Update on major clones of methicillin-resistant *Staphylococcus aureus* colonizing and/or infecting humans and its distribution in Brazil

Atualização sobre clones principais de staphylococcus aureus resistente à meticilina colonizando e/ou infectando humanos e sua distribuição no Brasil

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Abstract
Staphylococcus aureus is a bacterium well known for its ability to acquire genes for resistance to antimicrobial drugs. A few years after the discovery of penicillin, which initiated the era of antibiotics, resistance to this drug had already been reported in hospitals and in a few decades also became a problem within the communities. Likewise, shortly after the introduction of methicillin as a therapeutic option, the resistance was observed. The indiscriminate use of antibiotics is an important factor contributing to the emergence of new resistant strains. This pathogen has the ability to spread rapidly and asymptomatically among healthy individuals. Infections caused by Methicillin-Resistant Staphylococcus aureus (MRSA) have reached a global share and are increasing in hospitals and community, including countries that previously had a low prevalence of MRSA history, exposing a significant diversity of clones identified. Outbreaks of infections caused by strains of Community-Associated Methicillin-Resistant Staphylococcus aureus (CA-MRSA) have been reported worldwide, including Brazil, where there is currently an epidemic of CA-MRSA. The present article intends to review the molecular epidemiology of methicillin-resistant Staphylococcus aureus and its evolution, with a focus on the clones distributed in Brazil.

Palavras-chave

Staphylococcus aureus resistente à meticilina

Colonização nasal

Infecção

Genótipos

Resumo
Staphylococcus aureus é um bactéria muito conhecida por sua capacidade de aquisição de genes de resistência à drogas antimicrobianas. Alguns anos após a descoberta da penicilina, que iniciava a era dos antibióticos, a resistência a esta droga já foi relatada em hospitais e em poucas décadas também tornou-se um problema dentro das comunidades. Do mesmo modo, logo após a introdução de meticilina como uma opção terapêutica, a resistência foi observada. O uso indiscriminado de antibióticos é um importante fator contribuindo para o surgimento de novas cepas. Este patógeno tem a capacidade de espalhar-se rapidamente e assintomaticamente entre indivíduos saudáveis. Infecções causadas por Staphylococcus aureus resistente à meticilina (SARM) atingiu uma cota global e está aumentando em hospitais e comunidades, incluindo países que previamente tinham um baixa prevalência de história de SARM, expondo uma diversidade significante de clones identificados. Surtos de infecções causadas por cepas de Staphylococcus aureus resistente à meticilina de Comunidades Associadas (SARM-CA) foram relatados no mundo, incluindo Brasil, onde há atualmente uma epidemia de SARM-CA. O presente artigo pretende revisar a epidemiologia molecular de Staphylococcus aureus resistente à meticilina e sua evolução, com o foco em clones distribuídos no Brasil.

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1. Introduction

A wide variety of infections, both superficial and deep, may be caused by Staphylococcus aureus (DEURENBERG & STOBBERINGH, 2008; COREY, 2009; CECCARELLI, 2011).

S. aureus can be permanent or intermittently present in the microbiota of nares, skin, throat and intestinal tract of some individuals. This colonization allows those subjects to act as disseminators of this microorganism. Also, these individuals are at higher risk for infection (RAMOS, 1999; CONLY & JOHNSTON, 2003). Nowadays it is believed that 30% of humans have asymptomatic nasal colonization by *S. aureus* (CHAMBERS & DELEO, 2009; RODRIGUEZ-NORIEGA, 2010).

Transmission occurs by direct contact, usually through skin from a person colonized or infected having open lesions. Other routes such as fomites and hands of health professionals are also important means of transmission. More recently, several outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) have been associated with the presence of samples in food of animal origin (RIZEK, 2011).

The spread is facilitated by several reasons including the migration of population, including health professionals, combined with ineffective methods to control transmission of MRSA from colonized and infected patients, along with inappropriate use of antimicrobials (DEURENBERG & STOBBERINGH, 2008; RODRIGUEZ-NORIEGA & SEAS, 2010).

