REVIEW ARTICLE

Antimicrobial resistance in *Staphylococcus aureus* in Mexico

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ABSTRACT

Since the beginning of their selection, methicillin-resistant *Staphylococcus aureus* strains (MRSA) have disseminated worldwide. Although the problem was restricted at first to hospitals (HA-MRSA, hospital-acquired methicillin-resistant *Staphylococcus aureus*), in the 1990s the first cases in patients with no history of hospitalization were reported. These new strains were referred to as CA-MRSA (community-acquired MRSA). As a result of the increasing resistance in hospitals (from 2% to 64% in 30 years), there is a current threat to public health in the community. The mechanisms that contributed to the selection of CA-MRSA are still controversial. In Mexico, information regarding this problem has been reduced to reports from tertiary-care level hospitals. Frequency of MRSA strains is high (50-85%). Therapeutic options are multiple, but a careful selection of the type of infection and patient risk factors must be acknowledged. Until now, the only useful preventive measure to contain bacterial resistance is appropriate antimicrobial use.

Key words: antimicrobial resistance, MRSA, appropriate antibiotic use

INTRODUCTION

The first strains of *Staphylococcus aureus* able to produce penicillinase were selected 2 years after beginning the massive use of penicillin to treat bacterial infections in the 1940s. In 1960, almost 100% of strains were already resistant to penicillin and this mechanism was described in detail for *S. aureus*. Penicillin precursor, 6-aminopenicillanic acid, was isolated in 1959 and allowed the development of semisynthetic penicillins. Methicillin and isoxazolyl-penicillin (oxacillin) were the first semisynthetic penicillins resistant to beta-lactamase hydrolysis used to treat staphylococcus infections in the early 1960s.[1-2] Shortly after, new and less toxic antibiotics became available such as nafcillin, cloxacillin and dicloxacillin; however, the first methicillin-resistant strains were identified 1 year later as a result of the production of low-affinity penicillin-fixation enzymes. The PBP 2' protein, also known as 2a protein, is responsible for resistance in *Staphylococcus* spp. This protein is coded by *mecA* gene, which is part of SCC*mec* (Staphylococcal cassette chromosome mec) located at *mec* region of bacterium chromosome. This region is a resistance island that contains the structural gene for PBP2a and genes *mec1* (repressor) and *mecR1* (mec1 inhibitor), which act as transcription regulating agents. Although the *mec* region is highly preserved, there is a great variability on phenotypic expression of resistance.[3] Methicillin resistance in *Staphylococcus* spp. is equivalent to resistance of all beta-lactam antibiotics including penicillins, cephalosporins and carbapenems. It has been associated with resistance to multiple antibacterial drugs without structural affinity such as tetracyclines, macrolides, quinolones and aminoglycosides. In order to resolve this problem, vancomycin was used in several countries to treat infections due to methicillin-resistant strains. As a consequence, *Enterococcus* spp. developed resistance to glycopeptides and, 25 years later, a *Staphylococcus* spp. resistant to these antibiotics was found.[4,5] The present review describes the evolution of antibiotic resistance in *S. aureus* worldwide, emphasizing information available in Mexico.

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A Problem of the 21st Century

Since their selection, methicillin-resistant *Staphylococcus aureus* (MRSA) strains disseminated worldwide and were associated with hospital environments (hospital-acquired MRSA, HA-MRSA). In the 1990s, the first cases of patients appeared without hospitalization antecedents. These new strains were known as community-acquired MRSA (CA-MRSA). Because of behavior observed at hospitals (an increasing resistance from 2% to 64% in 30 years), it is possible that these strains spread efficiently and become a serious public health problem in this century. The alarm was raised when a larger number of severe skin and soft tissue infections were found in children and young adults without risk factors.[6]

According to records from the year 2005, 18,650 persons died in U.S. hospitals as a result of severe infections caused by MRSA. It was estimated that 14% of the cases had no hospitalization antecedent or risk factor that explained the infection.[6] Mechanisms that selected CA-MRSA are still controversial.[7]

Studies on molecular epidemiology have demonstrated differences between HA-MRSA and CA-MRSA. The main difference is that CA-MRSA is resistant to beta-lactams but generally sensitive to other anti-staphylococcal drugs. Due to these studies and advances in molecular biology, strains have been identified in greater detail. Identification is carried out by determining types and variants of SCC*mec* according to recombinase genes (allotypes ccrAB) and their general genetic structure.[8-12] Types I-V of SCC*mec* are defined based on the combination of one, two or three pairs of *ccrAB* gene class of *mec* complex *A, B, C,* and *D*. It appears that type IV was selected for CA-MRSA (Figure 1).

