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Infections Caused By *S. aureus* MRSA and Natural Antimicrobial Mechanisms to Reduce These Contaminants

Raquel Soares Casaes Nunes[1*], Rafaela Assumpção[2], Brenda Silva de Lima[3], Ynis Cristine de Santana Martins Lino Ferreira[4]

[1]Faculty member of the Institute of Animal Health and Production of the Federal Rural University of Amazon, Belem. To Brazil
[2]Master's student in postgraduate course at the Federal University of Amazonas
[3]Graduate student of the Natural Resources Management course, University Federal Rural of Amazon, Campus Tomé Açú/ Brazil
[4]Faculty member of the Instituto Ciberespacial da Universidade FederalRural of Amazon, Belém/Brazil

Abstract: The advance of *S.aureus* infections, strain/clone identification methods prevalent in hospitals and resistant to antimicrobials needs to be rapidly effective due to the shortage of new antimicrobial agents. ***Objective:*** of this work is to perform a literature review on the epidemiology of methicillin-resistant strains of S.aureus in circulation in Brazil. An integrative literature review was used, which allows summarizing previous research and obtaining general conclusions from them to analyze the scientific knowledge on the subject to be investigated. ***Methodology*:**The databases consulted were Latin American and Caribbean Health Sciences Literature (LILACS), International Health Sciences Literature (PubMed), Scientific Electronic Library Online (SCIELO). ***Literature Review*:** dissemination in Brazil are: Brazilian epidemic clone (ST239/SCCmecIII) and the Pediatric clone (USA400), are in circulation in hospitals in Brazil, these present a genetic pattern of virulence factors (SCC mec I to IV), PVL proteins, among others, differentiated between them and the Brazilian region with more studies is the Southeast region. ***Conclusion*:** Studies are needed to provide greater knowledge about the molecular epidemiology, evolution and antimicrobial resistance of methicillin-resistant S. aureus clones in Brazil, especially in the North and Northeast regions of the country.

Keywords: *S.aureus*; MRSA; clones.

Research Paper

***Corresponding Author:**
Raquel Soares Casaes Nunes
Faculty member of the Institute of Animal Health and Production of the Federal Rural University of Amazon, Belem. To Brazil

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INTRODUCTION

Antimicrobials are substances of natural or synthetic origin commonly used in this environment because they act on microorganisms by inhibiting their growth or causing their destruction, being used prophylactically and/or therapeutically, constituting a pharmacological advance of paramount importance and widespread use. The emergence of multidrug-resistant microorganisms (MMR) represents a global challenge worldwide, since therapeutic options are limited, resulting in thousands of deaths. In addition, there is an ongoing shortage of new and effective antimicrobial agents, especially against methicillin-resistant bacteria. This resistance is commonly found in hospital infections, which are considered more serious in the Intensive Care Unit (ICU), where patients dependent on intensive life support are treated (Carvalho *et al*., 2021).

Resistance of S. aureus to methicillin or oxacillin (ORSA/MRSA) is due to the acquisition of the mecA gene that encodes modified PBPs called PBP2a or PBP2', which have reduced affinity for all β-lactam antibiotics, although the MRSA phenotype is widespread, some strains are sensitive to these antimicrobials, the *S. aureus* sensitive to methicillin/MSSA (Silva, 2011; Aguayo-Reyes *et al*., 2018). Antimicrobial natural alternatives are being studied such as tea tree oil and is produced by steam distillation of the leaves and terminal branches of Melaleuca alternifolia and is currently used in traditional medicine as a topical antiseptic and anti-inflammatory agent and widely formulated in many cosmetic and personal care products (Edmondson *et al*., 2011)

Tanacetum vulgare is a perennial, erect, aromatic species, native to humid lands in Europe and cultivated in Brazil. The phytochemical content varies with plant growth and development, being higher in the leaves of plants in vegetative growth and beginning of flowering, increasing their concentration according to

light intensity and water availability. However, It is not frequently studied about the activity of Tanacetum vulgare oil against MMR, as well as the potential interaction (ie, restoring antibiotic sensitivity) between beta-lactams and *Tanacetum vulgare* oil (TTO) for S. aureus MRSA. It difficulty, management, prevention of nosocomial infections, as a starting point for developing measures to prevent and control nosocomial infections, it is important to identify the prevalent infections in this sector. The objective of this study was discussed around to bibliographical review about the occurrence of *S. aureus* in nosocomial infections is of it importance in health public, because it considered endemic bacteria antimicrobial resistent in hospitals.