The mechanism of resistance is also an important factor to be observed among these microorganisms. *S. aureus* is naturally susceptible to all antimicrobials that were developed (DANCER, 2008). The resistance to these drugs is generally acquired by horizontal gene transfer but chromosome mutation and selective pressure imposed by antibiotics are also important (DEURENBERG & STOBBERINGH, 2009). Thus, the diversity of S. aureus clones that exists nowadays is genetically descendant from a single common ancestor (KLEVENS, 2007; RODRIGUEZ-NORIEGA, 2010).

Currently, there is an increase of Community-Associated Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) infections worldwide, mostly characterized by cutaneous and soft tissue lesions among healthy individuals without predisposing risk factors. Nevertheless, after the emergence of CA-MRSA, symptoms of necrotizing pneumonia and fulminating necrotizing fasciitis became more common in infections, showing a particularly virulent characteristic of these strains (VANDENESCH, 2003; LO & WANG, 2011).

The present article proposes to make a brief review about main MRSA clones causing infection and colonization in Brazil.

2. Methods

The review was made using reports published from 1993 to nowadays, also including the first articles related to S. aureus resistance (dated from 1949). Data collection included a literature held in scientific search sites like PubMed, LILACS, Scielo, BIREME and Scholar google. Keywords used were: methicillin-resistant *Staphylococcus aureus*, nasal colonization, infection, genotypes, hospital, community and Brazil.

3. Results

A total of 63 articles, one homepage (International Working Group on the Staphylococcal Cassette Chromosome elements homepage) and one Brazilian Law (Law no. 9431/1997) were selected in order to characterize a review of the molecular epidemiology of major clones of MRSA pathogen to human, its evolution and distribution in Brazil.

3.1. Staphylococcus aureus history and evolution

The beginning of clinical use of penicillin occurred in 1940 and the first reports of resistant strains date from few years later when there was an epidemic of nosocomial infections caused by strains of *S. aureus* resistant to this drug in several countries, including Australia and the United States (RAMMELKAMP & MAXON, 1942). In the early 50s occurred the first cases of community-associated infections and the establishment of a pandemic (CHAMBERS & DELEO, 2009).

These strains produce a penicinilase, encoded by a plasmid, which hydrolyzes the beta-lactam ring of penicillin, essential for antimicrobial activity.

At this time, the hospital and community infections were often caused by a strain known as phage type 80/81(KENNEDY, 2008) and such infections became rare after the first use of methicillin in 1960.

In the year following the beginning of methicillin therapeutic aplication, the first cases of resistance to this antibiotic were published in England and at the end of the same decade methicillin-resistant strains were already endemic in hospitals (ERIKSEN, 1961; JEVONS, 1963; DEURENBERG & STOBBERINGH, 2009).

Methicillin resistance is conferred by the mecA gene, which is carried by a mobile genetic element known as Staphylococcal Cassette Chromosome mec (SCCmec) which encodes a penicillin-binding protein modified, called PBP2a or PBP2', which has a low affinity to beta-lactams, including penicillins, cephalosporins and carbapenems (KATAYAMA, 2000; KONDO, 2007; DEURENBERG & STOBBERINGH, 2008; ZHANG, 2009; SHORE, 2011).

According to publications, so far, there are eleven different allotypes of SCCmec, types I to XI, that have been revealed among MRSA strains (CHAMBERS & DELEO, 2009; IWG-SCC, 2011).

SCC*mec* presents the genetic components named *mec* gene complex and *cassette chromosome recombinases* (*ccr*) gene complex (ITO, 2004; KONDO, 2007; DEURENBERG & STOBBERINGH, 2008; 2009; ZHANG, 2009; SHORE, 2011). Variations within these gene complexes serve as the primary basis for classifying the various types of SCC*mec* (KONDO, 2007; CHAMBERS & DELEO, 2009).

The *mec* gene complex is composed of the *mecA* gene and its regulators, *mecI* and *mecRI*. This complex also may contain genetic components such as transposons, plasmids and insertion sequences, such as the IS431 (HANSSEN & ERICSON SOLLID, 2006; ZHANG, 2009). Five different classes of mec gene complexes, called class A, B, C1, C2 and D were described in the literature (KONDO, 2007; SHORE, 2011).

