentine Leukocidin (PVL). There is still a lot of confusion regarding the prevalence of MRSA in the community due to difficulty in differentiating HA-MRSA and CA-MRSA. A person may have become a carrier of MRSA during a hospital stay or following exposure to healthcare facility and transmit the pathogen in the community when he enters it. Such infections can be rightly called as community-onset MRSA rather than CA-MRSA.

**Epidemiology**

Patients infected with CA-MRSA and carriers are the most common sources of infection. Infections are commonly seen among children and young adults. According to CDC, athletes and other sports participants, military recruits, children, Pacific islanders, Alaskan natives, Native Americans, men who have sex with men and prisoners are at increased risk of CA-MRSA infections. Factors associated with spread of CA-MRSA are overcrowding, sharing of contaminated items and surfaces, skin to skin contact, cuts and abrasions on skin and improper maintenance of hygiene and personal cleanliness. MRSA carriage is a significant risk factor for subsequent development of skin and soft tissue infection (SSTI).

High CA-MRSA carrier state is seen in people living in mud-thatch houses where there is overcrowding, lack of hygiene, space and ventilation. A single clone of CA-MRSA is present in few regions whereas many clones may be responsible for infections in other parts of the world. The most common clone prevalent in North America is pulse-field type USA300 mostly causing SSTI, bacteraemia, necrotizing fasciitis and severe pneumonia. USA400 is the second most common clone predominant in Alaska causing SSTI and fulminant sepsis. Most common clones seen in Europe and Australia are ST80 MRSA IV and ST93 MRSA IV respectively. ST59 MRSA IV/V is seen in Taiwan. However, limited data is available from Asia. In spite of all the differences in definitions of CA-MRSA and limited number of population based studies, high incidence of CA-MRSA has been reported. Cynthia and colleagues observed a rise in prevalence of CA-MRSA from 17% in 1999 to 56% in 2003. Previous studies have shown a difference in the rate of CA-MRSA infections varying from 10.9% to 29%. In an international surveillance study conducted by Song et al., prevalence of CA-MRSA in Asian countries was 25.5% of which India accounted for 4.3%. The study also suggested that CA-MRSA with various genotypic characteristics have spread from community to hospitals and major endemic HA-MRSA strains have spread from hospital to community in some Asian countries.

**Virulence Factors**

CA-MRSA is known to produce many virulence factors.

1. **Cell wall polymers**
   
   Cell wall polymers include peptidoglycan and teichoic acid which have been implicated in shock. Other cell wall proteins

2. **Cell wall proteins**
   
   Adherence of CA-MRSA to host tissue is mediated by cell surface proteins called Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs). MSCRAMMs like clumping factor, fibronectin-binding proteins and protein A bind to host cell components like fibrinogen, fibronectin and Fc portion of Immunoglobulin G respectively. Other cell
surface proteins include iron regulated proteins, polysaccharide intercellular adhesins and capsular polysaccharides. MSCRAMMs are implicated in bone and joint infections and endovascular infections. One of the important MSCRAMMs in CA-MRSA, collagen adhesin protein is important in the pathogenesis of septic arthritis and osteomyelitis. The microcapsule present in a few clinical isolates of CA-MRSA help in evading host defenses by its antiphagocytic activity and induce abscess formation. A novel gene cluster bsa (bacteriocin of S. aureus) helps in invading an established microbial community and is implicated in quorum sensing and intercellular communication. CA-MRSA also have better tolerance to salt which may help colonization on skin.

3. Enzymes
CA-MRSA has the ability to produce different enzymes like coagulase, staphylokinase, lipase, deoxyribonuclease, protease and elastases which contribute to the pathogenesis of this organism. USA300 harbours a genomic island termed “arginine catabolic mobile element” (ACME) which encodes an arginine deaminase pathway. Arginine deaminase, a known virulence factor may further enhance the pathogenesis of CA-MRSA.

4. Superantigens
CA-MRSA produces various enterotoxins such as staphylococcal enterotoxin A (SEA), staphylococcal enterotoxin B (SEB), staphylococcal enterotoxin C (SEC), staphylococcal enterotoxin G (SEG), staphylococcal enterotoxin H (SEH), staphylococcal enterotoxin K (SEK), staphylococcal enterotoxin L (SEL) and staphylococcal enterotoxin O (SEO) which possess superantigen activity. Large number of T-cells are activated by these superantigens producing cytokines like IL-2 and interferon γ and macrophages produce IL-1 and TNF-β. This leads to most of the clinical manifestations of staphylococcal food poisoning, toxic shock syndrome (TSS) like illness and also epidemic furunculosis and necrotizing pneumonia. Superantigens SEB, SEC, SEA and SEH are produced by most of CA-MRSA isolates. SEB and SEC are implicated in non-menstrual TSS.

