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## CA-MRSA: Epidemiology of a Pathogen of a Great Concern

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### 1. Introduction

The emergence of community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) strains in individuals without traditional risk factors, has caused a drastic change in MRSA epidemiology since community acquired infections are etiologically caused by MSSA (methicillin sensitive *S. aureus*). Initially the most affected social groups were soldiers, men who have sex with men, prisoners, illicit injection drug users, and athletes; people with compromised skin and mucosa, poor hygiene habits and postpartum mastitis; Native Americans of the United States, and children due to their close contact with contaminated nasal secretions.

This change in epidemiology lead to molecular studies aimed at determining pathogenicity, virulence, resistance to different antimicrobial classes and the behavior of these strains against selective pressure of the human immunological system. Associating risk factors with the molecular studies gave rise to Molecular Epidemiology.

Humans are the main source of *Staphylococcus* spp., which can be found in the skin, throat, intestine and nose without causing damage to the host. In hospitals, the asymptomatic host can disseminate *S. aureus* to immunocompromised patients. Since they are ubiquitous, these bacteria can cause several types of infections such as: necrotizing pneumonia, skin and soft tissue infections, bacteremia, as well as food poisoning through enterotoxin production.

Individuals affected by CA-MRSA strains can develop from mild to metastatic and lethal infections, which are directly related to the synthesis of certain toxins, antimicrobial resistance and individual health conditions. One of the most discussed virulence factors is PVL (Panton-Valentine Leukocidine). Since its first association with skin and soft tissue infections, PVL is now believed to contribute to the elevated virulence potential attributed to CA-MRSA.

Methicillin resistance is conferred by *mecA* gene inserted in a mobile genomic island, the Staphylococcal cassette chromosomal (SCC<sub>mec</sub>). Some different SCC<sub>mec</sub> regions are responsible for mobility and regulation, and others for resistance to several antimicrobial classes. According to the presence, lack or genomic variations in these regions, the cassettes

can be classified in a range from type I to XI largely used to discriminate hospital and community types.

Community strains are usually more sensitive to other antimicrobial classes compared to multiresistant health care associated strains. In fact, CA-MRSA can be resistant to other antimicrobials besides beta-lactams, thus decreasing the options of drug choices. Another subject of concern is resistance to the drug of choice for treating MRSA, vancomycin. There are few antimicrobials to control the infections caused by MRSA and vancomycin is one of them. Reports of resistance and low level of sensitivity to this drug in health care environments have been reported worldwide.

All of the issues mentioned above, underscore the importance of further research on the behavior of CA-MRSA at the epidemiological and molecular levels enabling establishment and application of preventive measures and treatment in view of infections. The present chapter will outline the main features of CA-MRSA and epidemiological principles involved in the outcome briefly described above.

## 2. Resistance evolution background

*Staphylococcus* spp. are gram-positive cocci, catalase positive, belonging to the family Staphylococcaceae and the genus *Staphylococcus*, which currently comprises 45 species (Euzéby, 2011), from which 17 species can be isolated from samples from humans. *Staphylococcus aureus* is the most important species and can be found in both healthy and immunocompromised individuals (Santos et al., 2007).

The *Staphylococcus* genus is classified according to the synthesis of the enzyme coagulase, and those that synthesize are classified as coagulase-positive, represented by the species *Staphylococcus aureus*, *S. intermedius*, *S. hyicus*, *S. schleiferi* subspecies *coagulans*, *S. delphine* and *S. lutrae*, and in the absence of the synthesis, are represented by other coagulase-negative species (Baba et al., 2002). Both groups can cause infections in humans and, among them, the main species are: *S. aureus*, *S. epidermidis*, *S. saprophyticus*, *S. haemolyticus*, *S. hominis*, *S. warneri*, *S. capitis*, *S. saccharolyticus*, *S. lugdunensis*, *S. cohnii*, *S. xylosus*, *S. simulans*, *S. auricularis*, *S. caprae* and *S. schleiferi* (Layer et al., 2006).

Humans are the main reservoir of *Staphylococcus aureus*, which can colonize the skin, throat, intestine and nasal passages without causing damage to the host. Asymptomatic carriers in hospitals can spread *S. aureus* increasing risk to immunocompromised patients (Santos et al., 2007). This ubiquity favors the installation of various types of infections such as necrotizing pneumonia, skin and soft tissue infections, food poisoning bacteremia through the synthesis of enterotoxin (Santos et al., 2007; Cunha et al., 2006; Jarraud et al., 2002; Gandhinagar & Silva, 2004).

In 1940, staphylococcal infections were treated with penicillin; however, only two years after its introduction, nosocomial penicillinase producing strains grew resistant to penicillin by the inactivation of the penicillin molecules (Mimica & Mendes, 2007). Shortly thereafter, the same occurred with the strains of community origin necessitating the use of alternative antibiotics to treat infections caused by *S. aureus* (Ricardo, 2004).

In the late 1950s, in Europe, resistant nosocomial and community *Staphylococcus* spp. had penicillin resistance rates of 90% and 70%, respectively (Ricardo, 2004). This finding led to a

search for alternatives, and in 1959, adding the acid 6-aminopenicilanic in the penicillin molecule allowed for protecting the precursor of penicillin beta-lactam ring. This semi-synthetic penicillin (Named methicillin (and the analog oxacillin, used in Brazil) proved to be resistant to the action of beta-lactamase. However, both were effective for a short period of time, and in 1961, strains resistant to semisynthetic penicillins emerged. These emerging new strains were named MRSA (Methicillin-Resistant *Staphylococcus aureus*), so far unique to hospital settings (Ricardo, 2004; Salgado et al., 2003).

In the 1980s the first reports emerged of infections caused by *S. aureus* in patients without risk factors for acquisition of nosocomial MRSA (HA-MRSA), resulting in the designation of CA-MRSA (Community-Acquired Methicillin-Resistant *S. aureus*) in the 1990s when reports of CA-MRSA increased (Ricardo, 2004). The community-acquired infections are usually distinct from hospitals in terms of susceptibility and the carriage of the gene that codifies for the synthesis of Panton-Valentine Leukocidin (PVL) responsible for tissue invasion preceding the skin infections (Klevens et al., 2007).

According to criteria, it is considered that individuals affected by CA-MRSA should not report previous MRSA infections; the patient must have a positive culture for MRSA within 48 hours after hospital admission, and must not be hospitalized in the last 12 months, or admitted to nursing homes or homecare, and did not report undergoing dialysis, surgery, catheters or any prior or invasive treatment at the time of MRSA isolation (Salgado et al. 2003).

The transmission of the bacteria occurs through direct contact of susceptible individuals with asymptomatic carriers. There are frequent reports of the spread of CA-MRSA among men who have sex with men, soldiers, athletes, intravenous illicit drug users, prisoners, people with compromised skin and mucous membranes, poor hygiene, postpartum mastitis (Reddy et al., 2007), Native Americans from the U.S. (Klevens et al., 2007; Stemper et al., 2006) and among children due to the contact with contaminated nasal discharge (Klevens et al., 2007).