METHODOLOGY

This paper discusses *literature review* as a methodology for conducting *research* and offers an overview of different types of *reviews.*The realization of this research followed some basic steps:

1. Elaborate the theme of the study;
2. Carry out a bibliographical research on: a) the antimicrobial resistance of *Staphylococcus aureus* to methicillin (b) the importance of S. aureus for Public Health; c) Natural substances with antimicrobial action against *S.aureus*; d) Epidemiology of diseases caused by *S.aureus*;
3. Organize the collected data;
4. Interpret and evaluate the results of the study;

Articles in Portuguese and English were considered for review. There was restriction regarding the year of publication of the studies (2012-2023). The databases consulted were Latin American and Caribbean Health Sciences Literature (LILACS), International Health Sciences Literature (PubMed), Scientific Electronic Library Online (SCIELO). The terms used in Portuguese and English were: “Staphylococcus”; “Staphylococcus aureus”; “molecular epidemiology”; “methicillin”; “antimicrobial resistance”; “MRSA”; “epidemic clones”; “Public Health”, “Brazil”. Keywords were paired between groups using search operators (quotes, parentheses, “AND” and “OR”)

Methicillin-resistant S.aureus in regions of Brazil

Staphylococcus aureus is a causative agent of bloodstream infections - related to catheters and skin and soft tissue infections, but it is also one of the most frequent agents of pneumonia associated with mechanical ventilation. Oxacillin-resistant *Staphylococcus aureus* (MRSA), although not more pathogenic than oxacillin-sensitive isolates, can cause large and costly epidemic infections that are difficult to treat and control. MRSA is the term used to refer to S. aureus with intrinsic resistance to methicillin, oxacillin, cephalosporins, imipenem and aminoglycosides (De Carvalho *et al.*, 2019).

When colonization occurs by multidrug-resistant isolates, it becomes a risk factor both for the colonized person, therefore, it is of great clinical importance to identify which professionals are harboring multidrug-resistant clones that are sources of nosocomial infection (Stefani *et al.*, 2012). Approximately 30–94% of healthcare workers carry methicillin-resistant Staphylococcus aureus (MRSA) in their nasal passages, indicating that they can serve as important reservoirs and potential disseminators of these bacteria for non-colonized susceptible patients, in addition to being a source of nosocomial infections. (Paterson *et al*, 2014; Figueiredo & Ferreira, 2014).

S. aureus infections include simple folliculitis, impetigo, boils, carbuncles, bronchopneumonia, endocarditis, osteomyelitis, pyoarthritis, metastatic abscess formation, staphylococcal meningitis, toxic shock syndrome, and can also produce poisoning due to the elaboration of exotoxins during growth in contaminated food (Koneman *et al*., 2001).

In the city of Manaus, state of Amazonas in Brazil, there is still no data produced regarding the prevalence and/or levels of antimicrobial resistance to Gram-positive bacteria (MRSA/STs) that colonize health professionals. 239 strains of S. aureus were isolated, among which 232 were submitted to susceptibility tests: 44.0% (102/232) were resistant to oxacillin, with a prevalence rate of 15.5%. In the study by Furtado *et al*., (2019), the Staphylococcus aureus strains found showed high rates of clindamycin resistance (57.4%) and decreasing levels of resistance to oxacillin over time. Among the Gram-positive cocci (136; 48.7%) Staphylococcus spp. coagulase-negative (20.1%), with Staphylococcus hominis and Staphylococcus haemolyticus being the most frequent (Furtado *et al*., 2019).

Silva and Porcy (2016), in their studies, identified 119 positive samples for Staphylococcus aureus, approximately 39.5% of which were resistant to methicillin at a hospital in Macapá in 2015,. As a form of prevention, the authors suggest the practice of hand washing, especially for the nursing team, as it can minimize the transmission of the microorganism among nursing professionals as well as among patients. Resende et al., 2013, found in their study that twenty-three of the 39 (59%) bacterial species were multiresistant. A relevant prevalence of multidrug resistance was found for S. aureus (80%) in 34 patients.