5. Cytotoxins
Cytotoxins like α, β, γ, δ toxins and PVL are produced by CA-MRSA, which are hemolytic and toxic to leukocytes respectively.

Panton-Valentine Leukocidin (PVL): Most CA-MRSA carry pvl genes encoding for the PVL toxin, suggesting its role in virulence. PVL is an extracellular bi-component toxin produced as two non-associated secreted proteins LukS-PV and LukF-PV. LukS-PV is dimerized with LukF-PV after connecting to the polymorphonuclear cell membrane forming a heptamer. PVL targets and induces leukocyte death by creating pores in the cell membrane releasing cytokines and intracellular proteases. PVL at low concentration causes apoptosis by forming pores in mitochondrial membrane. Horizontal transmission and clonal expansion of pvl genes leads to spread among CA-MRSA isolates. However studies reveal that PVL negative CA-MRSA infections result in a worse outcome of SSTI when compared to PVL positive CA-MRSA. Few β-lactam antibiotics enhance PVL production while antibiotics like clindamycin inhibit its production.

α-toxin is a pore-forming toxin similar to PVL and causes dermonecrosis. It does not target neutrophils but lyses other cells like RBCs, macrophages, lymphocytes, platelets and fibroblasts.

6. Epidermolytic / Exfoliative toxins
CA-MRSA also produce exfoliative toxins such as exfoliative toxin A and B (eta and etb) that cause staphylococcal scalded skin syndrome and bullous impetigo.
Molecular Properties
Hartman and colleagues described the mechanism of methicillin resistance attributed to PBP 2a – an altered penicillin binding protein with reduced affinity to methicillin. SCCmec, a mobile DNA element carries the meca gene in a mec gene complex, which encodes PBP2a. It also carries direct repeat sequences, integration site sequence and chromosome cassette recombinase (ccr) gene in a ccr gene complex which integrates and excises SCCmec. Eight SCCmec types have been identified – Type I to VIII depending on the class of meca gene and the type of ccr gene complex. No drug resistant determinants other than meca has been associated with types I, IV and V, while multiple drug resistance determinants are seen in types II and III. Due to the small size of SCCmec IV, it can be transferred horizontally to other species resulting in a higher degree of methicillin resistance among CA-MRSA whereas SCCmec II and III, due to their large size, can be transferred vertically on selective antibiotic pressure as seen in HA-MRSA. Horizontal exchange of genes among Staphylococci has been further supported by identifying a few sequences of SCCmec IV identical in S.epidermidis. CA-MRSA that carry SCCmec IV also grow faster and reach high numbers in an infection. They are susceptible to a wide range of non β lactam antibiotics with susceptibility profile similar to that prevalent among methicillin susceptible S. aureus (MSSA). CA-MRSA associated with SCCmec IV cause SSTI (87.6%) and are recovered in high numbers in children than adults.

Clinical Significance
Infections caused by CA-MRSA are similar to those caused by S. aureus except for a few that have arisen in epidemic proportions like SSTI and necrotizing pneumonia. Skin infections are the most common clinical manifestation seen with CA-MRSA. The appearance of red lesions is usually confused with spider bites and may be ignored by the clinicians. Such lesions have the tendency to develop necrotic areas. Furunculosis is the most common clinical presentation associated with CA-MRSA. However, in a previous study done in Mangalore, deep abscesses were seen in 83% of patients in comparison to 16.7% patients with superficial skin infections. Several cases of impetigo, bullous impetigo due to CA-MRSA have been described although 17-20% of S.aureus isolated from bullous impetigo in Japan were PVL negative CA-MRSA. PVL producing CA-MRSA is responsible for another major clinical presentation- necrotizing pneumonia leading to septic shock and respiratory distress syndrome with high mortality. CA-MRSA also causes necrotizing fasciitis, musculoskeletal infections and septic arthritis. Toxins are also responsible for post antibiotic diarrhoea.