The transmission of MRSA among family members was reported in a study with 10 families. Strains with PFGE ST8 (USA 300), ST59 (USA 1000), and ST80 PVL-positive were found in this investigation (Huijsdens et al., 2006). Lung infections caused by these strains can be serious because the symptoms are similar to pneumonia in children; therefore, it is important to consider infection by MRSA especially if there were previous reported. (Huijsdens et al., 2006).

Among pathogens that can cause pulmonary infections, CA-MRSA is associated with pneumonia and is frequently associated with pulmonary viral coinfection. Studies indicate that CA-MRSA agents are commonly found in pneumonia during the influenza season, and about 85% of *S. aureus* strains isolated contained the PVL gene. In three cases of severe necrotizing pneumonia, strategies were carried out to prevent the synthesis of Leukocidin, including the administration of antibiotics such as rifampicin, linezolid and clindamycin, and/or applying intravenous immunoglobulin to block the lytic effect of PVL under polymorphonuclear cells (Rouzic et al., 2010). During the influenza season of 2006 and 2007, there were 51 reported cases of pneumonia in health centers caused by *S. aureus*, and 79% were MRSA. Most cases of pneumonia due to MRSA occurred during or after viral infection (Kallen et al., 2008).

The treatment of MRSA infections is variable. Within a hospital environment, there are several options such as linezolid, daptomycin, quinupristin/dalfopristin, but vancomycin is one of the most commonly used to treat several types of infections, but the emergence of strains resistant to this antimicrobial agent limits its use. Historically the emergence of vancomycin resistance occurred primarily in isolates of *Enterococcus* spp. in 1986 and reported only in 1988 in a European hospital. In 1989, in the United States, Vancomycin-Resistant Enterococci (VRE) were detected in clinical isolates and in 1993 accounted for 7.9% of the enterococci samples in nosocomial environments reported by the CDC. The most important reservoir is the gastrointestinal tract and transmission occurs mainly through contact with healthcare workers, and indirectly by contaminated hands in contact with the hospital objects where at least one of the patients had diarrhea (Mayall, 2002).

Vancomycin resistance in VRE is due to the presence of *van* genes (A to G) that encode for the synthesis of peptidoglycan by an alternative pathway that produces precursors ending in D-Ala-D-Lac or D-Ala-D-Ser instead of D-Ala-D-Ala. In *S. aureus*, however the main mechanism involved in vancomycin resistance relies on a thickened cell wall, production of abundant extracellular material that remains not well characterized and it ends up compromising the ability of division. These characteristics result in the synthesis of an altered peptidoglycan with an increased number of terminal D-Ala-Ala-D capable of binding free vancomycin in the outer cell wall, thus leading to a lower availability of the antimicrobial target molecule in the intracellular region. Strains of *S. aureus* with intermediate resistance to vancomycin (VISA) may contain 2 to 4 times more layers of D-Ala-D-Ala than susceptible strains, being capable of binding to three to six times more vancomycin molecules. Some chromosomal changes are necessary to maintain this resistance, and in addition require a larger amount of precursors than normal strains, thus compromising their fitness in an environment free of this antimicrobial. This may explain the reason for the loss of the vancomycin resistance of VISA strains when they are in environments without antibiotics, giving rise to heteroresistant strains called hetero-VISA (Van Bambeke et al., 2004).

### 3. MRSA colonization and decolonization

Studies on colonization intend to elucidate the mechanism by which certain individuals are persistently or intermittently colonized while others are non-carriers. MRSA colonization is an important predisposing factor, since colonized individuals are at increased risk of acquiring infections (van Belkum et al., 2009). Colonization is well studied in inpatients due to the risk of dissemination and the fact that it can facilitate severe infections.

Nasal colonization is the main form, and colonization can occur in other extra-nasal sites as in the skin, pharynx and perineum, but some sites are considered unusual such as the vagina, axilla and gastrointestinal tract. Studies may help to define carriers as in most cross-sectional studies only a culture classifies individuals as carriers or not, while longitudinal studies usually classify three categories of carriers: intermittent, persistent or non-carriers. Often cultures are harvested in three different time periods to define the carriers (Werthein et al., 2005). A study concluded that a "culture rule" which combines qualitative and quantitative results of two nasal cultures with an interval of one week could accurately classify nasal carriage (Nouwen et al., 2004).

Persistent carriers are usually colonized by a single strain of *S. aureus* over a long period of time, whereas intermittent carriers may carry different strains over time (Wertheim et al., 2005). MRSA colonization in individuals in the community remains a low burden as demonstrated in a study of high school boys where no individuals were found colonized with MRSA. The fact that there were no carriers among this population may be a reflection of improvement in hygiene practices among these individuals due to previous reports of outbreaks in team sports (Lear et al., 2011). Although they did not find MRSA in the population, other studies have found colonization rates in individuals in the community ranging from 0.8 to 3% (Keuhnert et al., 2006; Salgado et al., 2003; Ellis et al., 2004).

MRSA colonization in a hospital environment is a matter of utmost importance since it is characterized as a predisposing factor to infection. Nasal decolonization is usually performed with the application of mupirocin and is useful for reducing symptoms and its spread in hospital environments. However, the practice of decolonization with antimicrobials remains controversial because of the risk of acquiring drug resistance, which limits its use. Despite this risk, it is advised to perform decolonization in healthcare settings because of the risk of developing infections especially in individuals who are under invasive treatments and are immunocompromised (Coates et al., 2009).

But how should we manage individuals living in the community who are characterized as persistent carriers of CA-MRSA, but show no clinical manifestations and are healthy? This is a controversial subject because a previous study showed that individuals might be co-colonized with MSSA and MRSA, where the strains of MSSA have better fitness than MRSA, most likely due to the additional mechanism of resistance, which requires a cost in the feasibility and competitiveness of these strains. Thus, when decolonization is performed with mupirocin, both are eliminated and there will be competition, thus increasing the chances of colonization by resistant strains if both were competing for the same ecological niche (Dall'Antonia et al., 2005). Studies are needed to evaluate the cost-effectiveness of nasal colonization among residents in the community as a predisposition to infections, but there are chances of acquisition of resistant strains.

The nasal vestibule is composed of highly keratinized cells including apocrine and sebaceous glands and hair follicles. These factors are poorly studied compared to the mucosa and its linkage to mucins. Some of the pathogen virulence factors contribute to successful colonization; for example, the clumping factor B is highly associated with nasal colonization (Wertheim et al., 2007). Studies have reported the binding of *S. aureus* surface protein G (SasG) to a ligand in nasal epithelial cells. Other factors such as: Teichoic acid and cell wall components recognizing microbial surface adhesive matrix molecules (MSCRAMMS) responsible for the adherence protein in fibronectin, fibrinogen and collagen, may play an important role in colonization (Wertheim et al., 2005).

#### 4. Case reports

Case reports of CA-MRSA emerged worldwide revealing the severity, spread, which has helped to chart the epidemiologic distribution in the various communities and provide a better understanding of the behavior of virulence and resistance profile of these strains involved. Such isolates are associated with diseases of skin and soft tissue (Ribeiro et al., 2005). The infections develop from the skin surface where they penetrate to deeper layers,

disrupting natural barriers (Santos et al., 2007). The characteristics of the infection have to be similar to those caused by MSSA (methicillin-sensitive *S. aureus*) (Baba et al., 2002).

