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ORIGINAL ARTICLE

Staphylococcus aureus: changes in antimicrobial sensitivity profile and its relationship with SCC*mec* among clinical isolates

Staphylococcus aureus: alterações no perfil de sensibilidade antimicrobiana e sua relação com SCCmec entre isolados clínicos

Staphylococcus aureus: cambios en el perfil de sensibilidad antimicrobiana y su relación con SCCmec entre aislados clínicos

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ABSTRACT

Background and Objectives: *Staphylococcus aureus* is a pathogen of great clinical relevance, especially those resistant to methicillin, called MRSA. Over the years, *S. aureus* antimicrobial resistance patterns have changed. Understanding such changes is essential to update protocols and propose efficient therapeutic approaches. This study aimed to characterize the temporal distribution of *S. aureus* antimicrobial resistance in patients admitted to the hospital as well as to assess its relationship with SCC*mec* typing. **Methods:** a total of 9,949 cultures of clinical materials were analyzed, between January 2000 and October 2019, from patients admitted to a university hospital in southern Brazil. All isolates had their identification and antimicrobial sensitivity profile analyzed using manual and automated techniques. Furthermore, 86 isolates were selected for *mec*A gene research and SCC*mec* typing using conventional and multiplex PCR techniques, respectively. **Results**: when assessing the temporal distribution of *S. aureus* over 20 years, it was possible to observe a drop in the proportion of MRSA compared to methicillin-sensitive *S. aureus* (MSSA). Between 2000 and 2002, the frequency of MRSA was 58.5%, whereas that of MSSA was 36.7%. However, from 2003 onwards, there was a reversal of these percentages. At the end of the analyzed period, 55.2% of infections were caused by MSSA, whereas 36.2% contained MRSA isolates. Furthermore, in the period analyzed, the highest prevalence was of SCC*mec* type II. **Conclusion**: these data suggest an epidemiological change in *S. aureus* from clinical materials, with a change in the prevalent type of SCC*mec* and changes in the antimicrobial sensitivity profile exhibited by the isolates. Such facts must be considered by the clinical staff with a focus on effective patient management, the choice of appropriate antimicrobial therapy so that effective infection control measures are implemented.

Keywords*: S. aureus. Clinical Epidemiology. MRSA. MSSA.*

RESUMO

Justificativa e Objetivos: *Staphylococcus aureus* é um patógeno de grande relevância clínica, especialmente aqueles resistentes à meticilina, denominados MRSA. Ao longo dos anos, os padrões de resistência antimicrobiana dos *S. aureus* têm apresentado modificações. Compreender tais mudanças é fundamental para atualizar protocolos e propor abordagens terapêuticas eficientes. O objetivo do estudo foi caracterizar a distribuição temporal da resistência antimicrobiana de *S. aureus* proveniente de pacientes internados no hospital, bem como avaliar sua relação com a tipagem SCC*mec*. **Métodos**: foram analisadas 9.949 culturas de materiais clínicos, entre janeiro de 2000 e outubro de 2019, de pacientes internados em um hospital universitário no sul do Brasil. Todos os isolados tiveram sua identificação e perfil de sensibilidade aos antimicrobianos analisados por técnicas manuais e automatizadas. Ainda, 86 isolados foram selecionados para a realização da pesquisa do gene *mec*A e tipagem SCC*mec*, utilizando a técnica de PCR convencional e multiplex, respectivamente. **Resultados:** avaliando a distribuição temporal dos *S. aureus* ao longo de 20 anos, foi possível observar queda na proporção de MRSA em comparação com o *S. aureus* sensível à meticilina (MSSA). Entre 2000 e 2002, a frequência de MRSA foi de 58,5%, enquanto que a de MSSA foi de 36,7%. No entanto, a partir de 2003, houve uma inversão desses percentuais. Ao final do período analisado, 55,2% das infecções foram ocasionadas por MSSA, enquanto que 36,2% continham isolados de MRSA. Ainda, no período analisado, a prevalência maior foi do SCC*mec* tipo II. **Conclusão**: esses dados sugerem uma alteração epidemiológica em *S. aureus* provenientes de materiais clínicos, com alteração do tipo SCC*mec* prevalente e modificações do perfil de sensibilidade aos antimicrobianos exibidos pelos isolados. Tais fatos devem ser considerados pelo corpo clínico, focando para que haja um manejo efetivo dos pacientes, escolha da terapia antimicrobiana adequada e para que medidas de efetivas de controle de infecção sejam implementadas.