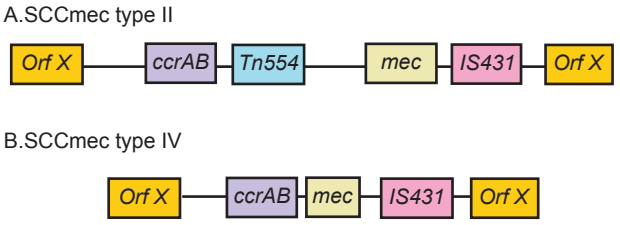

Figure 1. Typical SCC*mec* in a hospital strain (A) and a community strain (B). SCC*mec* type II codes for various antibiotic resistance, whereas type IV codes only for methicillin resistance. *Orf X* points to an open reading frame, *IS* points to sequence integration spots. Cassette chromosome recombinase (*ccr*) is found in a gene complex and it is responsible for SCC*mec* mobility. Transposon *Tn554* is found only on type II and codes for macrolide-lincosamide-streptogramin (MLS_B) and spectinomycin resistance. Gene *mec,* which codes for methicillin resistance, is found in full in SCC*mec* II but not in SCC*mec* IV. Insertion sequence *IS431* contains pUB110 plasmid that codes for tobramycin resistance.

Situation in Mexico

In Mexico there is no record in regard to the number of cases associated with severe infections and no record on outcome of cases of HA-MRSA or CA-MRSA. Reports of CA-MRSA in children are limited to case series or studies on current carriers. Velazquez et al. recorded the presence of MRSA carriers in 2,345 children in day-care facilities in Mexico.[13] They found an incidence of 10% *S. aureus* and 0.93% MRSA. Resistance to erythromycin, clindamycin, trimethoprim/sulfamethoxazole, gentamicin and ciprofloxacin were 72%, 32%, 22.7%, 18.1% and 4.5%, respectively. A total of 22 MRSA strains were characterized into six clones through pulsed-field gel electrophoresis (PFGE). One profile was similar with USA100 clone, which has documented resistance and was selected in a U.S. hospital. This manifests the dissemination capability of these microorganisms as a result of population migration.

In a similar study, Ammons et al. investigated MRSA presence and SCC*mec* elements in adults living on the Texas-Mexico border. From 375 nasal cultures, they isolated 57 cases and six MRSA strains. Analysis of SCC*mec* elements revealed type IV in 5/6 strains and this type was predominant also in non-*S. aureus* strains. They also found *spa* type, which matches USA300 and USA600 clones. The authors consider this may be associated with the ease of crossing the border into Mexico and buying antibiotics without prescription (which was possible at the time of the study). Because of this, there is selection and horizontal transference of resistance mechanisms among bacteria colonizing the nose and pharynx.[14]

Essentially, descriptions of MRSA clone mobilization in Mexico are obtained from tertiary-care hospitals both for adult and pediatric populations. A study including 1999-2003 data and carried out in a tertiary-care university hospital found a MRSA clone with type-2 *spa*, SCC*mec* type II and several virulence genes. This clone was predominant in the hospital during the years of the study with small variations in its genomic pattern when analyzed using PFGE.[15] Another pediatric hospital de-

tected a *S. aureus* clone during a similar period of time (7 years) and this clone was named "M" (because it originated in Mexico), having SCC*mec* type IV. This clone was eliminated due to control of antibiotic use, as well as its replacement, the New York/Japan multiresistant clone with SCC*mec* type II.[16]

A recent review revealed 32 articles in the literature containing information on MRSA clones found in Latin America until the year 2008. These articles highlight the existence of resistant clones in Brazil, Argentina, Chile, Colombia, Mexico and Paraguay since 1990, having diverse susceptibility profiles to antibiotics. It appears that there is a higher prevalence of the New York/Japan clone in Mexico than in other Latin America countries. However, most reports are limited to hospital cases and there is little information regarding the prevalence of this problem in the community.[17]