Outbreaks of infections caused by CA-MRSA are increasing worldwide among all age groups. Several countries reported their presence as an emerging pathogen, including the United States, Australia, New Zealand, Samoa, several EU countries (Ribeiro et al., 2005) and South America (Brazil, Uruguay and Colombia) (Alvarez et al., 2006). In Brazil there are several case reports confirming the presence of this pathogen in the community involving cases of furunculosis (Razera et al., 2009), metastatic infections with major complications (Strong et al., 2008) and pneumonia (d'Azevedo et al. 2009; Gelatti et al., 2009).

There is transmission of CA-MRSA between humans and animals, and these strains may carry genes codifying for Panton-Valentine Leukocidin (PVL) (Rutland et al., 2009; Van Duijkeren et al., 2005). A diabetic patient first diagnosed with cellulitis in the bicep region in December 2007 was positive for *S. aureus* in February 2008 from ankle biopsies and of nasal swab cultures; both isolates had the same profile of resistance to trimethoprim/sulfamethoxazole, clindamycin, erythromycin, tetracycline and ciprofloxacin, and were, therefore, treated both times with vancomycin. In February 2008, his eight-year-old female Labrador dog had widespread cellulitis in the neck, which did not respond to treatment with cephalexin. Tissue, blood, and secretion cultures were carried out identifying the same MRSA resistance profile as the dog's owner. Typing performed by pulsed-field isolates of the man and animal was inconsistent with the USA epidemic clones. A *spa* typing (staphylococcal protein A) was performed and identified as *spa3*, the samples were negative for the presence of PVL. Due to the resistance profile of isolates of the patient and his close relationship with the hospital, it is likely that the source of these isolates was the hospital. This study demonstrated that humans could be a source of multiresistant pathogenic microorganisms for their animals (Rutland et al., 2009).

A case study revealed that a woman with successive complications with MRSA transmitted the strain to her relatives as well as her dog. Samples collected from the nose and throat of other asymptomatic relatives were positive for MRSA. Everyone was treated with rifampicin and ciprofloxacin. After six months of treatment, no new samples were recovered in the tests for detection of CA-MRSA among the family members and the dog (Van Duijkeren et al., 2005).

CA-MRSA pneumonia can be hotbeds for metastatic infections leading to vital organ failure. In Sao Paulo, a previously healthy of 17-year-old patient was admitted to the hospital with upper respiratory infection that progressed with worsening of bronchopneumonia, septic shock and respiratory failure in just three days. The course of the infection followed with pulmonary cavitations, empyema and bronchopleural fistula requiring pleural drainage and tracheostomy. On the 16th day of hospitalization, the patient required total colectomy with ileostomy for ischemic colitis. In less than 48 hours, the patient had two blood cultures positive for Gram-positive cocci. Laboratory tests revealed MRSA with resistance to erythromycin and ceftiofur, with MIC for oxacillin of 3µg/ml and vancomycin sensitive (2µg/mL) and teicoplanin (2mg/mL). The strain was sensitive to trimethoprim/sulfamethoxazole and clindamycin. PCR analysis confirmed the presence of the *mecA* gene, SCC<sub>mec</sub> type IVa in the presence of genes for γ hemolysin, enterotoxin A (*sea*) and was negative for PVL. The treatment was maintained with

teicoplanin for 36 days, and from day 7 with meropenem for 14 days, showing progressive improvement and was discharged after 72 days from the hospital. No family member was colonized by CA-MRSA (d'Azevedo et al., 2009).

The presence of CA-MRSA infections involved in high morbidity has been reported. After infection of traumatic injury, a 27-year-old patient, healthy and without history of hospitalization in the previous 12 months, was admitted to the University Hospital Clementino Fraga Filho (Rio de Janeiro, RJ - Brazil) and treated with ceftriaxone and vancomycin. The examination by transthoracic echocardiography revealed a commitment of the anterior mitral valve and multiple blood cultures positive for MRSA, and molecular analysis detected the PVL toxin and the presence of cassette type IV. The vancomycin MIC performed by E-test was 2 µg/mL. Removal of the spleen due to an abscess was carried out, and the patient had a syncope and cerebral mycotic aneurysm. The patient was discharged after 3 months of the treatment (Strong et al., 2008).

Pneumonia and sepsis caused by a localized source of infection caused by CA-MRSA occurred in one patient in Porto Alegre, Brazil, treated at the Pediatric Emergency Room diagnosed with cellulitis and pneumonia. The X-ray of the lesion revealed bone involvement, liver and aneurysm of the pulmonary vessel. Blood culture revealed the presence of *S. aureus* resistant only to oxacillin and ceftiofuran. Testing by PCR revealed the presence of *mecA*, the PVL and the cassette type IVc. The clonal profile analyzed by PFGE found that the strain was similar to clone OSPC. The patient remained hospitalized for 50 days and was discharged after treatment with clindamycin and gentamicin (Gelatti et al., 2009).

Reinert et al. (2008), analyzed a culture collection grown between 1995 and 1999 and characterized them by PFGE (electrophoresis in pulsed-field gel). The results showed that the predominant profile (80%) corresponded to the Brazilian Epidemic Clone (BEC). Three of the 50 selected samples, harbored the cassette type IVc, and MLST (Multi Locus Sequence Typing) differed from each other: ST3, ST5 and ST88. These data showed that the presence of CA-MRSA in Brazil is longstanding and well established and must have passed unnoticed in clinical laboratories. It is necessary to detect and monitor these strains in the community and in hospitals for a better understanding of its epidemiology, as well as to inform public health strategies to control its spread (Reinert et al., 2008).

Risk factors for acquisition of CA-MRSA should be evaluated due to widespread character. In areas of close proximity among individuals, there is a greater risk of infection by *S. aureus*. Studies with people who maintain close contacts show that poor hygiene is an important factor in the acquisition of *Staphylococcus aureus*. In addition, younger individuals and the obese are more prone to colonization by MRSA. The objects of common use (soap and towels) and the environment are related to containing outbreaks of infections with this pathogen (Turabelidze et al., 2006).

Antimicrobial agents have different levels of concentration in certain sites of infection and, therefore, can reach subinhibitory levels during the treatment. Studies indicate that these levels may contribute to an increased expression of fibronectin binding proteins in samples having mutant genes for DNA gyrase and topoisomerase IV (*grlA* and *gyrA*, respectively) in MRSA strains. Bisognano et al. (1997) noted that the mutation sites that confer resistance to fluoroquinolones in subinhibitory concentrations of ciprofloxacin somehow increased the



FNB expression of genes that encode the fibronectin binding protein, but the mechanisms have not yet been defined. This may explain why patients who had prior use of ciprofloxacin have a higher likelihood of MRSA colonization.

The colonization by CA-MRSA in adults and children differs in the profiles of resistance to beta-lactam antibiotics, in which it is more typical that multi-sensitive strains colonize and affect children. This is mainly due to different environments they attend and hygienic practices follow. In addition, the antibiotics used in children may differ from those administered to adults, thus providing a different selective pressure in the community. Among adults CA-MRSA strains are more frequently resistant to gentamicin, tetracycline, ciprofloxacin, clindamycin and erythromycin than those observed in isolates from children (David et al., 2006).