Descritores*: S. aureus. Epidemiologia Clínica. MRSA. MSSA.*

RESUMEN

Justificación y Objetivos: *Staphylococcus aureus* es un patógeno de gran relevancia clínica, especialmente los resistentes a meticilina, denominado MRSA. Con el paso de los años, los patrones de resistencia a los antimicrobianos de *S. aureus* han cambiado. Comprender tales cambios es esencial para actualizar los protocolos y proponer enfoques terapéuticos eficientes. El objetivo del estudio fue caracterizar la distribución temporal de la resistencia antimicrobiana de *S. aureus* en pacientes ingresados en el hospital, así como evaluar su relación con la tipificación de SCC*mec*. **Métodos:** se analizaron 9.949 cultivos de materiales clínicos, entre enero de 2000 y octubre de 2019, de pacientes ingresados en un hospital universitario del sur de Brasil. Se analizó la identificación y el perfil de sensibilidad antimicrobiana de todos los aislados mediante técnicas manuales y automatizadas. Además, se seleccionaron 86 aislados para la investigación del gen *mec*A y la tipificación de SCC*mec*, utilizando técnicas de PCR convencional y múltiple, respectivamente. **Resultados**: al evaluar la distribución temporal de *S. aureus* durante 20 años, fue posible observar una caída en la proporción de MRSA en comparación con *S. aureus* sensible a meticilina (MSSA). Entre 2000 y 2002, la frecuencia de MRSA fue del 58,5%, mientras que la de MSSA fue del 36,7%. Sin embargo, a partir de 2003, se produjo una reversión de estos porcentajes. Al final del período analizado, el 55,2% de las infecciones fueron causadas por MSSA, mientras que el 36,2% contenía aislados de MRSA. Además, en el período analizado, la mayor prevalencia fue de SCC*mec* tipo II. **Conclusión:** estos datos sugieren un cambio epidemiológico en *S. aureus* a partir de materiales clínicos, con un cambio en el tipo prevalente de SCC*mec* y cambios en el perfil de sensibilidad antimicrobiana exhibido por los aislados. El personal clínico debe considerar estos hechos, centrándose en el tratamiento eficaz del paciente, la elección del tratamiento antimicrobiano adecuado y la implementación de medidas eficaces de control de infecciones.

Palabras Clave*: S. aureus. Epidemiología Clínica. MRSA. MSSA.*

INTRODUCTION

Staphylococcus aureus is a versatile pathogen, present in a wide variety of infections. These can be localized, both in soft tissues and in systemic infections, such as bacteremia. Due to the high potential to acquire antimicrobial resistance genes and high number of virulence factors, *S. aureus* has been prominent as a causative agent of infection in both hospital and community settings.[1]

Among *S. aureus* isolates, those with methicillin resistance (Methicillin-Resistant *S. aureus* - MRSA) are the one that, so far, are prevalent in infectious processes. Methicillin resistance occurs by the acquisition of the *mec*A gene, located in a mobile genetic element called the Staphylococcal Chromosome Cassette *mec* (SCC*mec*), which encodes a Penicillin-Binding Protein (PBP) with low affinity for beta-lactams called PBP2a.[2]

Multicenter studies have shown that the frequency and epidemiology of *S. aureus* has currently been changing in several geographic regions. Allied to this fact, MRSA isolates, commonly found in community settings, and called community-acquired Methicillin-resistant *S.*

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aureus (CA-MRSA), have been described in hospital settings. Similarly, isolates described as Hospital-Acquired Methicillin-resistant *S. aureus* (HA-MRSA) have been found in community settings. This interchange and emergence of infections caused by CA-MRSA and HA-MRSA has significantly altered therapeutic management.[3,4,5]

MRSA isolates, related to nosocomial infections, have often been described as multidrug resistant, i.e., besides to beta-lactam resistance, they are resistant to several other classes of antimicrobial agents, including macrolides, lincosamines, fluoroquinolones and aminoglycosides. In addition to the characteristic resistance profile, these isolates usually contain SCC*mec* elements types I, II or III. CA-MRSA, on the other hand, is routinely described as susceptible to most non-beta-lactam antimicrobial agents and carriers of SCC*mec* types IV and V.[6]

In Brazil, there are few data on the molecular epidemiology of MRSA and its relationship to antimicrobial susceptibility. Therefore, this study aimed to assess the distribution of *S. aureus* from these infections over the last 20 years according to antimicrobial resistance patterns and to establish a relationship with the SCC*mec* types circulating in a hospital in southern Brazil.

METHODS

A retrospective, observational, cross-sectional study was carried out with patients from a 431-bed Sentinel Network tertiary university hospital located in southern Brazil.

