

# CA-MRSA: AN EMERGING PATHOGEN

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**Abstract:** Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major problem in hospitals, and it is now spreading in the community. Community acquired MRSA (CA-MRSA) strains differ from hospital-acquired MRSA (HA-MRSA) by virtue of their genomic background and increased virulence because of Panton-Valentine leukocidin PVL gene. Though CA-MRSA was supposed to be less resistant to antimicrobial but acquisition of additional resistance genes are making them multi-resistant. Defining CA-MRSA by the absence of risk factors for healthcare exposure and anti microbial resistance pattern greatly underestimates the burden of epidemic CA-MRSA disease. Reports of CA-MRSA strain infiltrating hospitals and replacing the traditional HA-MRSA strains by virtue of less fitness cost are emerging. If true, this event would have serious consequences, because more virulent CA-MRSA infections in hospitals would occur among a more debilitated, older patient population.

## INTRODUCTION

Shortly after the introduction of penicillin in the 1940s, penicillin-resistant *S aureus* isolates were described first in hospitals and subsequently in the community. Today, the vast majority of staphylococcal isolates carry plasmids encoding a penicillinase-rendering penicillin resistance. Methicillin, a penicillinase-resistant semisynthetic penicillin, was introduced in 1961. Less than 1 year later, MRSA was reported. Today, MRSA is a common nosocomial isolate associated with hospital and accounts for more than 50% of *S aureus* isolates from intensive care units in the western countries<sup>1</sup>. There are reports of 30-85% MRSA prevalence from different parts of India<sup>2,3,4</sup>.

Several risk factors, such as recent hospitalization or exposure to a healthcare setting, residence in long-term-care facilities, invasive or surgical procedures, intravenous drug use, and prolonged exposure to antibiotics, could predispose a patient to acquire HA MRSA. *S. aureus* infections in the community are mostly caused by MSSA strains and MRSA in the community is infrequent. Complicating the problem is the emergence of community acquired MRSA (CA-MRSA) since 1990, which are genotypically different from HA-MRSA. These CA-MRSA are seen in individuals without the risk factors for HA-MRSA, usually less resistant to antibiotics but more virulent on account of presence of PVL toxin. Overall, infection with MRSA has been shown to carry a poor prognosis than infection with methicillin sensitive *S aureus* (MSSA) on account of less therapeutic options<sup>5</sup>.

## CURRENT GLOBAL EPIDEMIOLOGY OF CA-MRSA

In 1982, MRSA was first reported outside of the hospital among intravenous drug users in Detroit, Mich<sup>6</sup>. Subsequently, MRSA was described in Polynesian populations in western Australia and in pediatric populations in the southern and midwestern United States. In 1999, a report of the deaths of 4 children due to severe MRSA infections in Minnesota and North Dakota garnered much attention. A burgeoning body of literature continues to detail the emergence of CAMRSA. These community isolates are composed of a heterogeneous mix of strains, but most CA-MRSA isolates are from the USA300 and USA 400 clonal families.

CA-MRSA has become the most common pathogen of skin and soft tissue infection in many parts of the USA and causes 76.4% of *S.aureus* infection in community. The emergence of the USA 300

clone first epidemic and now established as endemic exemplifies the success of CA-MRSA. Not only CA-MRSA has strongly established itself in the community it is now being, particularly USA 300 CA-MRSA clone, widely disseminated in the hospital to cause various nosocomial infections, which is replacing traditional nosocomial MRSA strains in the hospital.