Resistance and Hospital Environment

Although antibiotic drugs are essential to medicine, both human and veterinary, they are regarded as responsible in selecting resistance in several microorganisms. Campaigns to improve the use of antibiotics started only 5 decades ago and this improvement is regarded as essential nowadays for public health systems. Resistance to antibiotics is unavoidable. After using a certain drug for a long period of time, the most well-adapted microorganisms survive because they develop resistance mechanisms either using mutation or by including genetic material from similar microorganisms. The time required to develop resistance varies for each bacteria; however, it is expected that a multidrug-resistant microorganism is selected after years of exposure to multiple drugs, which represents a threat to hospitals with high-risk patients. Better strategies are yet to be defined in order to prevent communication and treatment of resistant bacteria in pediatric hospitals. Therefore, many questions remain unanswered.[18]

At the end of 1990, the *Pediatric Prevention Network* evaluated the prevalence of colonizations by multiresistant microorganisms in children admitted at pediatric and neonatal intensive care units (PICU, NICU). MRSA incidence was low both in colonization (3%) and infection (2%),[19] which was similar to the frequency reported in Europe.[20] However, information from subsequent years shows alarming increasing percentages. The Centers for Disease Control and Prevention (CDC) reported a 300% increase of MRSA in NICUs between 1995 and 2004.[21] The National Healthcare Safety Network (NHSN)[22] reported that 5-10% of microorganisms associated with infections acquired from medical equipment in pediatric patients are multidrug resistant; however, detailed information is unavailable on infection outcome, costs, attributable hospital stay and use of antibiotics. Compared with NHSN data from 2006-2007, Rosenthal et al. and the International Nosocomial Infection Control Consortium (INICC) (2003-2008 report) found that resistance is greater in pathogens from ICUs that participated in their study (including PICUs and NICUs in Mexico).[23] MRSA frequency was 84.1% compared to 56.8% of infections associated with intravascular equipment.

Milstone et al. carried out a descriptive cross-sectional survey in several PICUs and found that up to 70% of facilities lack MRSA detection protocols at admission.[18] Units that carried out a detection protocol had a compliance rate of 50% and only 7% carried out detection prior to hospitalization. Of these institutions, only 30% use NHSN guidelines for culture-isolated microorganisms associated with nosocomial infections and 28% of units applied such definitions for samples from any anatomic site. These results reveal a diversity of approaches, definitions, interpretation and lack of knowledge of epidemiological surveillance studies, which are basic for any hospital.

In fact, *S. aureus* has shown an excellent adaptation to the environment and the diversity of strains resulting from interaction with both human and animal hosts. The amount of genetic material that can be acquired and exchanged is very large and includes virulence genes. These plasmid-specific genes code for resistance: *tetA, cat, str, smr, aadD, ble, ermC, blaZ, arsB, arsC, cadA, merAB, ermB, cadB, aacA-aphD*. These code for insertion elements *IS431, IS257, IS256, IS1181, IS1182* and transposons *Tn551, Tn552, TN554, Tn4001, Tn4002, Tn2491, Tn5405, Tn916*, as well as others that have yet to be described.

From a clinical viewpoint, there are multiple therapeutic options because the following antibiotic drugs were applied after vancomycin and teicoplanin to treat MRSA: linezolid, quinupristin/dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, telavancin, dalbavancin, oritavancin and razupenem (PZ-601, still in phase II studies). However, these drugs have a higher cost and do not offer advantages over glycopeptides against MRSA infections. Clinical trials have demonstrated that they are

equivalent but not superior and, in a few cases such as linezolid for pneumonia patients, they offer a significant advantage over vancomycin.