The *ccr* gene complex contains the ccrA, *ccrB* or *ccrC* genes. These encode two recombinases, which are required for integration and excision of SCC*mec* from the *orf*X region in the genome of *S. aureus*, thus allowing the horizontal transmission of the SCC*mec* (BERGLUND, 2005; HANSSEN & ERICSON SOLLID, 2006; ZHANG, 2009). Up to date, five allotypes of *ccr* have been described (*ccr*A1B1, *ccr*A2B2, *ccr*A3B3, *ccr*A4B4 e *ccr*C5) (KONDO, 2007; SHORE, 2011).

SCC*mec* III and IV, which are the most commonly found types in Brazil, have different characteristics according to the presentation of these mobile elements, as shown in Table 1.

First cases of CA-MRSA occurred in Australia in the early 90's in an indigenous population, by a clone known as Western Australia 1 (WA-1) (UDO, 1993). Such isolates were not related to the hospital and was susceptible to most antimicrobials that were not beta-lactams, unlike the hospital strains (LO & WANG, 2011).

Since then, CA-MRSA is now reported worldwide in numerous populations including athletes, children attending day care centers, prisoners, men who have sex with men, military, drug users and other individuals in healthy communities that do not present any risk of infection (KLEVENS, 2007; GORWITZ, 2008; KENNEDY, 2008; STEVENS, 2008). An increase of CA-MRSA infections also happened to be found in hospitals (SCHUENCK, 2009). Thus, there is not an individual or group that is not at risk for infection by CA-MRSA.

CA-MRSA strains usually carry SCC*mec* type IV and, less frequently, the type V and VII (DEURENBERG & STOBBERINGH, 2008; LO & WANG, 2011), and generally produce the toxin Panton-Valentine Leukocidin (PVL) (KLEVENS, 2007; CHAMBERS & DELEO, 2009).

Several important studies suggest that PVL is associated with skin infections and severe necrotizing hemorrhagic pneumonia in previously healthy patients without any risk factors for infection. These clinical features were rarely seen before the emergence of CA-MRSA strains (GENESTIER, 2005; LO & WANG, 2011).

Hospital-Acquired Methicillin-Resistant Staphylococcus aureus (HA-MRSA) differ from CA-MRSA in terms of genetic and phenotypic characterization, as showed in table 2, being the former more susceptible to tetracycline, clindamycin and trimethoprim-sulfzametoxazol (WALRAVEN, 2011).

Molecular techniques for genotyping isolates of *S. aureus* allow further study of this pathogen, allowing a more accurate understanding of the spread and evolution (ROBINSON & ENRIGHT, 2004; CHAMBERS & DELEO, 2009). The technique of Multilocus Sequence Typing (MLST), for example, allows clones to be classified and distinguished in Sequence Types (ST). In turn, the STs are grouped into Clonal Complexes (CC).

The clone multiresistant New York/ Japan (NYJ) is related to the clone USA100 and is ST5-SCCmecII. It can be found in some Latin American countries such as Mexico and elsewhere in the world including Australia, Belgium, Canada, China, Denmark, France and Germany and also is widely distributed in the U.S. and Japan (AIRES DE SOUSA, 2000; DEURENBERG & STOBBERINGH, 2008).

In Australia, the WA-1 clone, related to the USA400 clone, was one of the first CA-MRSA described in the world. This clone is ST1-SCC*mec*IV and usually does not produce PVL (DAILEY, 2005; SCHUENCK, 2009).

It is known that in most regions of the United States and Canada the main cause of severe infections, especially in skin, is the CA-MRSA clone known as USA300 which is ST8-SCC*mec*IV and PVL producer (KLEVENS, 2007; KENNEDY, 2008; CHAMBERS & DELEO, 2009).

Other CA-MRSA clone highly distributed worldwide is the Pediatric clone, which is ST5-SCCmecIV or SCCmecV and also related to the USA800 clone (SA-LEAO, 1999; DEURENBERG & STOBBERINGH, 2008).