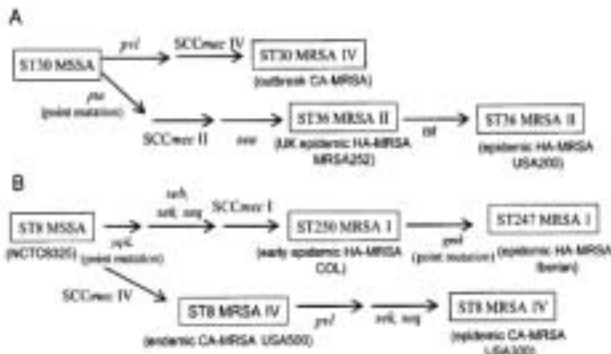
Emergence of European CA-MRSA clone has been reported in many European countries such as France, Germany, Spain, UK, Ireland, Belgium, Slovenia, Austria, Sweden, Switzerland, Denmark, and Netherlands. Also, USA 300 clone with SCCmec type IV, pvl gene and ST 8 was reported from various European countries. In Spain, MRSA accounted for 28 % of community-acquired infections in 2003 which had been continuously increasing from 7 % in 1993. The epidemiology of CA-MRSA in Asia has not been fully investigated. There is a paucity of Indian data on true CA-MRSA by genotypic classification. One study reported a prevalence of 0.8% in rural population and 12.3% in urban population<sup>7</sup>. According to the multinational surveillance study by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) with 7,284 isolates of *S. aureus* from 30 study centers of 9 Asian countries, the proportion of CA-MRSA accounted for 15.6% of MRSA isolates. Prevalence of MRSA among *S. aureus* infections in the community was the highest in Taiwan (40.5%) followed by Sri Lanka (38.8%), the Philippines (30.1%), Vietnam (28.2%), and Korea (20.5%)<sup>8</sup>.

## EVOLUTION AND GENETIC CHARACTERISTICS OF CA-MRSA

The original MRSA strains have become established in hospitals worldwide and are classified by multilocus sequence typing (MLST) as belonging to 5 distinct clonal complexes, CC5, CC8, CC22, CC30, and CC45. The 2 community-associated MRSA (CA-MRSA) lineages with the greatest medical impact belong to CC8 and CC30—the 2 background genomes that produced the very first MRSA strain and the second most common MRSA strain found in hospitals in the United Kingdom and the United States. Other CAMRSA strains belong to CC1, CC59, and CC80. It is not clear why certain MRSA strains predominate in hospitals and other MRSA strains predominate in community settings.

The evolution of contemporary hospital and community phenotypes within the CC8 and CC30 lineages—2 background genomes that produced historical pandemic MRSA clones—were associated with multiple horizontal acquisitions of virulence genes. The epidemic community phenotype of a CC8 strain, designated ST8:USA300,

was linked to the acquisition of staphylococcal cassette chromosome (SCC)*mec* type IV, the genes for Pantone-Valentine leukocidin (PVL), and the enterotoxin Q and K genes. Similarly, the epidemic community phenotype of a CC30 strain, ST30:USA1100, was linked to the acquisition of SCC*mec* type IV and the *pvl* genes. In contrast, the epidemic hospital phenotype of another CC30 strain, ST36:USA200, was associated with the acquisition of SCC*mec* type II, the enterotoxin A gene, and the toxic shock syndrome toxin 1 gene<sup>9</sup>. (Figure 1)



**Figure 1:** Proposed Genetic events leading to the emergence of epidemic strains of CA-MRSA and HA-MRSA in the CC30 and CC8 lineage (Francois)

**Table 1.** Difference between CA-MRSA and HA-MRSA

	CA-MRSA	HA-MRSA
Predisposing factors	Children, competitive athletes, prisoners, soldiers, selected ethnic populations (Native Americans/ Alaska Natives, Pacific Islanders), intravenous drug users, men who have sex with men admission	Residents in long-term care facility, patients with diabetes mellitus, patients undergoing hemodialysis/peritoneal dialysis, prolonged hospitalization, intensive care unit indwelling intravascular catheters
SCC type	Type IV	Type I,II and III
Antimicrobial resistance	Beta lactam resistance only usually	Multi drug resistance usually
Toxin and PVL	Frequent	Rare
Associated clinical syndromes	Skin and soft tissue infections, postinfluenza necrotizing pneumonia	Nosocomial pneumonia, nosocomial- or catheter-related urinary tract infections, intravascular catheter or bloodstream infections, surgical-site infections
Lineage	USA 300, USA 400	USA 100, USA 200