Because of the genomic characteristics of *S. aureus*, it is not unusual to find early reports on linezoid resistance. At the Hospital Infantil de Mexico Federico Gomez (HIMFG), we found one resistant SARM strain out of 45 with a minimum inhibitory concentration (MIC) equivalent to 8 µg/mL.[25] These strains were identified between the years 2003 and 2007 and we expect to find more resistant strains in the years to come. Linezolid does not require serum levels to be monitored, which is an advantage favoring this therapy. On the other hand, serum levels need to be monitored to optimize vancomycin dosages, especially in severely ill patients. Nevertheless, there is little evidence in favor of having certain levels in order to reach "optimal dosages."[26]

In Mexico there is insufficient information on antibiotic prescription practices, applied either in human or veterinary medicine and agriculture, to establish specific strategies and reduce resistance.[27] Several factors are involved such as quality of antimicrobial drugs, over-the-counter availability (up to August 2010) or the availability of "similar" medications that place Mexico among ideal regions to select more resistant microorganisms.

Before using a new antibiotic, we should try to combine other antimicrobial drugs to obtain a synergistic effect. A study carried out with 10 MRSA strains in pediatric patients revealed dicloxacillin + amikacin and cephalotin + amikacin showed higher synergetic activity in 90% and 100% of tested strains, respectively.[28] Synergy resulting from vancomycin + amikacin was effective only against one strain and 40% of strains showed an indifferent behavior. When combining vancomycin with a beta-lactam (cephalotin or imipenem), their effect was enhanced. Although concentrations required to reach this synergetic effect are obtained with usual dosages, a careful evaluation of combination, infection type and risk factors for each patient must be considered. These results explain the clinical behavior observed in patients treated with cephalotin + amikacin before carrying out laboratory tests.[29] In this study carried out at the Pediatric Hospital (Centro Medico Nacional Siglo XXI, Mexico), a therapeutic change was carried out at a NICU, replacing dicloxacillin with cephalotin + amikacin as an empirical schema in late neonatal sepsis. During a 2-year period of strict surveillance, a reduction in MIC50 was found for dicloxacillin at the end of the study with a statistically significant difference (p <0.05). Cephalotin resistance was increased during the first 6 months but decreased to 8.3% at the end of the study and amikacin resistance also decreased. No multidrug-resistant strains were selected and they remained endemic at NICU, which is frequent in these units. An unforeseen consequence in the hospital was the replacement of MRSA clones registered since 1997. MRSA frequency reduced from 20% to 4% in 2002 and 2003[16] and has continued to be <20% in recent years. Likewise, the number of isolations decreased significantly (100 vs. 35-40 in hemocultures per year). Results from these studies do not intend to replace recommended therapies by vancomycin, they only describe the hospital-acquired experience when applying a different treatment. Changes in empirical schemas are necessary when there are multidrug resistant microorganisms that require strict surveillance and advance planning with options, alternatives and prescription criteria before a possible selection of resistant strains. It is not possible to extrapolate interventions, rotation strategies or cycling of empiric and therapeutic schemas in all hospitals at the same time because results depend on hospital care level, available antibiotic drugs and local resistance data; therefore, active surveillance should include the evaluation of results at the end of previously determined periods.[30]

Therapeutic Options

There are multiple therapeutic options for MRSA patients. Recently, the Infectious Diseases Society of America (IDSA) published therapeutic guidelines for adults and children including different clinical conditions and therapeutic options for hospital-acquired and community-acquired strains.[31,32]

For CA-MRSA patients, antimicrobial treatment is recommended after abscess drainage in the following cases:

- Severe or disseminated disease (e.g., with multiple infection sites) or rapid infection and associated cellulitis progression
- Associated comorbidity or immunosuppression (diabetes mellitus, HIV/AIDS, neoplasms)
- Extreme ages
- Signs and symptoms of systemic infection
- End of life
- Abscesses in difficult-to-drain locations

- Associated septic phlebitis
- Lack of response to initial drainage

Therapeutic options for skin and soft-tissue infections do not differ from those usually applied to ambulatory patients. There are no studies that support the use of rifampicin combined with usually recommended drugs and it should not be used as monotherapy because of emerging resistant strains (Table 1). If oral treatment does not provide satisfactory results and infection progresses, the patient should be admitted. Because of the increased mortality risk in patients treated with tigecycline compared with other drugs, this medication was not included in the therapeutic guidelines. Ceftarolin, an advanced-generation cephalosporin, will be available in the near future. Treatment time varies according to patient response and, in general, lasts between 7 and 14 days.