Laboratory Diagnosis
CA-MRSA should be considered in the differential diagnosis of purulent SSTI. Clinical specimens should be collected based on the site and type of infection and processed without delay. Gram stain of the specimen can give an immediate clue of staphylococcus infection. Further, culture of the specimen on blood agar is needed to isolate the organism. Once isolated, S.aureus is identified by standard procedures involving colony morphology, gram stain, catalase test and coagulase test. Clinical Laboratory Standards Institute (CLSI) recommends disk diffusion test using cefoxitin (30 µg) disc for identifying methicillin resistance as it is a better inducer of meca gene. Alternative methods include latex agglutination test for PBP2a and agar screen method using Mueller-Hinton agar with 6 µg/ml oxacillin and NaCl (4% w/v). Chromogenic media like ChromID MRSA, MRSASELECT can also be used for detection of methicillin resistance among isolates. PCR can be used for the detection of meca gene that encodes for altered PBP.
Further typing of CA-MRSA can be done using various methods like SCCmec typing, pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST) and S.aureus protein A (spa) typing. SCCmec typing is done using PCR for the detection of the class of mecA gene complex and the type of ccr gene complex.

**Treatment of CA-MRSA Infections**
A new approach in empiric antibiotic therapy and management of staphylococcal infection is needed due to the emergence of MRSA in the community. For severe life-threatening infection and for infections among patients with associated risk factors, vancomycin should be used for empiric therapy. In low CA-MRSA prevalent regions, less severe infections and for patients with absence of healthcare risk factors, empirical therapy with first generation cephalosporin is adequate. Infections are generally not treated with fluoroquinolones as first line due to the risk of developing drug resistance. High resistance of MRSA to quinolones was reported in a previous study. Clindamycin is one of the most common antibiotics used for empiric therapy of CA-MRSA infections, co-trimoxazole is preferred when inducible clindamycin resistance is detected. However, co-trimoxazole must be avoided in paediatric cases less than 8 years due to the reported contraindications.

Non-antibiotic management of CA-MRSA infections have to be considered as drainage can manage many SSTI and must be considered as an adjunct to drug therapy. Simple skin infections caused by CA-MRSA can be treated with hot soaks, elevation, topical therapies, incision and drainage. Proper drainage and debridement can resolve cutaneous abscesses. Hospitalization and parenteral therapy may be necessary for more severe CAMRSA infections. Efforts should be made to collect appropriate specimens for culture and susceptibility testing in areas with high MRSA prevalence and / or in people with associated risk factors and severe infections.

**Prevention**
Basic principles for prevention of CA-MRSA infection as recommended by CDC include hand hygiene, avoiding sharing of personal hygiene items, covering draining wounds, early management of infections, environmental cleanliness and sterilization. Patients should be isolated with implementation of contact precautions if confirmed positive for MRSA infection or colonization. Since nasal colonization is associated with recurrent pyoderma, nasal culture can be done for individuals at high risk. Due to high mortality and morbidity associated with systemic invasive CA-MRSA infections, it is better to screen and treat colonization with mupirocin among individuals with recurrent skin infections and their contacts. This however is not recommended for general population due to the possibility of the development of drug resistance.

**CONCLUSION**
CA-MRSA has emerged in recent years as an important community acquired pathogen. To date, the true incidence of CA-MRSA infection is not known in many countries because most studies have characterized this organism in a relatively small group of patients over a short, fixed time interval. CA-MRSA differs from HA-MRSA in producing PVL, the type of infections caused and antibiotic resistance pattern. Normally, CA-MRSA is more susceptible to antibiotics such as tetracyclines, clindamycin, co-trimoxazole and gentamicin. It usually causes SSTIs, but can also cause severe deep seated infections such as necrotizing pneumonia. Early diagnosis and prompt treatment help in the management of the cases. In recent years, there have been reports of CA-MRSA causing hospital infections. Transmission of SCCmec IV via plasmids or bacteriophages could create bacteria that have
antibiotic resistance of HA-MRSA and the virulence of CA-MRSA.

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Table 1: Differences between CA-MRSA and HA-MRSA

<table>
<thead>
<tr>
<th>PROPERTIES</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting where the infection occurs</td>
<td>Community</td>
<td>Hospitals and other health-care settings</td>
</tr>
<tr>
<td>Population at risk</td>
<td>Children, homeless, athletes, military recruits, jail inmates</td>
<td>Hospitalized patients, patients who underwent surgery, catheterization</td>
</tr>
<tr>
<td>Important clinical manifestations</td>
<td>SSTI, necrotizing pneumonia</td>
<td>Surgical site infection, burn wound infection, intravascular catheter associated blood stream infection, ventilator associated pneumonia</td>
</tr>
<tr>
<td>Antibiotic resistance</td>
<td>Resistance mainly to β-lactams</td>
<td>Multi-drug resistance including β-lactam and other antibiotics</td>
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<tr>
<td>Panton Valentine Leukocidin</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Common Staphylococcal Cassette Chromosome (SCC) mec type</td>
<td>IV and V</td>
<td>II and III</td>
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