3.2. MRSA in Brazil

In Brazil, MRSA is a major cause of nosocomial infections. The epidemic clone of MRSA in most hospitals from north to south, reported since 1994, is characterized by being multiresistant, able to produce biofilms and, in most cases, doesn´t produce PVL toxin (DOS SANTOS SOARES, 2000; RODRIGUEZ-NORIEGA & SEAS, 2010). This Brazilian Epidemic Clone (BEC) is classified as SCC*mec*IIIA-ST239 (CC8) and belong to the same clonal complex of the first MRSA identified in the world (Figure 1) (SADER, 1994; OLIVEIRA, 2001; ROZENBAUM, 2006; ROZENBAUM, 2009).

The prevalence of nosocomial infections by *S. aureus* ranges from 40% to 80% in most Brazilian hospitals with more than 37% of these corresponding to multiresistant MRSA (VIVONI, 2006; SCHUENCK, 2009; RODRIGUEZ-NORIEGA, 2010). In recent study with MRSA samples of a university hospital in Recife, northeast of Brazil, BEC accounted for 70% of the total of samples (DE MIRANDA, 2007).

Samples of BEC are resistant to beta-lactams, chloramphenicol, ciprofloxacin, clindamycin, gentamicin, tetracycline, erythromycin, lincomycin, and trimethoprim-sulfamethoxazole. These clone is widespread among various hospitals in Latin America such as Argentina, Chile, Colombia, Ecuador, Paraguay, Peru and Uruguay, Europe such as Portugal, Russia and the Czech Republic and Asia such as Vietnam, Thailand and Taiwan (TEIXEIRA, 1995; MELTER, 1999; AIRES DE SOUSA, 2001; OLIVEIRA, 2001; AIRES DE SOUSA, 2003; PEREZ & D'AZEVEDO, 2008; RODRIGUEZ-NORIEGA & SEAS, 2010; RODRIGUEZ-NORIEGA, 2010).

In 1999 there were reports of BEC with resistance to mupirocin, a topical antibiotic used to eradicate colonization of patients and health professionals (RAMOS, 1999).

In Brazil, factors as hospitals overcrowding, transference of patients between hospitals and the lack of an effective control of infection and antibiotics use, facilitated the spread of BEC between the cities (OLIVEIRA, 2001).

Despite this, studies have reported an increase presence of non-multiresistant MRSA SCC*mec* type IV, characteristic of samples associated with communities, in individuals admitted to hospitals, showing a change in the molecular profile of samples in Brazilian hospitals (Figure 2) (RIBEIRO, 2005; SAID-SALIM, 2005; DE MIRANDA, 2007; REINERT, 2008; SCHUENCK, 2009; SCRIBEL, 2009; SILVA-CARVALHO, 2009;

SOUSA-JUNIOR, 2009; RODRIGUEZ-NORIEGA & SEAS, 2010; RODRIGUEZ-NORIEGA, 2010; ROSSI, 2011).

The NYJ clone has been identified in national studies since 2004, being found in hospital samples in Rio de Janeiro and Recife (MELO, 2004; DE MIRANDA, 2007).

The clone Oceania Southwest Pacific clone is SCC*mec*IV-ST30 and was the first of this type of SCC*mec* to be reported in the country and throughout Latin America in 2005 (RIBEIRO, 2005; RODRIGUEZ-NORIEGA & SEAS, 2010). This clone is PVL producer and causes primarily skin infections, septic arthritis and soft tissue infections in immunocompetent individuals in communities (SILVA-CARVALHO, 2009).

In 2009, a study conducted with samples of non-multiresistant MRSA, from a hospital in Rio de Janeiro, showed a presence of polyclonal SCCmec type IV (SCHUENCK, 2009).

As described in the literature, CA-MRSA infections are caused by different genotypes belonging to different sequence types (CHAMBERS & DELEO, 2009). In Brazil, SCC*mec* type IV samples belonging to sequence types ST1, ST3, ST5, ST8, ST30, ST72, ST88 and ST97 have already been found (REINERT, 2008; SCHUENCK, 2009; SILVA-CARVALHO, 2009).

Variants of the Pediatric clone which is SCC*mec* type IV have been reported causing infections in hospitals in Rio de Janeiro, Recife and Porto Alegre (ROZENBAUM, 2006; DE MIRANDA, 2007; SCRIBEL, 2009).