One study evaluated *S. aureus* strains isolated from blood cultures as the type of SCCmec, the presence of PVL and analyzed the clonal profile by PFGE. In this study, they mainly included cases of HA-MRSA defined by the following isolation criterion for MRSA: must be isolated for 48 hours after hospital admission, previous isolation of MRSA colonized or infected patient during hospitalization or surgical procedures in the 12 months preceding the isolation, patients who underwent installation of a catheter or invasive devices. Of all the samples analyzed, 65% had the cassette type IV and that PVL was present in 92% of these samples. The clonal profile of 92% of samples with SCCmec type IV was USA300-ST8 (Gonzalez et al., 2006). The isolation of *S. aureus* resistant to methicillin with the cassette type IV suggests that these strains, particularly the USA300, presents an adaptation that expands beyond the community environment which may cause a change in the epidemiology of CA-MRSA.

## 5. Genetic characteristics of CA-MRSA

As a result of these observations genetic studies began focusing on molecular mechanisms responsible for the resistance to antibiotics and identification of MRSA strains. These strains had acquired and integrated into their genome harboring resistance genes, called Staphylococcal cassette chromosome *mec* (SCCmec). SCCmec present the gene responsible for methicillin and other beta-lactamic antibiotic resistance (*mecA*), and can carry genes that determine resistance to other classes of antibiotics. Strains related to community-acquired infections contain the smaller and lighter mobile element, the types and subtypes of SCCmec IV or V (21 to 25 kb) (Zhang et al., 2005).

Strains of HA-MRSA carry heavier mobile elements (SCCmec I to III) because they have genes that encode for resistance to several antimicrobial classes (Okuma et al., 2002). The mobile element SCCmec is characterized by the presence of essential genetic elements: the *mec* complex (classes A to E), the *ccr* complex (Hanssen & Sollid, 2007), junkyard regions (J) (Zhang et al., 2009) and end 3' is connected to the open reading frame (ORF), *orfX*. The SCCmec is integrated into the chromosome of *Staphylococcus* called attBscC a specific site located downstream of *orfX* (Zhang et al., 2008). There are several types of SCCmec (I to XI) (IWG-SCCmec, 2011) in addition to subtypes IIA to E and the IVg to IVa (Hanssen & Sollid, 2007). The *ccr* complex has five different allotypes for the *ccrA* and the *ccrB*: *ccrA1* to *ccrA5*, the *ccrB1* to *ccrB4* and *ccrB6* and *ccrC1* (IWG-SCCmec, 2011). The allotypes of the SCCmec complexes are characterized by the presence of certain *ccr* genes (Ito et al., 2004). The *ccrA*

and *ccrB* genes encode for recombinases of the family "invertase/resolvases." These enzymes mediate the integration within and outside of the SCC*mec* thus giving mobility to the chromosome cassette (Zhang et al., 2005).

The J regions encode several pseudogenes apparently with functions related to the bacterial metabolism (Zhang et al., 2005), and also contain genes for resistance mediated by plasmids or transposons to non beta-lactam antibiotics and heavy metals (Zhang et al., 2009). They are divided into three segments: J1, which is the region between the *ccr* complex the right chromosomal junction and the *ccr* gene complex; J2, between the *ccr* and *mec* regions, and J3 which is located between *orfX* and *mec*. Variations in the J regions within the same *mec-ccr* gene complex are used for defining SCC*mec* subtypes.

The SCC*mec* can be found in several species of *Staphylococcus* spp., such as *S. aureus*, *S. epidermidis*, *S. haemolyticus*, *S. hominis* and *S. warneri* (Hanssen & Sollid, 2007). The origin of SCC*mec* is unknown, and there have been no reports that any other genus than *Staphylococcus* carries the Staphylococcal cassette chromosome. The presence of SCC*mec* type IV in *S. epidermidis* in healthy people suggests that this can be responsible for the conversion of CA-MSSA for CA-MRSA (Hanssen et al., 2004) where the transmission of the mobile element occurs mainly by transduction mediated by bacteriophages (Ito et al., 1999).

The *mecA* gene codifies a penicillin binding protein PBP 2 'or 2A (Menegoto & Picoli, 2007) present on the outer surface of the cytoplasmic membrane (Ricardo, 2004). In susceptible strains, conventional PBPs have a high affinity with the beta-lactam antibiotics which prevents the proper formation of cell walls. However, the second PBP has low affinity to this class of antimicrobials, which explains resistance to antimicrobials of the group of methicillin (Menegoto & Picoli, 2007; Ito et al., 2001).

The *mecA* gene is regulated by two genes *mecI* and *mecR1* that have similar functions of the *blaR1* and *blaI* mechanism that regulates the production of beta-lactamase (Chambers, 1997). The *mecA* gene is regulated by a repressor *mecI*, a signal transducer and trans-membrane sensitive to the beta-lactam *mecRI*; both are divergently transcribed. In the absence of beta-lactam antimicrobial, *mecI* represses the expression of *mecA* and *mecRI-mecI*. However in the presence of beta-lactam antibiotics, the *mecI* is cleaved autocatalytically, and a metalloprotease domain, located in the cytoplasmic portion *mecRI*, becomes active. What allows the *mecA* gene transcription and subsequent synthesis of PBP2a is the cleavage of the *mecI* by the metalloprotease and its connection on the operative region of the *mecA* gene (Berger-Bachi & Rohrer, 2002). The presence of insertion sequences IS431 and IS1272 results in the induction of the *mecA* gene (Katayama et al., 2001).

Other resistance mechanisms have been identified in strains that lack the *mecA* gene, for example, the overproduction of beta-lactamase responsible for the inactivation of oxacillin or modified resistance (MOD-SA) mediated by different types of PBPs with changed affinities to this antibiotic. Strains with this profile are called borderline resistant (Wey et al., 1990).

CA-MRSA can express resistance inducible clindamycin resistance, an option for treating both MSSA and MRSA in particular in cases of toxic shock syndrome. In MLSBi positive strains (macrolide-lincosamides-streptogramin B resistance), an inducer promotes methylase production expressed by the gene *emr* and leading to the subsequent methylation of the 23S

ribosome unit causing an expression of the resistance to lincosamides (e.g. clindamycin). Phenotypically the strains are resistant to erythromycin and clindamycin sensitive, but when the disk of erythromycin is set at 15mm from the clindamycin disk, the clindamycin-induced resistant strain expressed the resistance forming a D zone near clindamycin. The presence of the *mecA* gene in CA-MRSA does not fulfill the identification criteria in itself for the expression of the inducible clindamycin resistance (Patel et al., 2006).

Boyle-Vavra et al. (2005) conducted a study with patients who had skin and soft tissue infections and another with colonized individuals with CA-MRSA, in order to test the resistance to various antibiotics and isolate those carrying the *mecA* gene. The results showed that 94% of the strains recovered from these infections and 85.3% of the strains that colonized healthy individuals showed resistance to three or more non-beta-lactam antibiotics. The SCC<sub>mec</sub> IV was present in 34% of the samples from individuals who had at least one risk factor for acquisition of MRSA and 14.7% of the isolates showed a different SCC<sub>mec</sub> called SCC<sub>mec</sub> VT (Boyle-Vavra et al., 2005).