Biofilms

Staphylococcus aureus biofilms represent a unique microenvironment that directly contributes to bacterial fitness in hospital settings. Accumulation of this structure in implanted medical devices has often caused the development of persistent and chronic infections associated with *S. aureus*. Ica-independent biofilms are composed of a variety of bacterial products

and modulated by a regulatory network, so biofilm composition can vary between *S. aureus* strains. Biofilms are produced by several bacterial species and composed of different structural components, subpopulations of drug-refractory cells with distinct physiological characteristics may arise and result in therapeutic failures in patients with recalcitrant bacterial infections.

Virulence factors: Horizontal transfer of mec A genes

The combination of the complex class mec gene and the ccr gene allotype has been used for genetic typing of SCCmec into types I–XIII. Some types of SCCmec can be transferred between Staphylococcus species. SCCmec type IV, for example, can be found both in *S. aureus* and in *Staphylococcus epidemidis*. In Latin America, an incidence of 90% of MRSA has already been recorded in Chile (WHO, 2014). In Brazil, there are no randomized data on the incidence, only from some states such as Rio de Janeiro, where a rate of 46% of S. aureus samples as MRSA was observed (Bride, 2019). Some authors estimate that the incidence in the country is around 60% (Rossi, 2011).

This resistance was made possible by the acquisition of the mecA gene, which encodes a modified penicillin binding protein, PBP2a, with lower affinity to the beta lactam ring of antimicrobials of this class, allowing bacterial cell wall synthesis to continue. This gene is part of the staphylococcal mec chromosomal cassette (SCCmec), a mobile genetic element and island of resistance, and its acquisition by Methicillin-susceptible S. aureus (MSSA) makes it an MRSA (O'gara, 2017). In addition to resistance to beta-lactams in general, some SCCmec may also contain genes for resistance to aminoglycosides, tetracycline and metals such as Cadmium and Mercury. It is also common for MRSA strains to present other resistance mechanisms in addition to SCCmec,

Multidrug resistance to methicillin among several species *of S.aureus* may occur due to horizontal transfer of the *mec* gene, favoring the emergence of resistance. These results direct attention to hospitals and possibly to the region to implement actions to reduce the pathogenic clonal strains of *S. aureus* and *S. epidermidis*. Microbial resistance monitoring programs are important to prevent nosocomial infection outbreaks and the spread of pathogenic clonal strains.

Virulence factors: Accessory regulatory system agr

In *S. aureus*, the *agr* system is responsible for the balance between the expression of virulence factors in the colonization and invasion phases, and it has been suggested that the activation of this system implies the passage of *S. aureus* from a commensal phase, involved in adhesion and colonization, to an invasive phase of a pathogenic nature (Le and Otto, 2015). The *agr* locus was initially described as a regulatory element in the expression of extracellular proteins associated with virulence (Peng *et al*., 1988; Recse *et al*., 1986).

The *agr* system is a quorum sensing system, that is regulation of gene expression occurs through cell-cell communication and is dependent on cell density50. In this sense, there is an initial phase of low cell density and low expression of agr and adhesives. After this phase, the increase in cell density occurs and induces the expression of agr, which in turn causes the repression of the expression of adhesins that promote the degradation and consequent invasion of tissues (Liu, 2009). Activation of *agr* expression occurs in response to bacterial density, using a signaling pathway that is activated by an autoinductive oligopeptide (AIP)

Virulence factors: Panton-Valentine leukocidin (PVL)

S. aureus has a more complex genome than other non-pathogenic staphylococci and its virulence factors are largely encoded in mobile genetic elements such as pathogenicity islands, plasmids, transposons, insertion sequences and phages. S. aureus islands of pathogenicity (SaPI) are approximately 14 to 17 kb in size and usually consist of two or more genes encoding superantigens such as toxic shock syndrome toxin (tsst) and shock-associated enterotoxins B and C toxic and food poisoning.

