**Methicillin-resistant *Staphylococcus aureus* (MRSA) in developing and developed countries: implications and solutions**

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**Abstract**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a global public health problem, associated with considerable morbidity and mortality. The MRSA infections can be hospital- or community-acquired. Hospital-associated MRSA (HA-MRSA) characteristically colonizes or infects hospitalized individuals with predisposing risk factors, usually harbours SCCmec type I, II or III, and is multi-drug resistant (MDR). In contrast, community-associated MRSA (CA-MRSA) infects healthy individuals without any previous healthcare contact, often harbours smaller and more mobile SCCmec types, is usually Panton-Valentine leucocidin (PVL) positive, susceptible to non-β-lactam antimicrobial drugs, and frequently manifests as skin and soft-tissue infections. However, this distinction between CA- and HA-MRSA is gradually fading owing to the emergence of pvl negative and/or MDR CA-MRSA clones, and its invasion into hospitals. The incidence of HA- and CA-MRSA infections, as well as the relative abundance of different MRSA clones varies considerably among countries. The HA-MRSA is endemic in many hospitals worldwide. The CA-MRSA has a smaller fitness burden, higher transmissibility and virulence compared to HA-MRSA, and is epidemic in many geographical locations. In addition, some MRSA clonal lineages exhibit superior survival and transmissibility, and are more frequently isolated than others. Limited options are available for the therapeutic management of MRSA infections. The CA-MRSA-associated skin and soft-tissue infections are treated with oral antibiotics including doxycycline, minocycline, clindamycin, trimethoprim-sulfamethoxazole, rifampicin and fusidic acid. Severe CA-MRSA infections and HA-MRSA necessitate intravenous vancomycin therapy. Asymptomatic carriers represent an important MRSA reservoir. The transmission of MRSA infections may be limited by universal infection-control measures, patient education, screening and decolonization of asymptomatic MRSA carriers in both healthcare and community settings.

**Introduction**

*Staphylococcus aureus* (*s. aureus*) is a frequent cause of bacterial infections in both developed and developing countries.† It is a highly versatile and adaptable pathogen, causing a range of infections of varying severity affecting the skin, soft tissue, respiratory system, bone, joints and endovascular tissues.† The organism also exists as a commensal, colonizing the anterior nares of about one third of the healthy human population.‡,§ Asymptomatic nasal carriers are at a high risk of subsequent *S. aureus* infection and are presumed to be an important source of strains that spread and cause infection in contacts.‡,§ In addition, *S. aureus* represents a prototype for drug resistance, especially to β-lactam antibiotics. Although this bug has been naturally susceptible to almost every antibiotic developed so far, it frequently gains resistance by gene mutations and horizontal gene transfer, that protect the bug under antibiotic selection pressure,‡ and has been implicated

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in episodes of epidemic and pandemic proportions.1,4 The effectiveness of penicillin, introduced in the early 1940s, was annulled within a decade owing to the rapid spread of plasmid-encoded *S. aureus* β-lactamase.1,5 Resistance to meticillin, a penicillinase-stable β-lactam, was reported within two years of introduction in 1959, and rapidly spread worldwide.1,5 Methicillin-resistant *S. aureus* (MRSA) first emerged in hospitals in the 1960s, re-surfaced as a community-based infection in the 1990s, and is currently a frequently encountered antibiotic-resistant pathogen.1,2,4,6

**Emergence and resurgence of MRSA**

Unlike penicillin resistance that results from a plasmid-encoded penicillin-degrading enzyme (β-lactamase), methicillin resistance is genetically mediated by staphylococcal-cassette-chromosome (SCCmec), a mobile genetic element encoding for an altered penicillin-binding protein (PBP2a, mecA) with a decreased affinity to β-lactams.5-7 SCCmec probably evolved in penicillinase-negative *Staphylococcus sciuri*, a frequent colonizer in animals, under selective pressure of penicillin and was subsequently acquired by *S. aureus* following inter-species horizontal gene transfer.5-7 Eight different SCCmec types are known on the basis of mecA class and new types continue to emerge.5-7 Although nearly all clinically significant MRSA produce PBP2a, infrequent isolates with alterations to existing PBPs, named moderately-resistant *S. aureus* (MODSA) and isolates exhibiting low-level methicillin resistance due to penicillinase overproduction, named borderline oxacillin-resistant *S. aureus* (BORSA), have been rarely described.8 The clinical significance of such strains remains doubtful.8