## 6. Detection of phenotypic resistance to oxacillin

There are several tests that detect phenotypic resistance to oxacillin, such as the E-test with oxacillin agar screening test, or Kirb-Bauer disk diffusion test, cefoxitin disk diffusion, determining the minimum inhibitory concentration (MIC) (Felten et al., 2002), latex agglutination test to detect PBP2a (Bressler et al., 2005; Martins et al. 2010).

CHROMagar is used for the cultivation of *S. aureus* resulting in pink-colored colonies. Carricajo et al. (2001) tested the sensitivity and specificity of this medium compared with conventional (Columbia agar with 5% horse blood and chocolate agar). The CHROMagar allowed 22 strains of *S. aureus* grown from polymicrobial samples unlike conventional methods. Despite the high cost, this method had a sensitivity of 98% and specificity of 100% (Carricajo et al., 2001).

The latex agglutination test detects the PBP2a protein in the cell wall of staphylococci. To assess the effectiveness of this test, Bressler et al. (2005) compared it with PCR for *mecA* and determined the MIC of the MicroScan PC20 samples tested. The latex agglutination test had a 99% agreement with MicroScan; three strains that were false positive in the *mecA* agglutination had two strains that were resistant, and one presented sensitivity. The latter had a different amino acid in PBP2a, the M483I that conferred susceptible to oxacillin. This amino acid can increase the affinity for this antibiotic or eliminate the transpeptidase activity of PBP2a (Bressler et al., 2005).

The disk diffusion test in mannitol salt agar also showed favorable results in the detection of oxacillin resistance and a method almost as effective as the method of disk diffusion in Mueller-Hinton agar (Kampf et al., 1998).

The presence of heteroresistant strains can complicate the detection of the resistance by these methods due to the false-negative results. The disk diffusion test with cefoxitin is widely used due to the induction of *mecA* gene expression with the production of PBP2a, which promotes antibiotics in strains apparently sensitive to oxacillin (Felten et al., 2002). Factors such as lower incubation temperature (30 to 35 °C), osmolarity of the medium (2-4% NaCl), extended incubation period and inoculum density favor the detection of heteroresistant strains (Camarena & Sanchez, 2009).

The use of cefoxitin disk diffusion to detect strains carrying the *mecA* gene is widely applied, but there are laboratories that use only the broth dilution test to determine the MIC of a sample. One study showed correlation of the MIC of cefoxitin in the presence of the *mecA* gene for both *Staphylococcus aureus* and coagulase-negative *Staphylococcus* testing three brands of Mueller-Hinton broth. After testing, the strains were sent to the CDC for molecular detection of the *mecA* gene by PCR. For *mecA* negative *S. aureus* strains the MIC of cefoxitin was  $<4\mu\text{g}/\text{ml}$  and for *mecA* positive the MIC was  $\geq 6$  or  $8\mu\text{g}/\text{ml}$  when read in 18 hours of incubation, the result was highly sensitive and specific (99.7 and 100%). However, for coagulase-negative levels of cefoxitin were sensitive (at 24 hours, 94 to 99% for *S. epidermidis* and 91 to 100% non *S. epidermidis*), but not specific (24 hours, 85 to 91 % for *S. epidermidis* and 54 to 69% non *S. epidermidis*) to detect the presence of *mecA* (Swenson et al., 2009).

Screening with oxacillin agar supplemented with 4% NaCl proposed by CLSI, as well as the oxacillin agar dilution and broth microdilution with 2% NaCl is used with results close to 100% sensitivity for the detection of the *mecA* gene. However, when it comes to very diverse strains, detection of oxacillin resistance and the *mecA* gene are compromised, especially in disk diffusion testing, decreasing its specificity (classifying *mecA* negative strains as resistant) and agar screening, where low sensitivity values are obtained when more heterogeneous strains were tested (Swenson, 2002).

Experiments aimed at improving identification and detection MRSA strains, particularly heterogeneous strains, which are more difficult to detect by conventional methods. The sensitivity of disk diffusion testing using 1g oxacillin disk increased from 83.5% at 35 ° C to 91.7% when incubated at 30° C. Similarly, the sensitivity and specificity of the cefoxitin disk diffusion of 30  $\mu\text{g}$  were 100% at a temperature of 30°C. Tests with cefoxitin are effective, because this antibiotic is able to detect strains inducing heterogeneous subpopulations expressing the *mecA* gene better than oxacillin. The sensitivity of the test screening at 6  $\mu\text{l}$  oxacillin on Mueller-Hinton agar supplemented with 4% NaCl was 91.7% and specificity of 100% in 24 hours of incubation at 35°C. The latex agglutination test for detection of PBP2a can reach a sensitivity of 100%, being able to identify strains with low levels of PBP2a (Cauwelier et al. 2004).

Pereira et al. (2009) analyzed the sensitivity of the method of disk diffusion with oxacillin and cefoxitin disks, incubated for 24 h at 35°C in 100 samples of *S. aureus* isolated from pediatric and neonatal ICUs. They reported oxacillin disk sensitivity of 94.4% and specificity of 98%, while the cefoxitin disk presented 98% sensitivity and 100% specificity. The same authors also tested the screening method on Mueller Hinton agar with 6 $\mu\text{g}/\text{ml}$  of oxacillin and 4% NaCl and found a sensitivity of 98% and specificity of 100%.

Martins et al. (2010) compared the screening methods of disk diffusion and E-test for detection of oxacillin resistance. They found that approximately 45% of samples were positive for the *mecA* gene, and the disk diffusion method with oxacillin disk showed a sensitivity of 86.9% and specificity 91.1%, respectively. The screening method showed the same sensitivity and specificity of 91.3%, while the E-test showed the same specificity of other methods and a sensitivity of 97.8% (Martin et al., 2010).

The results found in several studies to determine the accuracy of these methods show that the results can vary depending on a number of factors especially the origin of the samples and the criteria used for its execution.

## 7. Characterization of strains of CA-MRSA

New typing multiplex PCR protocols have been proposed, which are fast, practical and economical for the differentiation of clones of CA-MRSA. Some techniques are able to differentiate the clone of the USA 300 from the USA 400, and detects the presence of the gene determining resistance to oxacillin the *mecA* gene target of the 16S rRNA that distinguish *Staphylococcus* spp. from other bacteria, the specific *nuc* gene of *S. aureus*, the PVL genes and other specific genes (Zhang et al., 2008). The multiplex PCR also allows the detection of genes encoding toxins and chromosomal cassettes responsible for antimicrobial resistance in a rapid and reliable manner compared to other methods (Oliveira & Lencastre, 2002).

The technique of Multilocus Sequence Typing (MLST) is widely used for typing of microorganisms and is based on amplification and sequencing of genes encoding proteins essential defining each strain based on the sequences of fragments of the seven loci of essential genes. As there are many allelic combinations for each of these genes, there are no identical profiles, and those that have, are considered members of a clone. This technique can be used to study evolutionary and population biology of bacteria (Enright et al., 2000).