SaPI are mobilized with high frequency and integrated through bacteriophages into the chromosome of S. aureus.One of the virulence factors is the leukocytotoxic activity of a bacterium that allows it to survive in the early stages of an infection. Panton-Valentine leukocidin (PVL) was described in 1894 by Van de Velde, being associated with SSTIs for the first time in 1932 by Panton and Valentine. In general, PVL is associated with infections caused by CA- MRSA, namely SSTIs and necrotizing pneumonia, can however also be found in MSSA strains (Shallcross *et al*., 2013. Löffler *et al*., 2013)

This protein is a leukotoxin composed of two subunits designated LukS-PV and LukF-PV. This toxin causes the lysis of neutrophils with the formation of pores in the cell membrane. Neutrophil lysis is mediated by binding of PVL to C5aR complement receptors (Spaan *et al*., 2013). The ability of a strain to express PVL depends on the presence of the luk-PV operon, which contains the lukS-PV and lukF-PV genes, which can be found integrated into the S. aureus chromosome through bacteriophages; Nawrotek *et al*., 2018)

Epidemiology and Distribution of hospital-acquired (HA-MRSA) and community-acquired (CA-MRSA) and methicillin-resistant *S. aureus* clones circulated in Brazil.

In the 1980s, the first cases of MRSA infection in the community were reported in specific population

groups such as intravenous drug users, residents of health institutions and patients with frequent contact with health institutions. Although these infections occurred in the community, they were considered infections associated with health care, due to the presence of risk factors for acquiring MRSA (Saravolatz *et al*., 1982).

Later years, the appearance of MRSA strains in the community was observed, which had genotypic and phenotypic characteristics distinct from the first ones (Lakhundi and Zhang, 2018; Turner *et al*., 2019). Thus, MRSA strains were differentiated into hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) (Turner *et al*., 2019).

There is a difference between the HA-MRSA strains, these are mostly associated with the virulence of *Staphylococcus aureus* associated with invasive infections, they present symptoms in patients such as bacteremia, pneumonia, mainly risk in patients with intravenous catheter, premature babies and immunocompromised patients present in the hospital environment resulting in increased morbidity, mortality, while CA-MRSA strains are mainly associated with skin and soft tissue infections (Turner *et al*., 2019). Furthermore, species of S.aureus HA-MRSA present genetic characteristics SCC mec I, II, III while CA-MRSA can be characterized by the presence of SCCmec types IV, V, VI and VII and by the presence of PVL (Millar *et al*., 2007; Stefani and Goglio, 2010).

Currently, a new change in the epidemiological of strains CA-MRSA has been observed with the migration of these pathogens to the hospital environment, adding to the traditional nosocomial multidrug-resistant clones. CA-MRSA infections have been frequently reported in hospitalized patients, associated with risk factors for infections in health institutions (MILLAR *et al*., 2007,DE MIRANDA *et al*., 2007). The literature describes that one of the genetic differences between community (CA-MRSA) and hospital isolates (HA-MRSA) is the presence of PVL cytotoxin genes in CA-MRSA (Millar *et al*., 2007), that is, PVL would be closely related to SCCmec types IV and V. However, Brust *et al.* (2013) observed, in a study with 16 isolates of *S. aureus* from Rio de Janeiro, the presence of the lukF-PV and lukS-PV genes associated with SCCmec type III in all investigated *S. aureus.* However, according to Carvalho *et al*., 2019, there is no specificity for the genetic content of HA-MRSA or CA-MRSA. There is no obvious pattern for the distribution of virulence genes and none virulence markers used differentiate HA-MRSA from CA-MRSA (De Carvalho *et al*., 2019).

Epidemic and pandemic clones

The main MRSA clones are: Clone Epidemic Brasileiro (BEC), USA100 (clone New York/Japan, NY/J, HA-MRSA), USA400 (CA-MRSA), USA500 (clone Iberico, HA-MRSA), USA600 (clone Berlin, BC, HA-MRSA), USA800 (Pediatric clone, PC, CA- and HA-MRSA) and USA1100 (Oceania clone Southwest Pacific, OSPC, CA-MRSA) (Deurenberg and Stobberingh, 2008; Rodríguezneriega *et al*., 2010). In Brazil, the nosocomial strains ST5-SCCmecI (Cordobes/Chileno clone), ST5-SCCmecIV (USA800; pediatric clone), and ST5-SCCmecII (USA100; NY/Japan clone) prevail in some hospitals (De Becker *et al*., 2012, Caiaffa-Son *et al*., 2013). Furthermore, MRSA isolates of the ST239-SCCmecIII lineage (Brazilian epidemic clone - BEC) are still predominantly detected in several regions of the country (Caboclo *et al*., 2013; Rodrigues *et al*., 2013).