The emergence of MRSA typically coincides with that of penicillin-resistant *S. aureus* (PRSA).9 It was first described in the 1960s, and has been traditionally regarded as a nosocomial pathogen, endemic in hospitals and health-care facilities of most countries.1,2,4,6 Hospital-associated MRSA (HA-MRSA) characteristically colonizes or infects hospitalized individuals with predisposing risk factors such as surgery, presence of indwelling medical devices (IMDs), an immuno-compromised state or prior antibiotic exposure.1,2,4,6 It is often isolated from wound infections, line-associated bacteremia and ventilator associated pneumonia.5,7 The strains usually harbour SCCmec type I, II and III, and are multi-drug-resistant (MDR).5-7

About three decades after the emergence of HA-MRSA, the organism spilled over to the community increasing the staphylococcal disease burden.1 The community-acquired strains evolved either from the hospital strains and underwent genetic changes or were the result of mec gene transfer to formerly susceptible subsets in the community.9 True community-associated (CA) MRSA, infecting healthy individuals without any previous health-care contact, was initially reported (1990s) in Australia, followed by reports from the United States of America (USA), and is now highly prevalent worldwide.1,2,4,6 The CA-MRSA infects healthy individuals without any health-care contact, harbours smaller and more mobile SCCmec types (IV and V), is susceptible to non-β-lactam antimicrobial drugs and typically manifests as skin and soft tissue infections. Life-threatening conditions, including osteomyelitis, severe necrotizing pneumonia, and fatal sepsis have also been reported.1,2,4-7 It has a superior epidemicity than HA-MRSA, courtesy the presence of more mobile SCCmec types, faster growth and relatively smaller fitness burden.1,5-7 Consequently, the CA-MRSA strains possess a high attack rate in outbreak settings, are more virulent than HA-MRSA, and have rapidly disseminated among countries.1 Panton-Valentine leucocidin (PVL), a prophage-encoded two-component cytotoxin ( lukS-PV and lukF-PV) presents itself in only 2-3 % of methicillin-sensitive *S. aureus* (MSSA), is frequently associated with CA-MRSA and may play a role in skin and soft-tissue infections and severe necrotizing pneumonia caused by
these bacteria.\textsuperscript{1,5-7} Moreover, these strains exhibit increased expression of chromosomally-encoded α-hemolysin, a pore-forming toxin that lyses many types of eukaryotic cells, as well as α-type phenol-soluble modulins (PSMs), amphipathic peptides that recruit, activate and destroy leukocytes.\textsuperscript{1,2} Both α-hemolysin and PSMs are over-expressed in CA-MRSA compared to HA-MRSA and are major determinants of its pathogenesis and virulence.\textsuperscript{1,2}

The CA-MRSA is evolving rapidly, and lineages differing in classical CA-MRSA characteristics, including \textit{pvl} negative and/or MDR clones, have also been reported.\textsuperscript{1,6}

\section*{Molecular epidemiology}

The MRSA is usually transmitted by direct skin-to-skin contact with a colonized or infected individual and occasionally via fomites.\textsuperscript{1,6} Five factors or “Cs” have been implicated in MRSA outbreaks — contact; lack of cleanliness; compromised skin integrity; contaminated objects; and crowded living conditions.\textsuperscript{1,6}

Methicillin resistance in \textit{S. aureus} isolates (mostly health-care-associated MRSA) varies from less than 1 \% in Norway, Sweden and Denmark, less than 5 \% in the Netherlands, 5 - 10 \% in Canada, 40 \% in Greece and the United Kingdom of Great Britain and Northern Ireland, 25 - 50 \% in the USA, 37.5 \% in India, to more than 50 \% in China, Hong Kong Special Administrative Region (Hong Kong SAR) and Singapore.\textsuperscript{6,10} About 51.6 \% of \textit{S. aureus} isolates among patients admitted to burns and orthopaedic units in India were reported to be MRSA.\textsuperscript{11}

