Methicillin/Oxacillin-resistant *Staphylococcus aureus* as a hospital and public health threat in Brazil

**ABSTRACT**

Methicillin-resistant *Staphylococcus aureus* is an established nosocomial pathogen (HA-MRSA, hospital acquired MRSA), but has recently begun to appear in the community (CA-MRSA, community acquired MRSA). The cause of resistance to methicillin and all other β-lactam antibiotics is the mecA gene, which is situated on a mobile genetic element, the Staphylococcal Cassette Chromosome mec (SCCmec). Seven major variants of SCCmec, type I to VII are distinguished. HA-MRSA disseminated worldwide and causes the majority of *S. aureus* nosocomial infections with a limited number of clones disseminated including the Brazilian Epidemic Clone (BEC, ST239-MRSA-III). CA-MRSA isolates are susceptible to non-β-lactam antibiotics, usually isolated from healthy individuals which do not possess any unknown risk factors for MRSA infection and are associated with a larger clonal diversity compared with HA-MRSA. However, during recent years distinction between HA-MRSA and CA-MRSA is beginning to fade. Actually, knowledge about MRSA disseminating clones is required to implement any strategies to control the transmission of MRSA either within hospitals or in community. For this reason, rapid identification of strains is an important issue. The rate of HA-MRSA can be reduced substantially through the implementation of interventions strategies, even in settings where MRSA is endemic as in most Brazilian hospitals. However, these policies could be quite complicated in the light of an increasing CA-MRSA prevalence in healthcare facilities, considering that distinction between HA-MRSA and CA-MRSA has started to disappear.

Keywords: methicillin-resistant *Staphylococcus aureus*, community acquired methicillin-resistant *Staphylococcus aureus*, nosocomial infections and community infections.

INTRODUCTION

*Staphylococcus aureus* has been recognized as an important pathogen associated with inpatients and community infections.1 As soon as methicillin was marketed in 1960, resistant isolates were reported after the screening of clinical isolates in England.2 By 1967 MRSA was reported from Switzerland, France, Denmark, Australia and India3 and mainly in the early 1980s multidrug-resistant MRSA was reported from several countries4 and now is currently endemic in various hospitals worldwide,5 mainly in developing countries as Brazil.6,7

Many studies have identified MRSA strains that appear to be well adapted to the hospital environment8 frequently isolated from bacteremia, wound infections and pneumonia.1 Risk factors for the acquisition of hospital infection caused by this MRSA comprehend: indwelling devices, prolonged hospitalization, and long-term antibiotic use. MRSA transmission occurs via person-to-person spread by healthcare staff hands and via environment-to-patient spread.1

In 1993, novel MRSA strains were reported from Indigenous Australian patients who had not been previously exposed to the health-care system.8 Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged worldwide during 80’s and has been described as an endemic pathogen in USA, Europe and Australia. These genuine community acquired MRSA strains, which were transmitted in the community and differed from conventional endemic nosocomially acquired MRSA strains in several ways,1 including: they were more susceptible to antibiotic classes other than β-lactam antibiotics,10 their geno-
types were not the same as isolates from hospitals, they mainly harbored different methicillin-resistance cassettes, and finally, community isolates were more likely to encode a putative virulence factor called Panton-Valentine leukocidin. In general, CA-MRSA is more virulent compared to HA-MRSA due to presence of various virulence factors.

Even since this recognition, community acquired MRSA has been isolated from children and adults with skin and soft tissue infections, septic arthritis, bacteremia, toxic shock syndrome, necrotizing fasciitis, and necrotizing pneumonia. It has been reported most often from indigenous populations, homeless people, jailed inmates, military recruits, children in day care centers and competitors athletes. Common to all these groups is a high intensity physical contact which might help with transmission.

Not unexpectedly, community-acquired MRSA has also found its way into hospitals where outbreaks have been reported but most of these infections were restricted to patients with frequent contact with health facilities, such as residents of long-term care facilities and intravenous-drug users. Several recent reports have described the transmission of this pathogen establishing a new nosocomial risk which needs to be considered by infection control professionals. The first reported cases in Brazil, were in the Hospital das Clínicas of University of São Paulo, involving bloodstream infections caused by non-multiresistant oxacillin-resistant Staphylococcus aureus, SCCmec IV. The emergence in Brazil of methicillin-resistant Staphylococcus aureus isolates carrying SCCmec IV, genetically related to the USA800 clone, was reported by Miranda et al. (2007) in hospitals in two cities, without considerations about the patients / medical records evidence of risk factors. Recently, the same group reported that some of these isolates (5/13, 32.8%) were characterized as CA-MRSA both by molecular characteristics and clinical origin, including outpatients who had not been hospitalized. Using gentamicin, chloramphenicol, rifampicin and trimethoprim-sulphamethoxazole as a phenotypic marker was reported by us, with only 13.6% of the MRSA infections were classified epidemiologically “as CA-MRSA infections” in 24 patients with medical record evidence of risk factors as invasive devices and hospitalization. CA-MRSA in the absence of classic risk factors for MRSA diseases has also been reported by Ribeiro et al. (2007) with the presence of international CA-MRSA clones in Rio de Janeiro and Porto Alegre encoding PVL genes. CA-MRSA SCCmec IV as cause of infection in hospitalized patients was also reported by Reinert et al. (2008) in three out 50 nosocomial strains obtained from a previous study in São Paulo.