Strains isolated in the United States were classified as pulsed-field types (PFT's) USA300, USA400, USA500, USA600, USA700, USA100 and USA800, USA900, USA1000, and USA1100 (Han et al., 2007). It is estimated that most CA-MRSA present the genetic profile of USA300, USA400, USA1000, and USA1100, which the predominant profile is USA300. Strains USA100, USA200 and USA500 are frequently associated with nosocomial infections, and mostly have chromosomal cassette multidrug resistance in type II (Klevens et al., 2007).

For MRSA typing techniques based on PCR, PFGE, ribotyping and plasmid typing, are widely used with successful results. The considerable genetic similarity between these microorganisms requires the use of more than one method for identifying more accurately (Oliveira et al., 2001).

*spa* typing involves sequencing the polymorphic region X of the gene of protein A (*spa*) that contains a variable number of repeated regions of 24 bp flanked by conserved regions as well. In addition to this grouping, based on the sequence of a locus, it is practical, inexpensive, fast, and has a lower probability of errors compared to PFGE and MLST techniques, and can be used in local and global epidemiological studies due to micro- and macro-variations that occur simultaneously in region X. The following types of protein A were characterized in CA-MRSA: t008, t019, t021, t044, T131, t216 (Hallin et al., 2007).

## 8. The role of the Pantone-Valentine Leukocidin (PVL)

One of the most important common virulence mechanisms in CA-MRSA is PVL (Panton-Valentine Leukocidin) production. Strains that harbor the *SCCmec* element may simultaneously carry the *lukS* and *lukF* genes which encode for PVL (Boyle-Vavra & Daum, 2007). Deep infections of skin and soft tissues such as skin boils and abscesses, and necrotizing pneumonia are attributed to the presence of PVL toxin in strains of *S. aureus* (Lina et al., 1999, Melles et al., 2006). The presence in the lungs causes hemorrhage, extensive necrosis of alveolar septa, destruction of the epithelium covering the bronchi and bronchioles (Zhang et al., 2005), and histological sections show necrotic lesions in the

mucosa of the trachea (Lina et al., 1999). Due to these facts, studies have proposed that the propensity of CA-MRSA infections cause severe skin and soft tissue lesions, and possibly necrotizing pneumonia, is due to the presence of the gene encoding the production of PVL (Saïd-Salim et al. 2005).

PVL was first described as a "substance leukocidin" by Van deVelde in 1894 but was first associated with skin and soft tissue infections by Panton and Valentine in 1932. The acquisition of genes encoding PVL is made by transduction of a specific type of bacteriophage, phiSLT, which causes cytolysis in carrier gene cells and transport this gene to another cell. From its transcription two exoproteins, the LukS-PV and LukF-PV are produced, acting through the synergistic action of both subunits (Melles et al., 2006, Saïd-Salim et al., 2005). When secreted, LukS-PV initiates a connection to the membrane of the polymorphonuclear leukocyte (PMN) and is dimerized with LukF-PV, alternating one and another until the complete formation of a heptamer. Calcium channels are formed by inducing the production of interleukins and inflammatory mediators. Because of this evidence, probably the PVL is not directly associated with tissue necrosis, but related to lysosomal granules released by cytotoxic lysis of PMN, the release of granulocyte reactive oxygen or even the inflammatory cascade (Boyle-Vavra & Daum, 2007).

The main target of PVL is human and rabbit neutrophils, having little or no effect on non-human primates and mice (Löffler et al., 2010). The reason for differences in sensitivities to PVL is not yet fully known but may be related to receptor/signal transducers that are species-specific (Löffler et al., 2010). Its action is directly related to the concentration: at high concentrations, it causes cell lysis; at low concentrations, it mediates caspase dependent apoptosis by forming pores in the membrane of mitochondria (Boyle-Vavra & Daum, 2007; Lo & Wang 2011). Sub-lytic concentrations induce apoptosis of human neutrophils within 6 hours, and at high concentrations leads to cell death in only 1 hour (Lo & Wang, 2011).

## 9. Other virulence factors of MRSA

The pathogenicity of *S. aureus* depends on several determinants, among them, the production of toxins and extracellular membrane components (Jarraud et al., 2002; Gandhinagar & Silva, 2004). The molecular basis of pathogenicity of *S. aureus* depends on the expression of broad classes of accessory genes producing components of the cell wall and extracellular proteins. The expression of these virulence factors is regulated by genes in the operon *agr* (accessory gene regulator), which regulates the expression of genes for toxins and adhesins (Purcell & Fergie, 2005). Enzymes such as coagulase and catalase are responsible for its evasion of the immune system (Gandhinagar & Silva, 2004).

The toxins are related to staphylococcal toxic shock syndrome (TSS), staphylococcal scarlet fever (both due to the toxin of toxic shock syndrome 1 [TSST-1] and staphylococcal enterotoxins), scalded skin syndrome (SSS due to exfoliatins) and food poisoning (SE's, staphylococcal enterotoxins) (Santos et al., 2007; Jarraud et al., 2002; Johnson et al., 1991). Genetic sequencing of a strain called MW2, CA-MRSA, revealed the presence of genes responsible for specific virulence factors such as the PVL toxin, staphylococcal enterotoxin H (*seh*) and staphylococcal enterotoxin C (*sec*) (Saïd-Salim et al., 2005).

Toxic shock syndrome was related primarily to the use of a particular brand of tampons in 1980. The TSS can occur in patients of any age, with the main presenting symptoms being

fever, rash, and toxicity, which often progresses to hypotension with a prior history of watery diarrhea, sore throat, nausea, vomiting and myalgia. A number of other symptoms involving dehydration and its effects are often related to the syndrome. Blood cultures may be negative for the pathogen. The strain that carries TSST-1 reacts with phage group I and is likely to produce toxins, including other enterotoxins, and exoproteins. It may also exhibit resistance to heavy metals, and proteolytic characteristics are not often haemolytic and usually tend to be pigmented. It is interesting that strains produce TSST-1 positive alpha-hemolysin in low quantities even if they have the gene, suggesting that certain genetic events leading to repression of some genes (e.g., hemolysin) at the same time the expression of other genes (i.e. TSST -1) is increased (Todd, 1988).

Scalded skin syndrome (SSS), better known as Ritter's disease was first described by German physician Baron Gotfried Ritter von Rittershain who observed the widespread phenomenon in 297 children calling it neonatal exfoliative dermatitis. This disease usually appears in children with clinical features ranging from localized to disseminated bullous impetigo, known for easily rupturing on the skin surface, releasing a fluid with features ranging from thin to thick, being opaque purulent yellowish, whitish or opaque. In neonates lesions are mainly located in the perineum, or both in the periumbilical region, and in older children the lesions are located near the umbilicus. This is the mildest form of the disease, in which the skin around the preserved area remains without systemic signs and symptoms. The generalized form of the disease is mainly spread across the surface of the skin and mucous membranes are usually spared. In infants, onset of symptoms begins between 3 to 16 days. Patients with systemic SSS present fever, malaise, lethargy, irritability, loss of appetite, followed by the appearance of erythematous papules that usually start in the head and neck and spread to the rest of the body in a few days (Ladhani et al., 1999).