The BEC clone demonstrates some characteristics that can provide a great capacity for worldwide dissemination, such as greater ability to produce biofilm, adhere and invade airway epithelial cells (Schuenck et al., 2012). This is responsible for a large number of HA-MRSA infections in other countries in South America and on other continents (Rodríguezneriega *et al.*, 2010). Chamon *et al.*, (2017), observed the complete replacement of BEC/ST239/SCCmecIII by other strains in both hospitals investigated in the study, suggesting a change in the epidemiological profile of MRSA in Brazilian hospitals. According to Carvalho *et al*., (2019) several studies report a significant increase in the presence of clones such as USA400 (ST1/CC1/SCCmecIV) and the Pediatric clone (USA800/ST5/CC5/SCCmecIV) in hospitals in Brazil.

Clone USA400 (ST1-SCCmec IV) is a CA-MRSA involved in skin and soft tissue infections in the US and Australia and is rarely found in Europe and South America. CA-MRSA infections are of great concern because the organism does not respond to beta-lactam antimicrobial agents commonly used to empirically treat many community-acquired infections (Rossato *et al.*, 2018). The first case of severe infection (generalized osteomyelitis generation) caused by CA-MRSA in Brazil was reported in 2009. The recovered isolate was related to clone USA1100 (ST30 strain) and showed susceptibility to all non-β-lactam antibiotics (Rozenbaum *et al.*, 2009). Shortly thereafter, a rare and severe case of osteomyelitis, it has also been described in the city of Rio de Janeiro, Brazil, in a previously healthy child (de Araújo *et al*., 2010).

The CC30 strains appear to employ virulence mechanisms that are distinct from the toxin-based mechanisms commonly seen in mouse infection models, causing mortality not through aggressive damage to the host, but through their ability to persist in the infected organism. This demonstrates that different sets of virulence factors can cause disease through different mechanisms, not always apparent in experimental models of infection. This should be taken into account when designing new therapies, and it is

probably more useful to think of different strains of *S. aureus* as being able to adapt to different host-specific conditions (Monecke *et al*., 2011).

Single nucleotide polymorphism (SNP) studies of ST5 MRSA isolates suggest that their spread probably occurred by multiple SCCmec insertions in different methicillin-susceptible S. aureus (MSSA) strains in different regions of the world and the spread of an ST5- MRSA in a wide geographic area (Nübel *et al*., 2008). On the other hand, phylogenetic evidence, also based on SNP analyses, suggested intercontinental spread of isolates from the ST239-SCCmecIII lineage (Harris *et al.*, 2010; Gray *et al*., 2011).

In Brazilian hospitals, the predominant MRSA strain was known as an endemic clone (BEC/ST239), and was replaced by the New York/Japan strain among BSI isolates (USA100/ST5 or ST105) (Cortês, *et al.*, 2018) . Lately, the emergence of USA1100/ST30, a CA-MRSA strain, has been detected in Brazilian hospital environments (Carvalho, 2019). In Brazil, the pandemic clone USA300/ST8/SCCmecIV and USA300-Latin American variant (LV)/SCCmecIV are frequently rare strains. These strains could carry the Panton-Valentine leukocidin genes and are considered hypervirulent, as once found in the environment they spread easily, resulting in infections with high mortality rates (Dos Santos *et al.*, 2021).

According to researchers, Jackson *et al.*, 2011, observed that each type of strain is characterized by a distinct consensus repertoire of virulence genes, although some clones show similarity between them. The CEB clone presents exotoxins (*eta, etb and tsst*), genes involved in adhesion and evasion of the immune system (*sak, aur, scn, lukD, lukE, hlb, hlgA, hlgB, hlgC, ica, spla, splB splA, splB and splE*) and absence of enterotoxins. The CEB differs from the pediatric clone in that it is associated with the cna, fnbA, fnbB genes and the ica locus, while the Pediatric Clone usually has fnbA and the ica locus (Schuenck *et al.*, 2012).