In 2007 the first report of USA300 in the country was published. It was collected in the end of 2003 in Porto Alegre (RIBEIRO, 2007). At the same scientific publication there was the report of WA-1 clone in Porto Alegre and Rio de Janeiro in samples collected in 2004.

One of the main pathogens of infective endocarditis, MRSA is the etiologic agent of 37.5% of these infections in Brazil (FOWLER, 2005). The first report of this disease caused by CA-MRSA in the country occurred in 2008, by a sample of SCC*mec* type IV and PVL positive (FORTES, 2008). Although BEC samples with intermediate resistance to vancomycin and teicoplanin have already been reported in northeastern Brazil in 2000 (DOS SANTOS SOARES, 2000), these isolates remain rare in this country.

4. Discussion

Despite the association of *S. aureus* with abscess formation and sepsis have been reported in the late seventeenth century, this bacterium remains an important cause of infections acquired in both hospital and community environments.

Staphylococcal infections vary from located, usually superficial, to deep, with high gravity (COREY, 2009).

Studies that characterize the circulating strains in specific environments help to control this pathogen, which is the major cause of infections in surgical wounds and sepsis in hospitalized patients (LINDSAY & HOLDEN, 2004; CHAMBERS & DELEO, 2009).

Currently, this bacterium has increasing clinical importance due to increased rates of infections related to health care and community infections caused by multiresistant strains (ALLEGRANZI, 2011).

Outbreaks occur throughout the world with a similar epidemiology and MRSA clones are rarely confined to a single hospital, affecting, generally, all the hospitals in a region (LEE, 2011). Despite this, the occurrence of specific clones, with specific standards of resistance, may vary according to the geographic region (SCHUENCK, 2009; RODRIGUEZ-NORIEGA & SEAS, 2010).

In Brazil, factors such as overcrowding hospitals, transfer of patients between hospitals and the lack of effective control of infection and antibiotic use has facilitated the spread of MRSA by cities (OLIVEIRA, 2001). In addition, studies have reported an increased presence of SCCmec type IV MRSA, characteristic of samples associated with communities, in individuals admitted to hospital with infections diagnosed after 48 hours of admission, indicating a change in the molecular profile of the Brazilian hospital samples (DE MIRANDA, 2007; SCRIBEL, 2009; SILVA-CARVALHO, 2009; SOUSA-JUNIOR, 2009; RODRIGUEZ-NORIEGA & SEAS, 2010).

In order to monitor infections related to healthcare in Brazil the Law no. 9431 of January 6, 1997 provides for the obligation of hospitals to maintain a Program of Control of Hospital Infections and create a Committee of Nosocomial Infection Control (BRASIL, 1997).

Factors such as the immediate increase in the treatment cost due to the use of more expensive alternative antibiotics and their impact on other micro-organisms demonstrate the importance of these infections in terms of public health.

Moreover, increased hospitalization, the potential loss of productivity of infected patients, the possibility of intractable infection and increased mortality indicate the urgency to the study and prevention of infections caused by MRSA.

5. Final considerations

The indiscriminate use of antibiotics is an important factor contributing to the emergence of new resistant strains. The correct identification of MRSA is essential to ensure proper treatment of patients. More studies are necessary to maintain the surveillance and to allow the identification of changes in the resistance profile of clones circulating in Brazil, allowing the updated of knowledge of epidemiology of MRSA and more targeted measures to appropriately control the dissemination of this organism.

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Anexos

Table 1. Main types of Staphylococcal Cassette Chromosome *mec* found in Brazil

(HANSSEN & ERICSON SOLLID, 2006; DEURENBERG & STOBBERINGH, 2008; CHAMBERS & DELEO, 2009; IWG-SCC, 2011).