From January 2000 to October 2019, 9,949 cultures of blood, skin and soft tissues, bone fragments, respiratory secretions, cavitary fluids, urine, among others, positive for *S. aureus*, were assessed using the AGTA Healthcare Information System database, LABHOS® module, of the microbiology sector of the hospital's clinical analysis laboratory.

The identification of all isolates, as well as their antimicrobial sensitivity profile, and Minimum Inhibitory Concentration (MIC), according to Clinical & Laboratory Standard Institute (CLSI), was performed using the MicroScan WalkAway® (Beckman Coulter), Phoenix® (Becton, Dickinson) or Vitek2® (bioMérieux- Durham, NC, USA) automated systems, according to the study period, following the manufacturer's guidelines.

Vancomycin's MIC, for *S. aureus*, was determined by the Etest® method, using plastic strips containing the antimicrobial in a concentration gradient from 0.16 to 256 µg/mL, according to the manufacturer's recommendations.

Isolates that showed a MIC for oxacillin ≥ to 4 µg/mL were designated MRSA, whereas those with a MIC for oxacillin ≤ 2 µg/mL were considered MSSA. Isolates that showed a MIC for benzylpenicillin < 0.12 µg/mL were categorized as PSSA.

After phenotypic analysis, for convenience, 100 *S. aureus* isolates, from clinical materials, previously stored in the bacteria bank of the microbiology department, were selected for molecular testing.

Total DNA was extracted using alkaline method protocol,[7] and the genetic identification of *S. aureus* was confirmed using the coagulase (*coa*) and thermonuclease (*nuc*) genes.[8,9]

The *mec*A gene research as well as the typing of SCC*mec* elements was performed using a multiplex PCR protocol.[10]

MRSA strains type I (NCTC10442), type II (N315), type III (85/2082), type IV (JCSC4744), and type V (WIS) were used as quality control.

The most frequent MIC50 and MIC90 for antimicrobial agents, which correspond to 50 and 90% of the isolates, were calculated and a comparison between MRSA and MSSA was traced. Of the 9,949 isolates, for convenience, 2,904 isolates were selected for data analysis relating to MIC 50 and MIC 90.

Results of MICs for oxacillin, benzylpenicillin, ceftaroline, erythromycin, clindamycin, ciprofloxacin, daptomycin, levofloxacin, prulifloxacin, gentamicin, sulfamethoxazole-trimethoprim, rifampicin, linezolide, fusidic acid, teicoplanin and tigecycline, and for *S. aureus* were assessed by the Vitek2®, MicroScan WalkAway® or Phoenix® systems, depending on period, using panel for gram-positive microorganisms, obtained using the Observa® data management system.

Statistical Package for the Social Sciences (SPSS - IBM Corp., New York, USA) version 20.0 for Windows was used for statistical analysis. MRSA annual trend as well as MSSA prevalence were studied by linear regression using GraphPad Prism v.6.01 (GraphPad Software Inc., La Jolla, CA). Chi-square test was used for categorical variables, and Fishers Exact test, for continuous variables, when appropriate. Value ≤ 0.05 was considered statistically significant.

The study was submitted to the *Universidade Estadual de Londrin*a (CEP/UEL) Research Ethics Committee, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação* Ética) 78657317.0.0000.5231, The study was approved under Opinion 2.344.065 and respected all the ethical precepts of Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health.

RESULTS

The results of 9,949 cultures positive for *S. aureus*, performed from January 2000 to October 2019, were analyzed. It was found that the frequency of *S. aureus* was higher in male patients (6,128/9,949; 61.6%). About age, there was a range from 0 to 98 years, with a median of 45 years.

As for material collection, *S. aureus* was isolated most frequently in skin and soft tissues (3,392/9,949; 35%), respiratory secretions (1,698/9,949; 17%), and blood (1,575/9,949; 16%). The majority of patients, 6,696/9,949 (67%), were hospitalized, and of these, 23.2% (2,308/9,949) were in Intensive Care Units (ICU). As for the clinical outcome, 79% (7,860/9,949) of patients were discharged from the hospital, whereas 21% (2,089/9,949) eventually died.

The overall resistance to oxacillin was 45% (1,306/2,904), with MIC50 and MIC90 of 0.5 µg/mL and 4.0 µg/mL, respectively. For ceftaroline, although 100% of MSSA isolates were sensitive, 5% (145/2,904) of the MRSA showed resistance (MIC50/90, 1.0/1.0 µg/mL), as shown in Table 1.