The CA-MRSA is highly prevalent in the USA, accounting for about 59% infections in emergency departments.\textsuperscript{2} However, Kallen \textit{et al.} have recently reported a decrease in health-care-associated community (17\%) as well as hospital (28\%) MRSA infections in nine geographically diverse metropolitan areas in the USA.\textsuperscript{12} An upsurge of MRSA has been reported in India.\textsuperscript{13-16} The MRSA isolation rates have increased from 9.83 \% (1992) to 45.44 \% (1998), with the strains being more common in south than in west or north India.\textsuperscript{13-16} In Japan, the percentage of MRSA isolated from skin infections has been shown to vary from 10 to 20\%.\textsuperscript{13} By comparison, CA-MRSA has not reached the same proportions in Europe.\textsuperscript{2} Although its incidence is steadily increasing in many European countries including France, the Netherlands and the United Kingdom,\textsuperscript{6} the overall prevalence of \textit{pvl}-positive CA-MRSA in Europe is about 1-3\%.\textsuperscript{2} It was reported to constitute 6.4\% \textit{S. aureus} isolates, 10\% MRSA and 1.8\% MRSA in Italy, Austria and Ireland respectively.\textsuperscript{6} A very low incidence of CA-MRSA has also been described in Switzerland (0.09\%), the United Kingdom (0.005\%), Spain and Portugal.\textsuperscript{6} However, the prevalence of CA-MRSA in Greece is very high, accounting for about 55\% MRSA infections.\textsuperscript{5}

Despite the increased global presence of MRSA, its carriage among healthy population remains low in most countries.\textsuperscript{6} Different studies have reported MRSA nasal carriage rates ranging from 0.26 to 9.2 \% in USA.\textsuperscript{1} Similarly, 1\% \textit{S. aureus} asymptomatic carriers harbour MRSA in the United Kingdom.\textsuperscript{6} About 3.89\% and 5.3\% healthy children and adults respectively, have been reported to be colonized with CA-MRSA in India.\textsuperscript{16,18} The carrier rate is generally higher in AIDS and diabetic patients, those who are frequently hospitalized or are on dialysis or are of advancing age. The HA-MRSA carriage rate is around 15.6 \% in inpatients and 1.8 - 2 \% among health-care workers in India.\textsuperscript{19,20}

The MRSA isolates are genetically characterized by multilocus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), SCC\textit{mec} typing (I-VIII), accessory gene regulator (\textit{agr}) typing and staphylococcal protein \textit{A} (\textit{spa}) typing.\textsuperscript{2,4} The MLST classifies \textit{S. aureus} isolates on the basis of allelic variation in seven housekeeping genes — clones consist of isolates with identical
sequences at all the seven loci and are assigned a unique sequence type (ST); clonal complexes (CCs) comprise closely-related STs differing by single nucleotide polymorphisms (SNPs) at lesser than three loci. It indexes slowly accumulated variation and can be used to measure long periods of evolution among strains. In contrast, PFGE involves the analysis of Smal-digested genomic DNA, and is more discriminatory but appropriate for evaluation of the recent evolution.

All MRSA clones have evolved from five groups of related genotypes (clonal complexes), each arising from a distinct ancestral genotype. The prevalence of different lineages varies with the geographical location probably due to socioeconomic factors and antimicrobial policies. Some clonal lineages have a superior ability to survive and transmit, and are consequently more frequently isolated than the others. Five major MLST clonal complexes (CCs) have been implicated in HA-MRSA infections globally, with the archaic clone being the first HA-MRSA clone to be identified. Although most HA-MRSA clones harbour SCCmec I-III, type IV has been reported in many lineages. The major clonal complexes include:

1. CC5: ST5-MRSA-I, ST5-MRSA-II (New York/Japan clone; PFGE type USA100), ST5-MRSA-IV (paediatric clone; PFGE type USA 800) and ST228-MRSA-I (southern German clone);
2. CC8: ST250-MRSA-I (archaic clone), ST247-MRSA-I (Iberian clone), ST399-MRSA-III (Brazilian/Hungarian/Portuguese clone), ST8-MRSA-II (Irish 1 clone), ST8-MRSA-IV (PFGE type USA500);
3. CC22: ST22-MRSA-IV;
4. CC30: ST36-MRSA-II (PFGE type USA 200); and
5. CC45: ST45-MRSA-IV (Berlin clone), ST45-MRSA-II (PFGE type USA600).

Many of these multidrug-resistant clones have disseminated globally and account for the majority of HA-MRSA infections in several regions. The ST5-MRSA-II (USA100) and ST22-MRSA-IV are the prominent HA-MRSA clones in the USA, Europe and Australia respectively. The ST36-MRSA-II (USA200) is the single most abundant clone in the United Kingdom hospitals. The Indian HA-MRSA strains are related to the Brazilian/Hungarian clone and belong to ST239-MRSA-III/IIIA. The same clone is also prevalent in China, along with ST5-MRSA-II that has a low prevalence. Among CA-MRSA, the ST1-MRSA-IVa (CC1; USA 400) was the predominant CA-MRSA clone in the USA till 2001. It was subsequently replaced by ST8-MRSA-IVa (CC8; USA 300) in most communities and is currently the leading cause of CA bacterial infections in the USA. It was isolated from more than 50% infections in the United States emergency departments. The USA 300 is more virulent than the USA 400 owing to over-expression of α-toxin, PSMs and many secreted proteases. It also harbours arginine catabolite response element (ACRE), a putative pathogenicity island encoding for arginine deaminase pathway. The ACRE promotes bacterial survival on acidic human skin, proliferation under low oxygen conditions such as in abscesses and evasion of host defences. Consequently, ACRE-positive lineages exhibit superior colonization and transmissibility in comparison to many other clones with similar virulence, such as ST8-MRSA-Iv (CC8; USA 500). However, USA 400 still remains the major cause of CA-MRSA-associated infections in some regions of North America and Canada. About 45 distinct CA-MRSA clones have been described in Australia; ST30-MRSA-Iva (CC30; USA 1100) and USA 400 are the leading cause of infections. The ST80-MRSA-IV is the...
A predominant CA-MRSA clone in Europe. The ST22-MRSA-IV and ST772-MRSA-V, ST59-MRSA-Iva and ST30-MRSA-Ivc have been reported from India, China (Province of Taiwan) and Singapore. 27, 28 Many recent CA-MRSA clones have been shown to have transmitted between animals and humans. 2 The ST398-MRSA-V, a PVL-negative strain, was first identified in pigs and pig farmers in Europe and has been subsequently reported from the USA and Canada. 2 Considering the universal use of multiple antibiotics such as tetracycline in livestock, the antibiotic resistance of these strains and their subsequent transmission to humans is a major concern. 2 Furthermore, CA-MRSA is now invading the hospitals. The CA-MRSA-infected individuals transmit these strains in the hospital setting and result in nosocomial infections. 2, 3 The USA 300 and USA 500 are currently a more notable cause of hospital-acquired MRSA infections than the USA 100. 2 The USA 300 accounted for about 20% nosocomial cases of MRSA blood stream infections in Atlanta, USA. 3 This epidemiological transition may pose a significant therapeutic challenge. The CA-MRSA clones have a relatively smaller fitness burden and enhanced virulence, and may therefore increase the seriousness of hospital-acquired drug-resistant S. aureus infections. 5

Therapeutic and prophylactic management
Methicillin resistance in S. aureus is usually detected by the cefoxitin disk and oxacillin-salt-agar screen test according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI), (USA). Many other methods including PCR-based mecA detection, latex agglutination test (PB2a detection), E test, agar and broth dilution, quenching fluorescence assay, as well as chromogenic media such as Spectra MRSA are also available for MRSA identification. 1, 8, 29