Another mechanism of virulence that has often been identified in samples of CA-MRSA is phenol-soluble Moduline . PSM was first detected in cultures of *S. epidermidis*. Antimicrobial activity against Group A *Streptococcus* (Cogen et al., 2010) and activities that stimulate the immune system of NFkB nuclear factor kB in THP-1 cells and cytokines in THP-1 monocytes and its role in the infection still need to be clarified (Mehlin et al., 1999). In PVL-positive CA-MRSA samples, the PSM effect is to intensify the effects of the toxin in the presence of both units (LukS-and LukF-PV) (Hongo et al., 2009).

The detection of PSM in CA-MRSA strains was higher than in HA-MRSA strains showing that *S. aureus* PSM activate human neutrophils triggering an inflammatory response and thereby contributes to staphylococcal virulence. CA-MRSA PSM has an important role in leukocyte cytolysis by CA-MRSA primarily participating in evasion of the host defense system (Wang et al., 2007).

PVL, alpha-toxin and protein A, represent the virulence factors involved in pneumonia caused by *S. aureus*. Alpha-toxins and PVL form pores in the polymorphonuclear cells and thus causes an exaggerated response by the release of cytokines and reactive oxygen specimens and contributing to damage in lung tissue (Hayashida et al., 2009).

Studies in the United States report that the USA400 strain responsible for lethal pneumonia in three children, had cytotoxins, such as virulence factors alpha and gamma, PVL, phenol-soluble Moduline (PSMs), staphylococcal enterotoxin (SE) B or C. The profile of toxigenic strains of USA300 is similar, except for staphylococcal-like enterotoxin (SE-I) Q present in

these strains. CA-MRSA USA 100 and 200 clones have emerged with alpha +/- and gamma-toxin +/-, PVL +/- PSM+ and TSST-1+ profiles. Probably the production of several cytotoxins combined with superantigen action culminates in a devastating disease (Schlievert, 2009).

Beta hemolysin was also related to lung injury as demonstrated by Hayashida et al. (2009). In this study, the hemolysin was attributed to the ability to increase the influx of neutrophils in the lung and alveolar spaces, causing leakage of serum proteins into the lung parenchyma and exudation of protein rich fluid into the air. The neutrophil migration is indirectly modulated by beta-hemolysin through the stimulation of other host factors. Thus, the virulence of hemolysin increases the regulation of various pro-inflammatory cytokines and generates an exaggerated response in the host (Hayashida et al., 2009)

## 10. Current antimicrobial drug choice

Given the great potential of CA-MRSA infections to develop into serious and/or systemic infections, there is an interest in reintroducing drugs such as trimethoprim/sulfamethoxazole, tetracycline and clindamycin for treatment of CA-MRSA. In severe cases where there is need for hospitalization and intravenous therapy, antibiotics such as vancomycin, linezolid and daptomycin are reliable options (LaPlante et al., 2008).

The combination of trimethoprim/sulfamethoxazole (cotrimoxazole) has been considered a good therapeutic option for the treatment of patients affected by CA-MRSA. *In vitro* tests show that it has excellent bactericidal activity, but its activity can be reduced in the presence of rifampicin. Several antimicrobial combinations were tested, such as linezolid and cotrimoxazole, rifampicin. Cotrimoxazole, minocycline, linezolid, clindamycin or moxifloxacin, cotrimoxazole alone proved to be more effective in *in vitro* tests (Kaka et al., 2006).

However, in another study with patients affected by CA-MRSA treated with trimethoprim/sulfamethoxazole, clindamycin and cephalexin resulted in a treatment failure rate of 26%, 25% and 33%, respectively. In addition, patients who received the drainage of abscesses in addition to antibiotic therapy had lower rates of treatment failure (25%) than patients who received only incision and drainage (60%) (Frei et al., 2010).

One of the main strains in the community, the USA300 had plasmid-mediated resistance to tetracycline, clindamycin, and mupirocin (Han et al., 2007). In addition, there is the possibility of clindamycin inducible resistant strains resulting in treatment failure. In places where there is high frequency of isolation of strains with this characteristic, it is necessary to choose alternative treatments. It is estimated that this phenomenon occurs in approximately 13% of CA-MRSA strains (LaPlante et al., 2007) and from 36% to 56% of HA-MRSA (Siberry et al., 2003). The treatment of clindamycin-sensitive strains was assessed showing that the best options were daptomycin, clindamycin, doxycycline, vancomycin, linezolid and trimethoprim/sulfamethoxazole, respectively, with the latter three being equally effective. Treatment with daptomycin was better than vancomycin and linezolid, the latter two having equal effect, but all three overcame the effects of clindamycin since these strains can show induced resistance and the treatment with clindamycin also induces the emergence of constitutive resistance (LaPlante et al., 2008).



Choosing the best option for treating infections caused by CA-MRSA has risks and benefits of each antimicrobial agent that must be considered before prescribing. The ideal antimicrobial agent would be one of low toxicity to the individual, the rapid bactericidal activity, excellent tissue penetration, consistent pharmacokinetics and pharmacodynamics that would allow a predetermined dose, low potential for development of resistance during therapy and a proven clinical efficacy and microbiological (Nguyen & Graber, 2010). Finding a single antimicrobial agent with these characteristics may be complex, whereas a combination of agents can be a successful alternative.

It is not enough to choose antimicrobials with these characteristics; it is also essential to observe antimicrobial participation in the various mechanisms of virulence of the microorganism. In several reports of infections caused by CA-MRSA, PVL appears simultaneously as a virulence factor. The use of antimicrobials may act in the synthesis of Leukocidin improving the patient's condition in cases of pneumonia caused by CA-MRSA PVL positive strains treated with linezolid and clindamycin which suggests that this is a good choice, acting on the protein production mechanism, these antibiotics prevent PVL production compared with vancomycin and nafcillin (Stevens et al., 2007).

## 11. Vancomycin resistance

Another concern is the emergence of resistance to the antibiotic of choice for treating MRSA, vancomycin. Few drugs are available to control MRSA, and vancomycin is one of them. Reports of resistance and low sensitivity to this antibiotic are present in nosocomial environments worldwide (Martins & Cunha et al., 2007).

The first case of reduced susceptibility to vancomycin was reported by Hiramatsu (1997) in a pediatric patient with positive culture for MRSA who was treated with glycopeptide. Phenotypic analysis showed that the MIC for this strain was 8 µg/mL in the microdilution test, and molecular analysis did not detect the presence of *vanA* or *vanB* genes. Strain Mu50, recovered from this patient, represents the first strain of *S. aureus* to demonstrate this level of resistance to vancomycin (Hiramatsu, 1997).

The first report of vancomycin resistance in the U.S. was described by Sievert et al. (2002). The patient was treated with several courses of antibiotics including vancomycin and subsequently developed MRSA bacteremia due to a hemodialysis catheter. He received vancomycin, rifampin and required removal of this catheter. The cultures of the catheter revealed the presence of *S. aureus* resistant to oxacillin and vancomycin. After one week, VRSA and vancomycin-resistant Enterococcus (VRE) were isolated. Cultures did not recovered VRSA from the patient being treated with trimethoprim/sulfamethoxazole, successfully. Molecular analysis revealed the presence of the *vanA* gene from enterococci, which explains the resistance to glycopeptides, and *mecA* (Sievert et al., 2002).