Resistance to fluoroquinolones was found ranging from 4% (398/9,949), for ciprofloxacin, and 3% (298/9,949), for levofloxacin, in MSSA isolates, to 85% (8.456/ 9,949) and 89% (8,854/9,949), respectively, for MRSA isolates. However, for prulifloxacin, a new fluoroquinolone, no resistance rates were found.

The macrolide, lincosamine and streptogramin B resistance phenotype (MLSB) was more frequent for MRSA (85% - MIC50/90, 8/8 µg/mL) than for MSSA (30% -MIC50/90, 0.25/0.25 µg/mL).

As for vancomycin, intermediate resistance was seen in 7.5% of MSSA isolates (MIC50/90 1.5/2.0 µg/mL) and in 5% of MRSA isolates (5% - MIC50/90, 1.5/3.0 µg/mL). All isolates were sensitive to linezolid (MIC50/90, 2.0/2.0 µg/mL), daptomycin (MIC50/90, 0.25/1.0 µg/mL) and tigecycline (MIC50/90, 0.12/0.12 µg/mL) (Table 1).

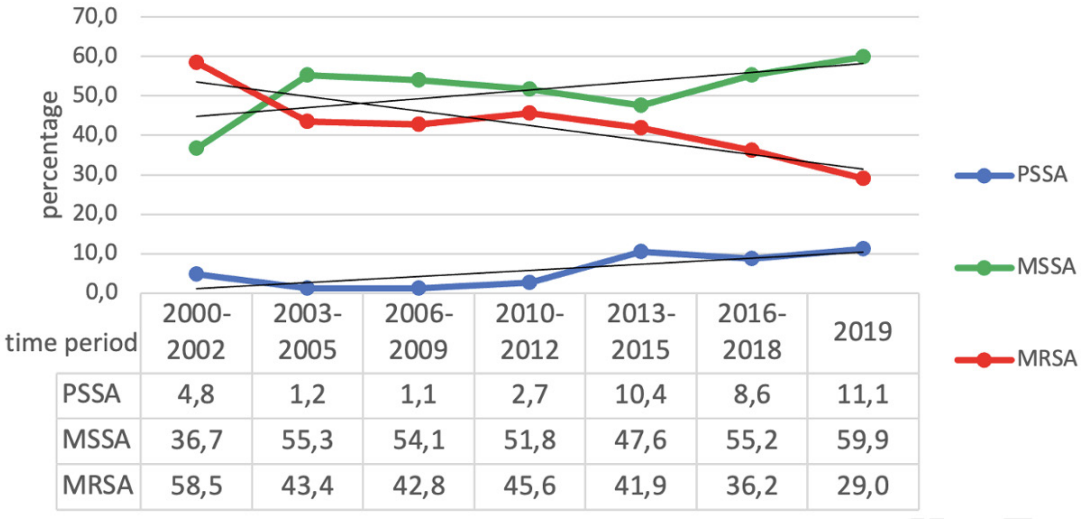
Between 2000 and 2002, a higher percentage of MRSA (58.5%) causing infectious processes was found in MSSA (36.5%). However, starting in 2003, a reversal in the frequency of *S. aureus* with respect to methicillin susceptibility was observed. MSSA infections increased to 59.9% in 2019, whereas those caused by MRSA reduced to 29%. Another important fact was the positive trend of PSSA isolates as promoters of the infectious process, which increased from 4.8% in 2000 to 11.1% in 2019 (Figure 1).

Between 2000 and 2002, a large proportion of isolates (88%) belonged to antibiotypes A and B. However, there was a significant reduction in microorganisms be-

Table 1. Minimum Inhibitory Concentration (MIC50 and MIC90) and percentage of resistance to antimicrobial agents of 2,904 S. *aureus* and vancomycin from 303 isolates identified in a hospital in southern Brazil from March 2012 to October 2019.