CA-MRSA is distinct from HA-MRSA, both genetically and phenotypically. The *mecA* gene (responsible for MRSA) is located on a genetic island called the staphylococcal cassette chromosome *mec* (SCC*mec*), and differences in SCC*mec* are used to categorize MRSA. HA-MRSA strains carry SCC*mec* types I through III, whereas CA-MRSA strains carry SCC*mec* IV (and the more recently isolated SCC*mec* V). Hospital-associated SCC*mec* II and III are large genetic elements that also carry genes for resistance to non-beta-lactam antibiotics, whereas the small SCC*mec* IV carries only methicillin resistance. Thus, HA-MRSA tends to be multi-resistant, whereas CA-MRSA tends to be susceptible to narrow-spectrum non-beta-lactams such as clindamycin, trimethoprim sulfamethoxazole (TMP-SMX), and tetracyclines. But, CA-MRSA isolates from Asian countries shows high resistance rates to non- $\beta$ -lactam agents such as gentamicin (61.6%), ciprofloxacin (50.6%), clindamycin (69.9%), erythromycin (86.7%), and tetracycline (65.8%), therefore making hazardous to distinguish them from HA-MRSA by antibiogram only.

Another distinguishing genetic feature of CA-MRSA is that a high percentage of strains carry genes for PVL, an exotoxin that is lethal to leukocytes. Genes for PVL are largely absent from HA-MRSA strains. PVL, perhaps in combination with other exotoxins, appears to be responsible for the enhanced pathogenicity of CA-MRSA strains

and instrumental in producing necrotic skin lesions and necrotizing pneumonia. Severe invasive disease, such as necrotizing pneumonia and necrotizing fasciitis, appears to be more common with CA-MRSA than methicillin-sensitive *S aureus* (MSSA) or HA-MRSA<sup>10</sup>. Furthermore, unlike HA-MRSA, which is considered an opportunistic pathogen, CA-MRSA causes infection in healthy, predominantly young hosts who have no predisposing comorbidities<sup>11</sup>.

CA-MRSA isolates from the United States shows a high frequency (77%) of Pantone-Valentine-Leukocidin (*pvl*) gene, while only 4% of nosocomial MRSA strains had this gene. But, the prevalence of the *pvl* gene among CA-MRSA isolates varied in Asian countries from 100% (India), 60% (China) 9.3% (Taiwan). MLST analysis also showed very diverse clonal complexes among Asian strains<sup>7,12</sup>. These genetic features suggest that Asian CA-MRSA strains are a heterogeneous group.

With regard to genotypic characteristics, CA-MRSA strains can be classified as USA-300, 400, and 800 clone, while most of the nosocomial MRSA isolates belong to USA-100 or 200 clone based on the pulsed-field gel electrophoresis. These CA-MRSA clones from the United States typically showed SCC*mec* type IV with only *mecA* gene<sup>12</sup>. Table 1 highlights differences between CA-MRSA and nosocomial MRSA.

## PATHOGENESIS

Community-acquired MRSA strains tend to have associated exotoxins. The most common and probably important is the Pantone-Valentine leukocidin (PVL) toxin which is lethal to neutrophils and is associated with skin and soft tissue infections (specifically cellulitis, cutaneous abscesses, and furuncles) as well as severe necrotizing pneumonia<sup>13</sup>. Historically an uncommon virulence factor (present in <5% of isolates), PVL is emerging with CA-MRSA and probably in part explains the predilection for skin and soft tissue infections. Recent *in vitro* work revealed that PVL-positive strains of *Staphylococcus* bind preferentially to damaged respiratory epithelium<sup>14</sup>. This correlates clinically with data showing that PVL-associated pneumonias are associated with prior influenza like illnesses. It is postulated that PVL contributes to enhanced community fitness, perhaps through enhanced transmission from draining wounds. Other exotoxins, including that responsible for staphylococcal scalded skin syndrome, have been described in community strains<sup>15</sup>.

## CLINICAL SYNDROMES

It is important that the clinicians be aware of the spectrum of disease by CA-MRSA, which differs from that of HA-MRSA in distribution and pattern of infection. Patients infected with CA-MRSA tend to be significantly younger than those infected with traditional strains of MRSA<sup>16</sup>. Unlike traditional MRSA strains, which often are isolated from the bloodstream and the respiratory and urinary tracts, skin and soft tissue infections are the predominant forms of the disease caused by CA-MRSA and accounts for 77% to 96% of infections. CA-MRSA can cause a range of cutaneous manifestations, including folliculitis, impetigo, cellulitis, carbuncles, paronychia, deep subcutaneous abscesses, and necrotizing fasciitis<sup>17</sup>. Localized necrosis seems to be a very typical feature of CA-MRSA skin infections it is more common for these infections to arise spontaneously on apparently unbroken skin. Spontaneous furuncles with a necrotic center often are mistaken by patients for spider bites. Necrotizing fasciitis is an uncommon, rapidly progressive, life-threatening disease that requires prompt recognition and surgical debridement for cure. PVL production appears to be a key factor in the propensity of CAMRSA Although representing less than 5% of all *S aureus* strains,

PVL-producing strains caused 93% of furuncles.