Cases of *S. aureus* with intermediate resistance to vancomycin (VISA) in addition to presenting heteroresistance are increasingly common in health centers where MRSA infections are treated with vancomycin (Trakulsomboon et al., 2001; Van Duijkeren et al., 2005; Kim et al., 2000).

Kim et al. (2000) observed that the vancomycin-resistant strains showed changes in the cell wall due to selective pressure caused by prolonged use of vancomycin in the treatment of

infections caused by MRSA. On the other hand, *in vitro* gene transfer of *vanA* resistance was observed from vancomycin-resistant *Enterococcus* strains to *S. aureus* (Sievert et al., 2002).

The detection of resistance is a matter of controversy. Some authors defend the idea that the disk diffusion method may not be effective in detecting resistance to glycopeptides, particularly vancomycin (Kim et al., 2000; Walsh et al., 2001).

In San Francisco, USA, a patient with subsequent complications was initially diagnosed with MRSA susceptible to trimethoprim-sulfamethoxazole. A more accurate survey was conducted showing that the strain belonged to the PFGE USA 300-0114 of community origin and had intermediate resistance to vancomycin. This strain is closely related to infections of skin and soft tissues as well as lung disease. Surveillance in the United States in San Francisco shows an explosive increase of infections by USA300 CA-MRSA, can also replace other strains (Graber et al., 2007).

## 12. Resistance in *Staphylococcus* spp.

Coagulase-negative staphylococci (CoNS) are part of the microbiota of the skin, most often presenting a benign relationship with the host. However, they are the major opportunistic pathogens of immunocompromised patients in hospitals (Bisno & Stevens, 1996; Cunha et al., 2004). Important infectious processes related to CoNS have been reported in recent decades. They are commonly isolated from blood cultures of patients undergoing invasive procedures such as prostheses, catheters, organ transplants, as well as from premature infants (Cunha et al., 2004).

The main species of CoNS that are involved in infections in humans are *S. epidermidis* (may cause bacteremia, osteomyelitis, peritonitis, surgical site infections, infections due to the installation of catheters and prostheses, endophthalmitis, etc.), *S. haemolyticus* (urinary tract infection, peritonitis, injuries, etc.) and *S. saprophyticus* (urinary tract infection and septicemia) (Cunha et al., 2004). Specifically regarded to the occurrence of bacteremia in hospitals, the species *S. epidermidis* was found to be the etiologic agent in 80% of cases (Gongora-Rubio et al., 1997).

Resistance to methicillin in species of CoNS (MRSCoN) colonizing healthy individuals can overcome MRSA in the same population as demonstrated by a Japanese study (Hisato et al., 2005). Analysis of 818 children revealed that 35 (4.3%) carried MRSA, while 231 (28.2%) MRSCoN. The fact that MRSCoN strains are prevalent in the community suggests that they are important reservoirs of *SCCmec* that can be carried to strains of *S. aureus* (Hisato et al., 2005).

Strains of vancomycin-resistant CoNS are common in hospitals due to this antibiotics' selective pressure in this environment, but few studies have been published on this community. A surveillance study assessed the cultures of saliva collected from employees of a private school and 37 hospital staff. The identification of specimens recovered from samples revealed that 98.5% were carriers of *Staphylococcus* spp. and 76.5% were carriers of more than one *Staphylococcus* spp. species. Four strains were resistant to vancomycin according to phenotypic tests isolated from two school officials and two hospital employees, and two identified as *S. capitis* and the other two as *S. haemolyticus* and *S. epidermidis*. All samples carried the *mecA* gene of resistance to oxacillin and were negative for the genes

*vanA*, *vanB* and *vanC*. The samples relating to employees of the hospital were also resistant to other classes of antimicrobials (Palazzo et al., 2005).

MRSCoN may be involved in severe infections and present different resistances, as well as virulence factors able to offer health risks of individuals with impaired immune systems or in development as in the case of neonates. Despite its great importance in critically ill patients, its presence in healthy individuals deserves special attention mainly because they are both sources of genes for virulence and resistance.

### 13. Future prospects

The emergence of *S. aureus* resistant to methicillin in the community as the main agent of serious infections of skin and soft tissue is disturbing since oxacillin would be the drug of choice to treat infections caused by strains resistant to other antibiotics. Several techniques can be used to detect resistance to oxacillin, but PCR is the safest and most effective. In addition to PCR, other techniques allow genetic characterization of CA-MRSA detailing an arsenal of toxins and differentiation of clones involved in outbreaks. These techniques help epidemiologist determine correct measures in controlling the spread of this pathogen.

Studies in Epidemiology associated with molecular studies represent good tools for understand the distribution and inform treatment success. The detection of antimicrobial resistance in strains from patients living in the community reveals that the alternatives available to the medical community for successful treatment are decreasing gradually, thus, presenting an opportunity to research new drugs, and antimicrobial agents considered older and well established such as trimethoprim/sulfamethoxazole, which is re-emerging as an option for treating infections caused by CA-MRSA.

The presence of CA-MRSA strains involved in nosocomial infection implies the need for greater control of its spread among hospitalized patients, since the reports of strains of community origin suggest they are also more virulent compared to strains of nosocomial origin, and may lead to serious complications of rapid evolution. Treatment strategies that may delay or prevent the expression of these factors will need to be established, as well as administering the correct treatment quickly and effectively.

### 14. Conclusion

The presence of resistant strains in the community, especially *S. aureus*, poses a risk to public health since the treatment may fail, delaying the elimination of pathogens involved in these infections. This delay can result in serious complications leading to early death of the patient. New treatment alternatives and the rediscovery of antimicrobials that are no longer being used provide to the medical community a new opportunity for successful treatment.

In addition to antimicrobial resistance, community strains have become more virulent, which provides another challenge to the attending physician to choose the best treatment strategy possible. Attention should also be directed to CoNS strains resistant to methicillin, which can serve as reservoirs of resistance genes *S. aureus* that are more virulent. The detections of virulence factors and antimicrobial additional resistance can be truly challenging and lead to treatment failure if it is not detected quickly. Fortunately there are new approaches that are becoming affordable to microbiology laboratories that can detect as

far as the patient is attended. But to reach the 100% of the treatment success it will need more than top notch technologies.

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## **Epidemiology Insights**

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This book represents an overview on the diverse threads of epidemiological research, brings together the expertise and enthusiasm of an international panel of leading researchers to provide a state-of-the-art overview of the field. Topics include the epidemiology of dermatomycoses and *Candida* spp. infections, the epidemiology molecular of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from humans and animals, the epidemiology of varied manifestations neuro-psychiatric, virology and epidemiology, epidemiology of wildlife tuberculosis, epidemiologic approaches to the study of microbial quality of milk and milk products, Cox proportional hazards model, epidemiology of lymphoid malignancy, epidemiology of primary immunodeficiency diseases and genetic epidemiology family-based. Written by experts from around the globe, this book is reading for clinicians, researchers and students, who intend to address these issues.

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