	MSSA (1.638)		MSSA (1.266)		
	MIC_{50}/ MIC_{90} (µg/mL)	R (%)	MIC_{50}/MIC_{90} (µg/mL)	R (%)	p-value
Benzylpenicillin	0.5/ 0.5	83	0.5/ 0.5	100	-
Oxacillin	0.25/ 0.5	00	4.0/ 4.0	100	< 0.05
Ceftaroline	0.25/ 0.25	00	1.0/ 1.0	5	< 0.05
Erythromycin	0.25/ 8.0	37	8.0/ 8.0	89	< 0.05
Clindamycin	0.25/ 0.25	30	8.0/ 8.0	85	< 0.05
Ciprofloxacin	0.5/ 0.5	4	8.0/ 8.0	85	< 0.05
Daptomycin	0.25/ 1.0	0	0.25/ 1.0	0	-
Levofloxacin	0.25/ 0.25	3	8.0/ 8.0	89	< 0.05
Prulifloxacin	0.5/ 1.0	0	0.5/ 0.5	0	-
Gentamicin	0.5/ 0.5	1	0.5/ 16.0	14	< 0.05
Rifampicin	0.5/ 0.5	1	0.5/ 0.5	8	< 0.05
Linezolid	2.0/ 2.0	0	2.0/ 2.0	0	-
Tigecycline	0.12/ 0.12	0	0.12/ 0.12	0	-
Fusidic acid	0.5/ 0.5	1	0.5/ 0.5	2	-
Teicoplanin	0.5/ 0.5	3	0.5/ 0.5	8	< 0.05
Sulfamethoxazole/trimethoprim	0.5/ 0.5	3	0.5/ 1.0	10	< 0.05
Vancomycin** (303)	1.5/ 2.0	7.5	1.5/ 3.0	5	-

*Caption: MSSA – methicillin-sensible Staphylococcus aureus; MRSA - methicillin-resistant Staphylococcus aureus; MIC - Minimum Inhibitory Concentration; R - antimicrobial resistance; **Minimum inhibitory concentration assessed by E-test® for 303 isolates.*



time period	2000-2002	2003-2005	2006-2009	2010-2012	2013-2015	2016-2018	2019
PSSA	4,8	1,2	1,1	2,7	10,4	8,6	11,1
MSSA	36,7	55,3	54,1	51,8	47,6	55,2	59,9
MRSA	58,5	43,4	42,8	45,6	41,9	36,2	29,0

Caption: PSSA – penicillin-susceptible Staphylococcus aureus; MSSA – methicillin-susceptible Staphylococcus aureus; MRSA – methicillin-resistant Staphylococcus aureus.

Figure 1. Temporal distribution of beta-lactam resistance for 9,949 *S. aureus* identified in cultures of clinical materials in a hospital in southern Brazil from January 2000 to October 2019.

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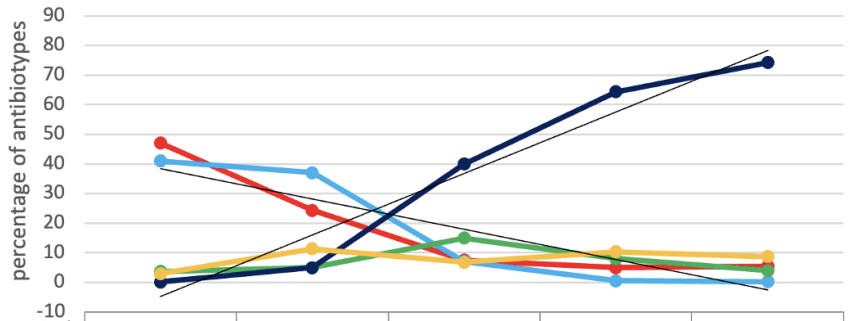
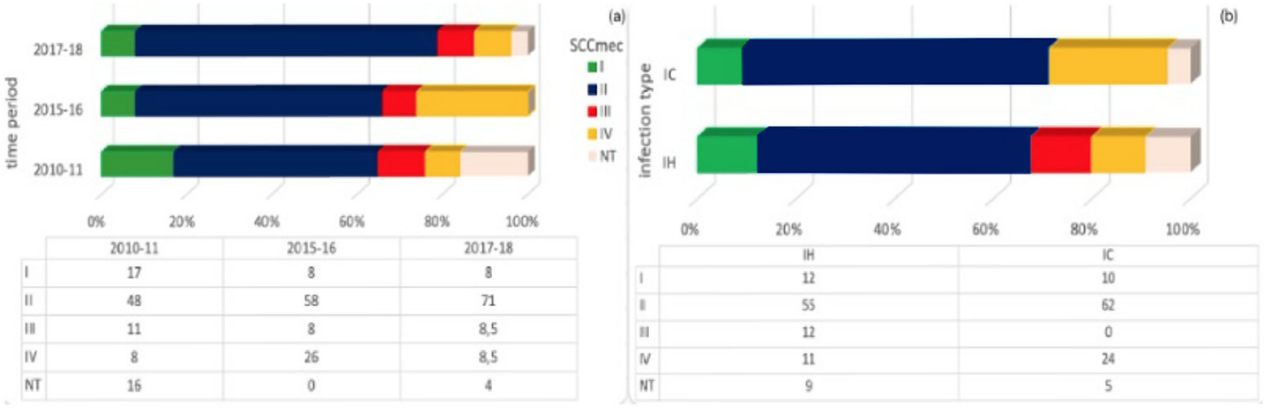


time period	2000-2002	2006-2009	2010-2012	2013-2015	2016-2018
MRSA A	47	24	7,5	5	6
MRSA B	41	37	7,1	0,6	0,3
MRSA C	4	5	15	8	4
MRSA D	0	5	40	64	74
MRSA G	3	11	6,8	10	9