Although CA-MRSA CAP is rare, at 2% of CA-MRSA infections, reports of lethal community-acquired pneumonias (CAPs) due to CA-MRSA are mounting. This is predominantly seen in young healthy adults and children with preceding influenza-like illness of proven influenza A infection. CA-MRSA CAP presents as PVL positive necrotizing pneumonia with hemoptysis and fulminant course carrying a high mortality rate of 42%<sup>18</sup>. Community-acquired MRSA has also been reported less frequently in endocarditis, brain abscesses, bacteremia, sinusitis, and musculoskeletal infections.<sup>30-34</sup><sup>19</sup>. Such diverse manifestations may become recognized more frequently over time as the prevalence and physician awareness of this pathogen increase.

Community-acquired MRSA should be considered in the differential diagnosis of skin and soft tissue infections, particularly among patients at risk or slow to respond to  $\beta$ -lactam therapy. Furunculosis and cutaneous skin abscesses are the most common manifestations, but simple cellulitis also can occur.

## TREATMENT

When choosing an empirical antimicrobial for skin and soft tissue infections, one should consider the likelihood that MRSA is the etiologic agent, the severity of the infection, and pertinent host factors including immunologic status (eg, diabetes mellitus and human immunodeficiency virus), allergies, and factors that may impede follow-up.  $\beta$ -Lactam agents currently remain the antimicrobial of choice for most skin and soft tissue infections in many if not most parts of the country. But if CA-MRSA is strongly suspected on the basis of local prevalence data or epidemiological and/or clinical clues, empirical CA-MRSA directed therapy is indicated. For small (<5 cm) cutaneous abscesses with no significant surrounding cellulitis or systemic symptoms, drainage alone is sufficient, provided close follow-up is available. Empirical antimicrobial therapy is indicated for patients with larger abscesses, cellulitis, systemic symptoms, or serious comorbidities. Moderate cases treated early and appropriately may permit successful outpatient therapy.

Therapy for SSTI due to CA-MRSA includes, oral clindamycin or the combination of TMP-SMX plus cephalexin (which covers group A *Streptococcus*) is recommended in complicated infections. For uncomplicated infections in adults doxycycline is a good choice. Linezolid is an excellent option reserved for failure of narrow-spectrum antibiotics. Expense, drug interactions, and the potential for promoting linezolid resistance make this drug undesirable for widespread outpatient use. Newer fluoroquinolones (e.g., gatifloxacin, moxifloxacin, and levofloxacin) have enhanced activity against *Staphylococcus*. Increasing fluoroquinolone resistance among CA-MRSA isolates and limited experience for this indication suggest that fluoroquinolones should not be first-line agents for empirical treatment. Daptomycin and quinupristin-dalfopristin are relatively new parenteral agents, each with activity against MRSA and with Food and Drug Administration approval for skin and soft tissue infection. Each appears to be similar in efficacy to vancomycin for skin and soft tissue infection. Daptomycin is taken once daily, making it an attractive option for outpatient therapy. Cost and concern about promoting resistance weigh against its routine use over vancomycin. Adequate drainage and debridement in serious infections remains crucial for the favorable outcome.