Nonfocal bacteremia in adults can be managed with vancomycin or daptomycin for at least 2 weeks (Table 2). When a patient presents endocarditis or complicated bacteremia, treatment may last between 4 and 6 weeks.

Bacteremia patients should be tested with control hemocultures 2-4 days after treatment initiation to verify microbiological effectiveness. Monitoring of vancomycin serum levels is recommended in adults and dosages should be adjusted by 15-20 μg/mL in severe MRSA infections. Variations should be considered for patients with obesity, renal alterations or alterations in distribution volume. Usefulness of these studies has not been determined in the pediatric population; however, they should be considered as an auxilliary tool to manage patients with severe infections or persistent bacteremia. When using a drug other than vancomycin, there should be a susceptibility report. If a microorganism is sensitive to beta-lactams, this will be the ideal therapy because of its higher antibiotic effect unless a patient is allergic.

In conclusion, MRSA infections have moved beyond the hospital barrier and it is possible to find these infections in the community. Although the problem does not bear a significant magnitude in Mexico, we expect an efficient dissemination and transfer of resistance mechanisms towards sensitive strains because of the number of resistant strains reported by hospitals that manage at-risk patients. Until now, one of the most effective preventive measures to reduce antibiotic resistance is the appropriate and rational use of antibiotics in order to prolong their useful life as much as possible.

Table 1. Therapeutic options for skin and soft tissue MRSA infections

Skin and soft tissue infections	*Treatment*	*Evidence/Recommendation**	*Comments*
Abscesses, furuncles	Incision and drainage	A II	Consider comorbidities and infection extension
Cellulitis with purulent exudate (with abscesses)	Clindamycin	A II	A higher frequency of *Clostridium difficile* is expected
	TMP-SMX	A II	Not recommended in pregnant women during last trimester or in babies <2 months old
	Doxycycline	A II	Do not administer to children <8 years old or during pregnancy
	Minocycline	A II	
	Linezolid	A II	Higher cost than other options
Complicated infections	Vancomycin	A I/A II	
	Linezolid	A I/A II	For children >12 years old; Pregnancy type C
	Daptomycin	A I/NA	Pediatric studies in progress; Pregnancy type B
	Telavancin	A I/NA	Not approved for pediatric use Pregnancy type C
	Clindamycin	A III/A II	Pregnancy type B

*Classified according to recommendation strength and evidence in adult/pediatric patients.
NA, not available. TMP-SMX, trimethoprim/sulfamethoxazole.

Table 2. Therapeutic options for some MRSA systemic infections

Systemic infections	*Treatment*	*Evidence/Recommendation**	*Comments*
Bacteremia Endocarditis (native valve)	Vancomycin	A II	Do not routinely add gentamicin (A II) or rifampicin (AI)
	Daptomycin	A I/C III	Some experts recommend higher dosages for adults Pregnancy type B
Endocarditis (prosthetic valve)	Vancomycin, gentamicin and rifampicin	B III	
Pneumonia	Vancomycin	A II	
	Linezolid	A II	Children >12 years old Pregnancy type C
	Clindamycin	B III/A II	Pregnancy type B
Osteomyelitis	Vancomycin	B II/A II	Drainage and debridement are essential (A II). Some experts recommend adding rifampicin (B III)
	Daptomycin	B II/C III	
	Linezolid	B II/C III	Children >12 years old
	Clindamycin	B III/A II	
	TMP-SMX and rifampicin	B II/NA	
Septic arthritis	Vancomycin	B II/A II	Always drain purulent material (A II)
	Daptomycin	B II/C III	
	Linezolid	B II / C III	
	Clindamycin	B III / A II	
	TMP-SMX	B III / NA	
Meningitis	Vancomycin	B II	Some experts recommend adding rifampicin (B III)
	Linezolid	B II	Children >12 years old
	TMP-SMX	C III/NA	
Brain abscess, subdural empyema	Vancomycin	B II	Some experts recommend adding rifampicin (B III)
	Linezolid	B II	
	TMP-SMX	C III/NA	

*Classified according to recommendation strength and evidence in adult/pediatric patients.
NA, not available; TMP-SMX, trimethoprim/sulfamethoxazole.

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