Caption: A - sensitive to tigecycline and linezolid. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim, rifampicin; B - sensitive to tigecycline, linezolid and rifampicin. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim; C - sensitive to tigecycline, linezolid, rifampicin and sulfamethoxazole–trimethoprim. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin; D - sensitive to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, and gentamicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin and clindamycin; G - sensitive to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, gentamicin, erythromycin, ciprofloxacin and clindamycin. Resistant to oxacillin and penicillin.

Fugure 2. Temporal distribution of the most frequent antibiotypes for 3,517 clinical MRSA isolates from January 2000 to October 2019.



	2010-11	2015-16	2017-18
I	17	8	8
II	48	58	71
III	11	8	8,5
IV	8	26	8,5
NT	16	0	4

	IH	IC
I	12	10
II	55	62
III	12	0
IV	11	24
NT	9	5

Caption: HI - healthcare-related infection; CI - community-related infection; SCCmec types: I, II, III, IV; NT - non-typeable.

Fugure 3. Temporal distribution of SCCmec types identified among MRSA isolates from skin and soft tissues from January 2010 to May 2018 (a) and SCCmec elements identified among MRSA from healthcare-related infections and from community-acquired infection from January 2010 to May 2018 (b).

longing to these antibiotics, falling to 61% between 2006 and 2009 and just 1.2% in 2019 (Figure 2).

On the other hand, antibiotype D, which had not been identified before 2005, gradually started to increase in 2006, jumping from 5% to 74% in the last period of analyses, between 2016 - 2018. This antibiotype, currently, is the predominant.

Among the isolates selected for molecular analysis, the *mec*A gene was found in 86% (86/100) of assessed isolates. These were typed for SCC*mec* elements. Typing revealed SCC*mec* type II as the most frequent, being described in 48.8% (42/86) of the isolates. SCC*mec* types IV, I and non-typeable isolates were identified at lower frequencies, 13.9% (12/86), 11.6% (10/86) and 8.1% (7/86), respectively.

Comparing the types of SCC*mec* identified among MRSA related to hospital-acquired and community-acquired infections, type II was found to be the most frequent in both groups, with 36/65 (55.3%) and 13/21 (61.9%), respectively. The percentage of isolates with SCC*mec* type IV was higher in the group of community-origin infections (5/21; 23.8%) than in the group of hospital-origin infections (7/65; 10.7%). On the other hand, the proportions of SCC*mec* type I were very similar in both, community-origin infections (2/21; 9.5%) and hospital-origin infections (8/65; 12.3%).

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SCC*mec* type III was identified only in isolates from patients with hospital-origin infection (8/65; 12.3%) (Figure 3).

When assessing the distribution of identified SCC*mec* types over time, it is possible to see an upward trend in the frequency of isolates with cassette type II from 17/36 (48%) in the first period (2010-2011) to 15/26 (58%) in the second (2015-2016) and to 17/24 (71%) in the third (2017-2018) (Figure 3).

However, there was a decrease in the frequency of isolates carrying SCC*mec* type I from 16.6% (6/36), between 2010 and 2011, to 7.6% (2/26), between 2015 and 2016, and 8.3% (2/24), between 2017 and 2018. In the period analyzed, therefore, there is maintenance in the frequency of isolates carrying SCC*mec* type III and an increase in *S. aureus* carrying type IV from the first to the second period (8.3%; 3/36), in the first period (2010-2011) and (26.9%; 7/26) in the second period (2015-2016), decreasing to 8.3% (2/24) in the third period assessed (2017 to 2018).

A relationship was made between the antimicrobial resistance profile, antibiotypes, and SCC*mec* type presented by isolates from skin and soft tissues infections.

MRSA isolates that had SCC*mec* type I were characterized as belonging to antibiotype C in all samples analyzed (100%). Similarly, 90% of *S. aureus* with SCC*mec* type II belonged to antibiotype D, and 87.5% of type III belonged to antibiotypes A and B (Figure 4).