Ribeiro *et al.*, (2005) described the first cases of community-acquired MRSA infection in South America. Samples were obtained between June 2002 and September 2003 at the clinics of two different hospitals in the city of Porto Alegre, Rio Grande do Sul, Brazil. Patients were from the community and did not have risk factors associated with MRSA isolation, history of hospitalization. All isolates carried SCC mec type IV and exhibited patterns identical to clone ST30 (clone Oceania Southwest Pacific).

In 2014, 178 health professionals working in a pediatric hospital were evaluated. It was observed that the colonization rate for S. aureus was 33% and for MRSA 5.1%. Prolonged contact between nursing staff and patients was found to be a risk factor for MRSA colonization. The five major MRSA strains (CC5, CC8, CC2, CC45, and CC30) circulate internationally and cause the majority of MRSA-associated infections worldwide. (Diaz, 2016).

In the study by Furtado and researchers, 2019 genetic characteristics were identified, the same clonal types of MRSA (ST5, ST15) were also detected in the same sample site (nasopharynx and lab coat) in health care workers at the Fundação de Hematologia e Hemoterapia do Amazonas – HEMOAM- (Furtado *et al*., 2019). Some virulence factors are present in the species to overcome host immunity, contributing to the successful development of this pathogen (BIEN, *et al.*, 2011). More research in regional hospitals and in the community is needed for a more accurate view of the epidemiological distribution of these clones in the Brazilian region.

Antimicrobial resistance and nosocomial infection commission

One of the world's main concerns regarding the rational use of drugs is related to antimicrobials. The increase in bacterial resistance to various agents in controlling infections and contributes to increased costs in the health system. Monitoring the consumption of antimicrobials can help assessments at different levels, such as prescribing habits, introduction of new drugs and variation in the local bacterial flora. The use of antimicrobials varies considerably from hospital to hospital, in different wards, specialties, etc. Thus, the consumption characteristics of an organ should be broadly studied, in order to establish action priorities (Furtado *et al*., 2019)

Furtado *et al.*, 2019, analyzed the variations of antimicrobials used in the wards and in the ICU of a university hospital in the North Region of Brazil over five years (2012 to 2016). Currently, the hospital infection control commission (CCIH) monitors multidrug-resistant bacteria and the necessary preventive measures. In addition, molecular protocols are being used to identify multidrug-resistant pathogens to expand treatment. Some virulence factors are present in the species to overcome host immunity, contributing to the successful development of this pathogen (BIEN, *et al*., 2011). More research in regional hospitals and in the community is needed for a more accurate view of the epidemiological distribution of these clones in the Brazilian region. Currently, the hospital infection control commission (CCIH) monitors multidrug-resistant bacteria and the necessary preventive measures. In addition, molecular protocols are being used to identify multidrug-resistant pathogens to expand treatment.

Antimicrobial action of essential oils against *Staphylococcus aureus*

Antimicrobial natural methods such as essential oils (EOs), are volatile, natural and aromatic liquids that can be extracted from different parts of

plants (mainly leaves and flowers) with antibacterial and anti-inflammatory properties. Given their broad-spectrum antimicrobial activity, along with the possibility of restoring susceptibility to antibiotics, several efforts have been made to consider the use of EOs for the treatment of a wide range of infections. structural integrity of the cell membrane, leading the bacterial cell to death, with Gram-positive bacteria being more susceptible than Gram-negative ones (Xiao *et al*., 2020).

Tea tree oil (Melaleuca alternifolia) on the decolonization of positive wounds for methicillin-resistant *Staphylococcus aureus* and its influence on the decolonization of positive wounds for *Staphylococcus aureus* MRSA. Melaleuca alternifolia essential oil, tea tree oil, has proven antimicrobial and anti-inflammatory properties, is useful in methicillin resistant Staphylococcus aureus (MRSA) decolonization regimens and is reputed to have 'wound healing' properties , more data are needed to support these indications. (Falagas, *et al.,* 2016)

In the study by Xiao *et al.,* 2020, among the vegetable oils used by researchers to eradicate persistent S. aureus in vitro were *Oreganum vulgare, Santalum spicatum, Amycris balsamifera* with MIC of 0 (µg/ mL), and Cymbopogon martin, Lemongrass (flexuosus 0.015MIC (µg/ mL/%), found in a drug combination study with essential oil (oregano) and antibiotics that some in vitro combinations, such as oregano plus quinolones or rifampicin, were effectively effective in eliminating *S. aureus* (Xiao *et al*., 2020).