Since the 90s, virulent community-associated MRSA (CA-MRSA) clones, spread worldwide, first in the community, but later also in healthcare facilities. At the moment, the restriction between CA-MRSA and HA-MRSA is beginning to fade.

Worldwide and Brazilian burden of HA-MRSA

Presently, MRSA is the most commonly identified antibiotic-resistant pathogen in many parts of the world, including Europe, the Americas, North Africa, the Middle East and East Asia. It is a common hospital pathogen and cause severe infections in which its multiple antibiotic resistance is a serious complication. MRSA rates have been increasing worldwide over the past decades, as data from continuing surveillance initiatives such as the National Nosocomial infection Surveillance System and European Antimicrobial Resistance Surveillance System. It was observed that MRSA prevalence was 23% in Australia, 67% in Japan, 40% in South Pacific, 32% in USA, and 26% in Europe. A limited number of MRSA clones are disseminating worldwide each of them with a specific genetic background and SCCmec type.

There is evidence that hospital-acquired MRSA infection increases morbidity, mortality risk and costs. In Brazil, data from the first five years of SENTRY Antimicrobial Surveillance Program® MRSA correspond to 56% of nosocomial and community infections evaluated and was the most common among prevalent pathogens.

According to data from Hospital de Clínicas of Federal University of Uberlândia MRSA correspond to 63.7% of blood infection, 100% of urinary tract infection and 46.7% of Ventilator-Associated Pneumonia (VAP) caused by Staphylococcus aureus. Moreira e Gontijo Filho (2008) re-searching the VAP’s etiology in the adult critical care unit of the same hospital reported 41.2% of S. aureus isolates with 41.2% of MRSA.

Resistance determinants and Staphylococcal Cassettes Chromosome mec (SCCmec)

The understanding of the evolution of MRSA has benefited from the development of molecular methods that provide characterization of both the strain phylogeny and the meticillin-resistance determinant. Consistent molecular epidemiological evidence supports the view that the evolution of MRSA and of S. aureus as a species is predominantly clonal, but as in others organisms horizontal transfer of DNA from other strains or species occurs and plays an important part in resistance acquisition in S. aureus and is brought about mainly by insertion of insertion sequences, transposons, prophages, and incompletely understood events. MRSA originates from the introduction of a large mobile genetic element called SCCmec into a methicillin-susceptible S. aureus strain.

The mecA gene which encodes an additional penicillin-binding protein (PPP2A) with reduced affinity of β-lactam antibiotics is located on a mobile genomic island, called Staphylococcal cassette chromosome mec (SCCmec). At the moment seven main types of SCCmec (type I to VII) are recognized. Types IV, V, VI and VII, cause only β-lactam antibiotic resistance while SCCmec
I, II and III cause resistance to multiple classes of antibiotic, due to additional drug resistance genes integrated into SCCmec, i.e. integrated plasmids and transposons. For its mobilizations SCCmec carries specific genes designated cassette chromosome recombinases (ccrA, ccrB or ccrC). The Brazilian/Hungarian clone correspond to SCCmec III, ST 239 and MLST profile 2-3-1-1-4-4-3.

Origins, reservoirs and distribution of SCCmec types
There are several lines of evidence about the origin of SCCmec but is know that methicillin resistance is highly prevalent in S. epidermidis isolates (over 70%) and less common in S. aureus suggesting that S. epidermidis is the reservoir for SCCmec.

Health-care associated and community-acquired MRSA strains have been proved genetically distinct with respect to the SCCmec type they contain, and most health-care associated MRSA strains carry one of three types of SCCmec (type I, II, or III), whereas most community-acquired MRSA strains carry mainly SCCmec type IV. Type V has also been identified in community-acquired MRSA isolates. The extreme heterogeneity of the genetic backgrounds in community-acquired MRSA strains and the small size of SCCmec types IV and V suggests that these SCCmec allotypes are more readily transmissible between staphylococci than the larger SCCmec types and, once introduced do no compromise the fitness of the pathogen.

MRSA nomenclature is currently based on the Multilocus Sequence Typing (ST) of fragments of seven housekeeping genes that refers the S. aureus lineage, resulting in an allelic profile designated ST, and the type of SCCmec element. The detection of divergent MRSA lineages by different molecular typing techniques, including Multilocus Sequence Typing (MLST) suggests, as previously mentioned, that MRSA have arisen by the introduction of SCCmec into distinct successful methicillin-susceptible S. aureus lineages.