Among MRSA containing SCC*mec* type IV, this relationship was not so evident. Most strains were associated with antibiotype G (43%), which is characteristically sensitive to non-beta-lactam drugs; however, this genotype was also identified in more resistant isolates, such as antibiotypes A, B and C in 8% each, and D in 15% of the isolates analyzed.

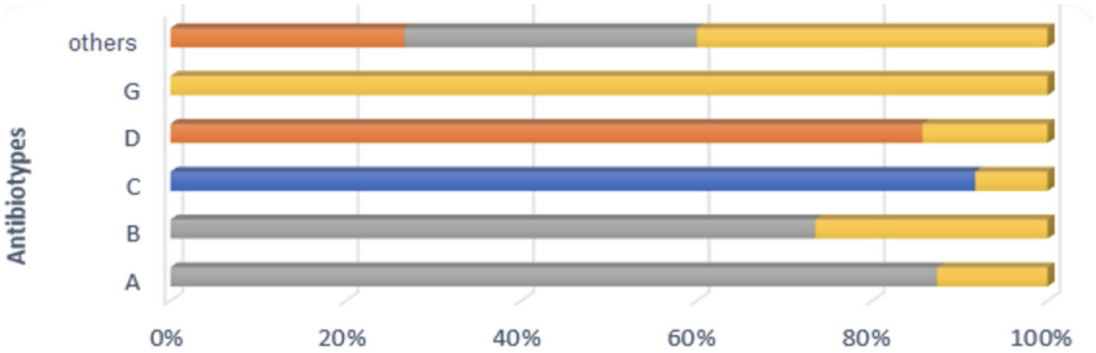
DISCUSSION

In this study, there was a change in the epidemiology of *S. aureus* over a 20-year period. Our data indicate a decline in the frequency of MRSA and a corresponding increase in MSSA as well as PSSA. In addition to this, there was evidence of a change in the SCC*mec* types of MRSA isolated from skin and soft tissues infections, and a relationship between the changing pattern of *S. aureus* resistance and molecular characteristics.

Studies have pointed to a change in the epidemiology of *S. aureus* in recent years.[11,12,13] Going against this statement, this paper reports a change, as it verified a decline in the proportion of MRSA, with a consequent increase in MSSA, which may indicate an important epidemiological change.

In a publication by the multicenter antimicrobial surveillance program, SENTRY, 191.460 *S. aureus* obtained from diverse sites were assessed over a 20-year period. The overall frequency of MRSA was 77,146 (40.3%) and ranged from 26.8% in Europe and 47.0% in North America. Methicillin resistance trend analysis over time showed that the proportion of MRSA among *S. aureus* isolates increased from 33.1% from 1997-2000 to 44.2% in 2005-2008 and then decreased to 42.3% from 2009-2012 and 39.0% from 2013-2016. Such data reinforce the results of this study and are in line with data from a study carried out in Germany with 146,561 isolates, whose data demonstrate a drop in the percentage of MRSA causing infectious processes.[12, 13.]

There was a reduction in the antimicrobial resistance profile exhibited by MRSA isolates between 2010 and 2015. Resistance to last-line antimicrobial agents,



	A	B	C	D	G	outros
I	0	0	100	0	0	0
II	0	0	0	90	0	10
III	62,5	25	0	0	0	12,5
IV	9	9	9	15	43	15

Caption: I, II, III, IV- types of SCCmec; A - sensible to tigecycline and linezolid. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim, rifampicin; B - sensible to tigecycline, linezolid and rifampicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin, clindamycin, gentamicin, sulfamethoxazole–trimethoprim; C - sensible to tigecycline, linezolid, rifampicin and sulfamethoxazole–trimethoprim. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin, clindamycin, gentamicin; D - sensible to tigecycline, linezolid, rifampicin, sulfamethoxazole - trimethoprim, and gentamicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin and clindamycin; G - sensible to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, gentamicin, erythromycin, ciprofloxacin and clindamycin. Resistant to oxacillin and penicillin.

Fugure 4. Correlation between antibiotypes and SCCmec types for 86 MRSA isolates obtained from skin and soft tissues from January 2010 to May 2018.

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including ceftaroline, daptomycin, linezolid, tigecycline, vancomycin, and teicoplanin, remained almost non-existent.[12] Concerning the time trend of MRSA, we found higher resistance rates for clindamycin, ceftaroline, and vancomycin, which may be explained by sampling divergence.