The MRSA has markedly influenced the empirical therapy for suspected staphylococcal infections. 1, 4, 5 Most β-lactam antibiotics are ineffective against both HA- and CA-MRSA. 1, 5, 7 The HA-MRSA isolates are usually MDR 1, 5, 7 The CA-MRSA strains are often susceptible to non-β-lactam drugs 1, 5, 7 although MDR clones are also emerging. 1, 6 Unlike methicillin resistance, the prevalence of MRSA resistance to non-β-lactam agents varies geographically and may change over time. 30 Local susceptibility patterns of community S. aureus isolates should therefore be regularly monitored to frame policies for MRSA management. 30

Cutaneous abscesses need surgical incision and drainage irrespective of the antibiotic susceptibility pattern 1, 4 of the causative organism. Antibiotics provide little or no benefit in most cases, and are not routinely recommended except for patients of advanced age or those with severe disease symptoms of systemic illness, immunosuppression or abscess in an area that is difficult to drain. 1, 4 The CA-MRSA-associated skin and soft-tissue infections are often treated using oral antibiotics including doxycycline and minocycline, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), rifampicin, and fusidic acid. 1, 4, 31 Clindamycin is active against CA-MRSA strains as well as against the Group A streptococci, and is therefore an appealing therapeutic choice. 1 However, clindamycin resistance seems to be increasing. 1 In India, about 15.65% and 7.23% CA-MRSA strains were shown to exhibit inducible and constitutive clindamycin resistance respectively. 32 A D-zone test is therefore recommended for identification of inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible S. aureus isolates. 30 Long-acting tetracyclines (doxycycline and minocycline) and TMP-SMX are also efficacious against CA-MRSA. 1, 4 The prevalence of tetracycline resistance remains low among MRSA isolates in the community and the resistance described so far (tetK mediated) has been specifically associated with tetracycline, not doxycycline and minocycline. 32 However, their activity against
Group A streptococci is variable and these antibiotics are contraindicated in children younger than eight years (tetracyclines) or pregnant women (tetracyclines and co-trimoxazole). Rifampicin or fusidic acid may be used as adjuncts to another active drug but never singly — monotherapy frequently results in emergence of resistance. 1,4,33 As rifampin achieves high concentrations in mucosal surfaces, it may promote eradication of MRSA carriage theoretically. 30 In India, use of rifampicin as an anti-MRSA drug is discouraged owing to the high prevalence of tuberculosis. Fluoroquinolones are usually not recommended for MRSA treatment. 30 Therapy with these agents frequently results in selection of resistant mutants, and consequent relapse and treatment failure. 30

Vancomycin remains the first-line intravenous drug for severe CA-MRSA and HA-MRSA infections. 1,4 However, high rates of microbiological and clinical failure, nephrotoxicity and emergence of non-susceptible strains have limited the effectiveness of this drug. 1,4 Fortunately, the number of VRSA isolates has remained limited worldwide and availability of highly (chromatographically) purified vancomycin has shown a falling incidence of nephrotoxicity. Linezolid exhibits an excellent anti-staphylococcal activity, comparable to that of vancomycin, and can also be administered orally. 1,4 Resistance to this drug has been rarely reported. 1,4 Nonetheless, owing to the expense and potential toxicity, linezolid has been approved by the Food and Drug Administrator (FDA), United States of America, for the treatment of serious MRSA infections only. 1,4 In addition, daptomycin and tigecycline have been approved by the FDA for MRSA management. 1,4 Many glycopeptide derivatives including telavancin, dalbavancin and oritavancin, and two cephalosporins (ceftobiprole and ceftaroline) are also effective against MRSA, both in vitro and in animal models. 1 Telavancin has now been approved by the FDA for treatment of complicated skin and soft-tissue infections. 1 Ceftobiprole has been approved for clinical use in Canada and Switzerland. 1 However, they are broad-spectrum drugs, and require parenteral administration. 1,4 Orally-bioavailable alternatives, such as an oxazolidinone with an eight-fold higher activity than linezolid, are in early stages of development. 34 Iclaprim and quinupristin/dalfopristin have also been reported to be effective against Gram-positive pathogens including MRSA. 3