RESULTS AND DISCUSSION

The 26 articles were selected with the theme suggested in the study (Table 1). Figure 1 below shows the result of the correlation between the keywords found in the 26 articles selected below. Figure 2 analyzes the correlation between the 60% of terms in the most relevant title and abstract in the study.

Tabela 1: Artigos de revisão selecionados na Revisão Bibliográfica

Bibliographic Review	Thematic	Authors	Bibliographic Review	Thematic	Authors
Antimicrobial resistance and nosocomial infection commission	Antimicrobial resistance in hospitals	Otter, and Frenc, 2012; Furtado *et al.,* 2019	**Virulence factors: Accessory regulatory system *agr***	S. aureus, the The function of the agr system, its role in the expression of virulence factors and colonization,invasion bacterial	Le and Otto, 2015; Brust *et al*., 2014
Methicillin - resistant *S.aureus* in regions of Brazil , emphasis on the North region	S. aureus MRSA and Status of reports on S.aureus MRSA in regions of Brazil	De Carvalho *et al.,* 2019 Aries, 2017; Carvalho, 2016; Silva E Porcy, 2016; Carvalho and Fontes, 2014	**Virulence factors: Panton-Valentine leukocidin (PVL)**	PVL protein is associated with infections caused by S.aureus	Shallcross *et al*., 2013; Löffler *et al.,* 2013; Dos Santos *et al*., 2021
Virulence Factors Related to Methicillin Resistance: Horizontal Transfer of Mec A Genes	*SCC mec* in *S.aureus* and its transfer mecA gene in Staphylococcus species.	Figueiredo and Ferreira, 2014; Paterson *et al.,* 2014	**Epidemiology and Distribution of HA-MRSA and CA-MRSA strains and epidemic|pandemic methicillin-resistant *S. aureus* clones**	Genotypic characteristics of S.aureus HA-MRSA, CA-MRSA Worldwide S.aureus clones brazilian clones	Stefani and Goglio, 2012; Caiaffa-Filho *et al.,* 2013; Becker *et al.* 2012; Cabloco *et al.,* 2013; Chamom *et al*., 2017
Biofilms	Biofilm is a virulence factor and is due to the presence of the ica locus	Guimarães *et al.,* 2012	**Antimicrobial action of essential oils against Staphylococcus aureus**	Essential oils are active against Gram positive and negative bacteria Melaleuca alternifolia and oreganum vulgare oil	Xiao *et al.,* 2020; Falagas, *et al.,* 2016; Xiao *et al.,* 2020

Several studies comment about the antimicrobial resistance of staphylococci aureus in hospitals, as mentioned in the studies (Otter *et al.,* 2019). MRSA resistance S aureus is widely studied in the Southeast region and rarely observed in the North and Northeast regions of Brazil. Several factors are

important for the virulence and adaptation of *S.aureus* in hospitals, including the presence of genes for resistance to antibiotics, biofilm formation and the presence of proteins linked to monocytes. Frequently, there is a genetic plasticity with diversity of clones predominant in regions of the world. As mentioned, the clones USA400 (ST1/CC1/SCCmecIV) and the Pediatric clone (USA800/ST5/CC5/SCCmecIV) have replaced the clone ST239-SCCmecIII since 2009. The *antimicrobial* activity of *plant* extracts was evaluated with microbial bioactive properties that have microbicidal effects when used with low doses of antibiotics, as mentioned in the study by XIAO *et al*., (2020).