In a study from Wisconsin state, USA, that assessed 309 clinical isolates of *S. aureus* collected from microbiology laboratories, as part of another multicenter surveillance study, resistance to penicillin was reported in 86% of isolates, to methicillin, in 56.8%, to levofloxacin, in 25%, and to clindamycin, in 20.5%. In addition, MRSA was found to have higher resistance rates for clindamycin, erythromycin and levofloxacin when compared to MSSA isolates.[14]

Almost all *S. aureus* demonstrated sensitivity to ceftaroline, dalbavancin, telavancin, and vancomycin (MIC90 of 1 µg/mL). The proportion of MRSA decreased continuously from 16% in 2010 to 10% in 2015. Interestingly, according to studies using *S. aureus* isolated from blood stream infections in Canada and Finland, there was a reduction in penicillin resistance and decrease in MRSA isolates, a fact also observed in this study.[15,16]

Also according to another study, treatment with penicillin in patients infected with penicillin-sensitive isolates has some advantages, such as low spectrum of action, low cost, and less association to secondary infections, as *Clostridium difficile* infection. They also offer advantages in terms of pharmacokinetics and pharmacodynamics, since they have a lower MIC compared to wild-type strains than cloxacillin and cefazolin, requiring a lower dose to reach an effective therapeutic concentration.[15]

On the other hand, MRSA carrying community-acquired SCC*mec* type IV (CA-MRSA) has been frequently reported in hospital-acquired infections. *Staphylococcus aureus* has been noted as a frequent infectious agent in outpatients; however, a modification in the epidemiology of these infections has been occurring in recent years.[17, 18]

With this epidemiological shift in mind and its relationship to the antimicrobial sensitivity profile in isolates from bloodstream infections, a study with 792 patients with MRSA infections, admitted in a hospital in Japan, between 2010 and 2016, was investigated. The authors found that isolates carrying SCC*mec* type II, characteristic of HA-MRSA, prevalent in 2010, were replaced by SCC*mec* type IV MRSA related to CA-MRSA. Moreover, according to them, there was a change in the sensitivity profile, supporting the molecular finding. Importantly, in this study, there was also an increase in the frequency of SCC*mec* type IV MRSA isolates.[19]

In another study, 45 MRSA isolated from patients admitted to ICUs between 2005 and 2010 were assessed. All isolates tested showed resistance to clindamycin, erythromycin, and levofloxacin. Regarding SCC*mec* elements, isolates showed types III (66.7%), II (17.8%), IV (4.4%), and I (2.2%). In this study, the isolates with SCC*mec* type III were related to the Brazilian endemic clone (ST239, CC8, SCC*mec* type III), predominant between 2005 and 2007, whereas the USA100/CC5/SCC*mec* II strain, which emerged in 2007, was more frequent in recent years.[20]

In our study, differently, SCC*mec* type II conductor isolates were the most frequent throughout the assessed period, with type III, throughout the assessed period, decreasing in frequency. This change in the prevalent clone as well as decrease in the frequency of isolates with SCC*mec* type III is in line with what was reported.[21]

Other authors have reported that similar events, such as emergence, expansion and decline of one MRSA clone with replacement by another clone, have occurred repeatedly in the MRSA evolutionary process. Furthermore, there is the report of CA-MRSA clones will likely become dominant in hospitals due to the fact that there is an expanding reservoir of MRSA in the community and its continued influx into the hospital.[22,23]

In a study conducted between 2014-2015, it was observed that 27% of *S. aureus* bloodstream infections were caused by isolates carrying SCC*mec* type IV related to the community ST80 clone. This finding indicates that clones of community origin, when within hospital settings, behave more like HA-MRSA and can cause more severe infections with more difficult treatment.[24,25]

Furthermore, the potential for these isolates to become multidrug resistant in healthcare settings is a worrisome factor. In fact, the authors identified an ST80-IV isolate resistant to seven different classes of antimicrobial agents, such as fluoroquinolones, macrolides, clindamycin, tetracyclines, fusidic acid, rifampin, and gentamicin.

With these 20-year analyses, we observed an increase in the population of PSSA and MSSA as a cause of infections, and a consequent reduction in MRSA. Moreover, the antimicrobial sensitive prefile has changed. Antimicrobial resistance is a life mechanism that needs constant monitoring and knowledge of local epidemiology for institutions of the best clinical therapies.

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Felipe Crepaldi Duarte: contributed to article conception, design, analysis and writing. **Livia Marina Finger:** contributed to article conception, design, analysis and writing. **Renan Hayami Obata:** contributed to article conception, design, analysis and writing. **Diogo Cesar Carraro**: contributed to article conception, design, analysis and writing. **Marcia Regina Eches Perugini:** contributed to article planning, design, review and final approval. **Philipe Quagliato Belinati** contributed to article planning, design, review and final approval.

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