Characteristics	SCC*mec* type	
	III	IV
length (Kb)	60-67	21-24
mec gene complex	A	B
ccr gene complex	A3B3	A2B2
Numbers of IS431	4	1
Numbers of Tn554	2	0
pUB110	(-)	(-)
pT181	(+)	(-)
pI158	(+)	(-)
Other resistance genes	erm, tc e Hg	(-)

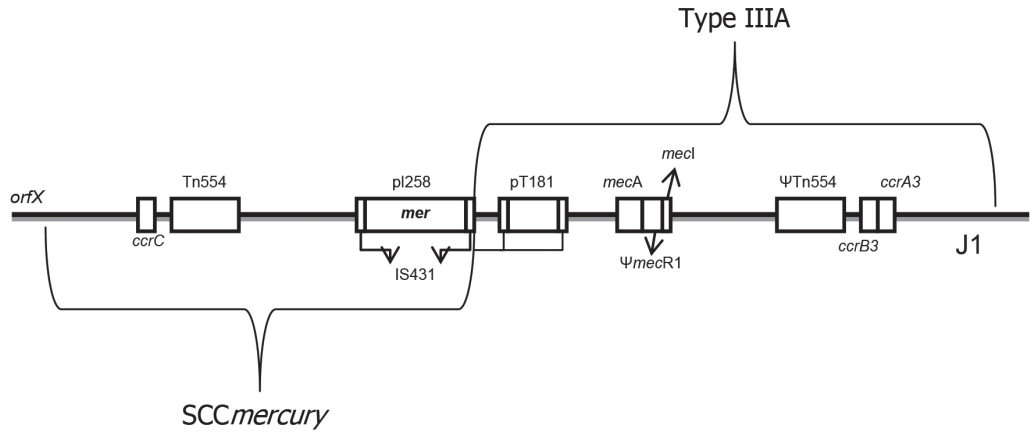
IS: Insertion Sequence; **Tn**: Transposon; **p**: plasmid; **Erm**: erythromycin resistance gene; **tc**: tetracycline resistance gene; **Hg**: mercury resistance gene; **(+)**: presence; **(-)**: ausence.

Table 2. Comparison of infections associated with community setting (CA-MRSA) and hospital-acquired infections (HA-MRSA).

Characteristics	Type of MRSA		References
	HA	CA	
Year of discovery	1961	1993	(DEURENBERG & STOBBERINGH, 2008)
Risk factor for infection	Inpatients, users of intravenous catheter,patients on dialysis, burned.of intravenous catheter, patients on dialysis, burned.	Children, athletes, prisoners, miitary, injecting drug users, men who have sex with men, HIV-positive	(CHARLEBOIS, 2002; STEVENS, 2008)
Main clinical manifestations	Bacteremia, hospital-acquired pneumonia, ventilator-associated pneumonia.	Skin and subcutaneous tissue infections, community acquired pneumonia, bacteremia, osteomyelitis.	(NAIMI, 2003; LO & WANG, 2011)
Type of SCC*mec*	I, II, III	IV, V, VII	(CHAMBERS & DELEO, 2009)
antimicrobial resistance	Multiresistant. Including β-lactams, macrolides, TMP-SMX, lincosamides, tetracyclines, rifampin, quinolones and glicopepitide resistance cases.	β-lactams. Variable susceptibility to macrolides, TMP-SMX, tetracyclines and lincosamides.	(WALRAVEN, 2011)
PVL Production	Rare	Frequent	(VANDENESCH, 2003)

TMP-SMX: Trimethoprim-sulfamethoxazole

Figure 1 - Schematic representation of SCCmec type IIIA, carried by the Brazilian Epidemic Clone. Adapted from (HANSSEN & ERICSON SOLLID, 2006; KONDO, 2007; DEURENBERG & STOBBERINGH, 2008)



IS: Insertion Sequence; **Tn**: Transposon; **p**: plasmid; ***orf***: open reading frame; ***mecA****:* gene that encodes PBP2; ***mecR1*** and ***mecI***: genes that control *mecA* expression, encoding the signal transducer protein ecR1 or encoding the repressor protein MecI, respectively; **ccr**: cassette chromosome recombinases; ***mer***: *mercury* resistance operon; **J**: J regions, which constitute nonessential components of the cassette.

Figure 2 - MRSA clones circulating in Brazil.

BEC: Brazilian Epidemic Clone; **OSP:** Oceania Southwest Pacific clone; **NYJ:** New York/Japan clone; **WA1:** Western Australia 1 clone