Patient education is a critical aspect of MRSA management. 30 Patients, their care-takers and household members should take appropriate precautions, such as good hygiene practices, and proper cleaning, coverage and management of draining wounds for limiting the spread of infection in their household and close contacts. 30

Asymptomatic carriers, both patients and health-care workers, constitute important MRSA reservoirs. 35 The use of hand hygiene, environmental cleaning, patient isolation as well as barrier precautions such as gloves, gowns and masks plays an important role in preventing MRSA transmission in hospital settings. 35 Routine screening of health-care workers and patients is also effective in preventing the MRSA spread and is cost-effective in the long run. 35 Inclusion of swabs from colonization sites other than the anterior nares has been shown to increase the sensitivity of MRSA screening from 80 to 92%. In addition, prophylactic approaches based on the use of vaccines, and/or passive immunization with antistaphylococcal antibodies directed against PVL/PSMs/α-toxin are also being studied. 1

Decolonization presents an effective strategy to prevent infection in MRSA carriers as well as its transmission to non-carrier population. 1,2,4,36 Many topical and systemic antimicrobial agents, and antiseptic bodywashes have been employed in decolonization regimens to prevent MRSA outbreaks in health-care settings and community. 30 Mupirocin is the best topical antimicrobial currently available, and is a very
effective MSSA and MRSA decolonizing agent. Completion of nasal mupirocin treatment (2%) can successfully decolonize 81.5 to 100% patients. However, poor compliance in some community settings, recolonization following regimen completion, and development of resistance to this drug may limit the widespread use of such interventions. In India, 2-5% and 1% of MRSA strains have been reported to exhibit high-level (plasmid-mediated) and low-level (chromosomal mutational) mupirocin resistance respectively. A plasmid encoding for mupirocin resistance has been detected in the genome of CA-MRSA USA300. Apart from mupirocin, chlorhexidine washing can also reduce the risk of MRSA infection and colonization.

**Conclusion**

S. aureus has a remarkable ability to develop antibiotic resistance, leading to four distinct resistance waves that have occurred in the past sixty years. The advent of PRSA, then MRSA and now vancomycin resistance has resulted in a steady decline in the efficacy of these valuable antibiotics. The MRSA first emerged as a nosocomial pathogen (HA-MRSA; in the 1960s), then further surfaced as a community-based infection (CA-MRSA; in the 1990s) and has subsequently increased the staphylococcal disease burden. It is a global public health problem and represents the most commonly identified antibiotic-resistant pathogen. The incidence of HA- and CA-MRSA infections as well as the prevalence of different MRSA clones varies considerably among countries. Some MRSA clonal lineages are more frequently isolated than others owing to their superior survival and transmissibility. The HA-MRSA is endemic in many hospitals worldwide. The CA-MRSA has a smaller fitness burden, higher transmissibility and virulence compared to HA-MRSA and is epidemic in many countries. In addition, the distinction between CA- and HA-MRSA is gradually fading, owing to the emergence of pvl negative and/or MDR CA-MRSA clones and its invasion into hospitals as well. The MRSA has markedly influenced the empirical therapy for staphylococcal infections. Limited therapeutic options are available for the management of these infections. Most β-lactam antibiotics are ineffective against both HA- and CA-MRSA. The HA-MRSA is usually MDR but CA-MRSA is often susceptible to non-β-lactams. Resistance to non-β-lactam drugs varies geographically and may change over time. The CA-MRSA-associated skin and soft-tissue infections are treated with oral antibiotics including doxycycline, minocycline, clindamycin, trimethoprim-sulfamethoxazole, rifampicin, and fusidic acid. Severe CA-MRSA infections and HA-MRSA demand intravenous vancomycin therapy. Transmission may be prevented by following universal infection-control strategies and decolonization therapy.

**References and bibliography**