It was recently reported that approximately 50% of MRSA isolates recovered from skin/soft tissue infections in the United States belonged to a CA-MRSA clone called USA300 (SCCmecIV, ST8, lukSF+). Ribeiro et al. (2007) reported a diversity of clones isolated from Porto Alegre and Rio de Janeiro including USA300, Ocean South Pacific Clone (OSPC) e USA400 corresponding to tree clonal complex: ST8, ST30 and ST1 respectively.

Furthermore, the larger clonal diversity of CA-MRSA compared to HA-MRSA suggests that more S. aureus lineages is able to become CA-MRSA. In spite of the majority of the CA-MRSA isolates harbor SCCmec type IV, V or VII, several studies have also observed CA-MRSA harboring SCCmec type I, II or III. However, the majority of the studies have concluded that PVL, together with SCCmec type IV or V and specific genetic background, is a genetic marker for CA-MRSA.

Until recently, it was believed that the dissemination of PVL-positive CA-MRSA clones was related to components, i.e. the ST1 and ST8 clone in USA and the ST 80 clone in Europe. Recent studies have shown that this observation is starting to change. Today, five major PVL-positive CA-MRSA clones is observed worldwide: ST1 clone is observed in Asia, Europe and the USA, ST30 clone in Australia, Europe and South America, and largest diversity of CA-MRSA clones in countries with numerous international exchanges, such as travel hubs.

Control of MRSA
Screening of patients
Colonized and infected patients represent the most important reservoir of MRSA in health-care facilities. Culture from body sites such as the anterior nostrils alone will identify 80% of patients colonized with MRSA. These patients, who do not have clinically evident infection but are carriers of MRSA, can serve as reservoirs from which the organism is transmitted to other patients. On the basis of the evidence available, several published guidelines have recommended screening of inpatients at high risk of carrying MRSA, as those admitted to intensive-care wards.

Isolation and barrier nursing
Patients colonized or infected with MRSA should whenever possible be housed with other patients who have MRSA, measure that is no realistic in Brazilian hospitals. Effectiveness of the use of gloves and gowns to care for patients with MRSA has been established in epidemiological studies, although there is no randomized trials supporting their use, so contact precautions are not effective in interrupting transmission of endemic MRSA.

Environmental cleaning
How important are contaminated environmental surfaces as a reservoir for MRSA? The US Centers for Disease Control and Prevention isolation guidelines recommend that hospitals have adequate procedures for routine care, cleaning, and disinfection of environmental surfaces frequently touched. Further studies are needed to find out if thorough decontamination of rooms occupied by patients with MRSA will affect MRSA transmission rates.

Hand hygiene
Transient contamination of health-care workers’ hands has been documented on many occasions and is widely believed to be the predominant method by which MRSA is transmitted to patients.

Decolonization therapy
Widespread use in a hospital or long-term use of mupirocin in patients should be avoided since these practices have been associated with emergence of mupirocin-resistant strains of MRSA.
However, comprehensive MRSA-control program that have included screening cultures to detect patients colonized with MRSA, use of contact precautions, appropriate hand hygiene, automatic alerts of readmission of colonized patients, with or without decolonization of colonized individual, have reported success in controlling or reducing transmission of MRSA nationally, regionally, and institutionally.52

CONCLUSIONS

Guidelines have suggested that alternatives to β-lactams antibiotics be used as empirical therapy for patients presenting with SSTIs in areas were the prevalence of CA-MRSA exceeds 10 to 15%.51 However, β-lactams antibiotics continue to be prescribed empirically to a great proportion of patients who have an infection with CA-MRSA.62 Although some studies have found that the use of an inactive antimicrobial regimen for CA-MRSA infection is not necessarily associated with adverse outcomes, more-recent data suggest that there is a difference in clinical cure rates based on adequacy of the antibiotic prescribed.63

The present success of the few pandemic hospital-acquired-MRSA clones has been accounted for by the acquisition of additional fitness traits by already widespread and successful colonizing strains, with the view that gaining β-lactam resistance yields a decisive advantage over competitors in hospitals.64 Because of the higher pathogenicity of community strains, community acquired MRSA in hospitals could change its predominantly opportunistic behavior and cause infections in patients who are no seriously ill or even in health-care workers.64 The recently published genome sequence of another very successful clone of community-acquired MRSA, USA300, lends further support to the theory that successive genomic alterations led to the evolution of fitter clones that combine antimicrobial resistance with transmissibility and virulence.65 In spite that is often thought that CA-MRSA and HA-MRSA belong to different lineages within a geographic area, and the proportion of CA-MRSA is an increasing trend there is also evidences that the distinction between these two organisms is beginning to fade. If the new community-acquired MRSA clones are, however, sufficiently fit to sustain endemic levels by transmission in the community, the MRSA situation in hospitals still remains out of control in many countries as Brazil and could potentially become explosive.

REFERENCES