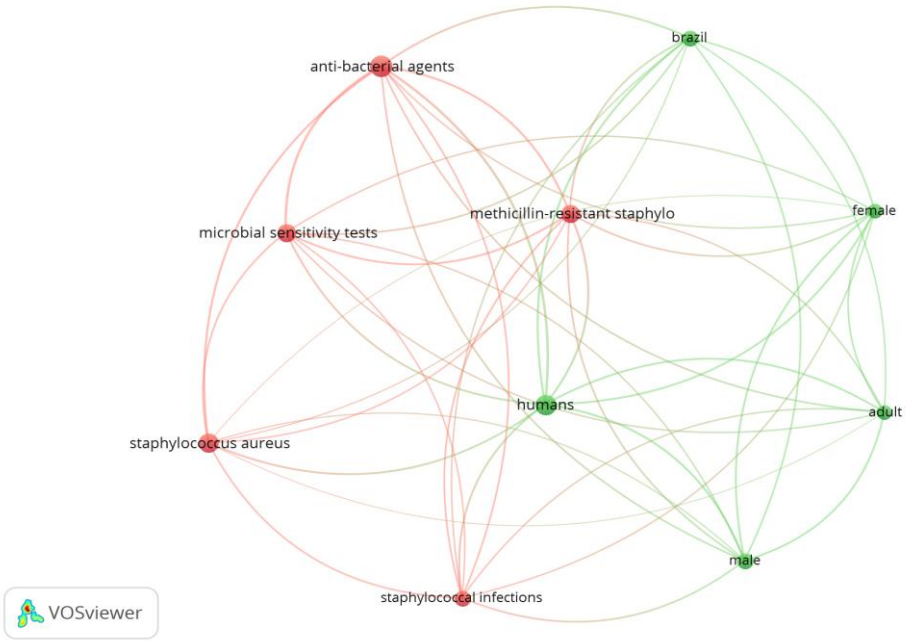

Figure 1: Relationship between keywords among articles selected in the VOSVIEWER program

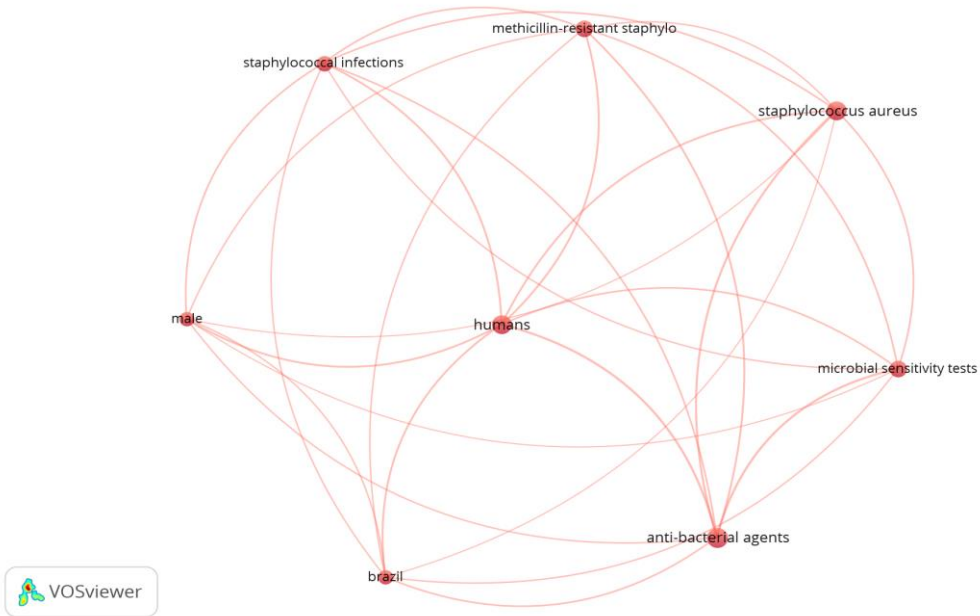

Figure 2: Relationship between common relevant words found in the abstract used in the studies.

CONCLUSION

In the hospital , the emergency sanitary caused by *S.aureus* MRSA is a worldwide concern, new clones are emerging in Brazil and spreading in hospitals. These isolates cause severe infections and cause great clinical impact due to the lack of effective therapies due to the frequent characteristic of multidrug resistance to antimicrobials. More studies are needed so that there is greater knowledge about the molecular epidemiology,

virulence and antimicrobial resistance of S. aureus clones to methicillin in Brazil, especially in the North and Northeast regions of the country.

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