Although CA-MRSA pneumonia is much less common than skin and soft tissue infections, the high morbidity and mortality associated with this entity makes it imperative to have high index of suspicion. Severe necrotizing pneumonia post influenza like illness in young adults warrants that empiric therapy against MRSA should be

administered immediately as the course can be fatal in matter of 1-2 days. The 2007 IDSA/ATS guidelines recommend adding either vancomycin or linezolid to standard ICU therapy for suspected CA-MRSA pneumonia. Case reports have documented instances of vancomycin treatment failure in CA-MRSA CAP, followed by improvement after switching to linezolid<sup>20</sup>. Unlike vancomycin, linezolid is concentrated in alveolar fluid and may remain above minimum inhibitory concentration (MIC) in lung tissue long enough to be effective<sup>21</sup>. Linezolid and clindamycin also significantly reduce PVL production, whereas vancomycin has no effect on protein synthesis. Daptomycin should not be used for treatment of pneumonia as it is inactivated by surfactant lining the alveoli of the lungs. Intravenous immunoglobulin neutralizes PVL toxin in vitro, but the clinical relevance of this remains undefined.

## EMERGING TREND

The most remarkable feature of the CA-MRSA genotype is its evolutionary success, resulting in its rapid worldwide clonal emergence. The reason being is the small SCCmec IV allele seems to carry little fitness cost, allowing CA-MRSA to thrive and spread readily outside the hospital environment, unlike HAMRSA strains, which require the hospital milieu for sustained survival. Also the presence and expression of two functional recombinant genes (which are not present in HA-MRSA) provide the molecular basis for its extensive movement into both nosocomial MRSA and community-acquired MRSA clonal types.

The expanding community reservoir of CA-MRSA has led to the inevitable infiltration of CA-MRSA into hospitals. This phenomenon has become a major public health threat and it is postulated that CA-MRSA will become the dominant MRSA strain in hospitals, with competitive exclusion of the traditional HA-MRSA strain<sup>22</sup>. To that effect, several hospitals have already documented the predominance of CA-MRSA over HA-MRSA strains as a cause of hospital-acquired infections<sup>22</sup>.

Another area of concern is that though CA-MRSA was considered as less resistant to antimicrobials but more lethal, this distinction is getting blurred. Huang et al has reported that CA and HA strains are exchanging genetic material, resulting in an organism uniquely adapted to produce aggressive SSTI like CA-MRSA strain which carry PVL gene as well as possessing resistance to multiple antimicrobial agents, like current HA strains<sup>23</sup>. Such an event has the potential for catastrophic consequences, because multi-resistant CA-MRSA can cause severe infections, which will now occur among debilitated, immunocompromised hospitalized patients.

## CONCLUSION

CA MRSA is an emerging pathogen and the epidemiology of MRSA seems to be changing. The rise in the number of reports of community-acquired MRSA, and the suspicion that some community-acquired strains are highly virulent is of great concern, because the reported serious infections caused by CA-MRSA strains will now occur among hospitalized patients, who are a more debilitated and older patient population. There is a dearth of Indian data on CA-MRSA, but it can be assumed that the threat is real and challenging. Clinicians should be aware of CA-MRSA and its varied presentation and reconsider the presumptive treatment of community acquired staphylococcal infections with cephalosporins.

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## DRUG PROFILE

### Trospium Chloride

**Indications and Usage:** Trospium is an anticholinergic drug, indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. **Dosage and Administration:** The recommended dose is 20mg twice daily. The drug should be given with water on an empty stomach, at least one hour before the meal. **Contraindications:** The drug is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions. **Warning and precautions:** The drug should be administered with caution to patients with clinically significant bladder outflow obstruction or gastrointestinal obstructive disorders due to risk of urinary or gastric retention. In patients with narrow angle glaucoma, it should be used only with careful monitoring. The drug is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/Min). Alcohol should not be consumed within 2hrs of administration, of the drug. **Adverse reactions:** These include dry mouth (10.7%) and constipation (8.5%). **Drug Interactions:** Trospium is metabolized by ester hydrolysis and is excreted by kidneys through tubular secretion and glomerular filtration. Concomitant use with digoxin did not effect the pharmacokinetics of either drug. The oral bioavailability was reduced following a high fat-content meal. **Use in specific population: Pregnancy:** Use not advisable, drug is excreted to a limited extent into the milk; avoid in lactating mothers. **Pediatric :** The safety and effectiveness of the drug in Pediatric patients have not been established. **Renal Impairment:** Trospium is not recommended for use in patients with moderate to severe renal impairment. Caution is advised when the drug is used in patients with severe hepatic impairment.

## CONFERENCE NEWS

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