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Exploring the *Staphylococcus aureus* in patients infected of the tertiary- care university hospital: results of the retrospective cohort study

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Palavras-chave

Infecção Hospitalar
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Keywords

Cross Infection
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Abstract

To establish a baseline of knowledge regarding about inappropriate therapy, virulence and resistance in a cohort of patients infected with *S. aureus*. Retrospective cohort study in tertiary-care university hospital was employed to evaluate the risk factors and the impact of inappropriate therapy among patients with *Staphylococcus aureus* infections, resistance and virulence. To assess the presence of the genes was performed PCR. Patients with MRSA were older and hospitalized 17 days longer than those with MSSA infection, which were in ICU with a bloodstream infection. 50.0% received inappropriate antibiotic therapy and we found virulence factors associated with MRSA (*mec*A, *Luk*S, *fnb*B and *clf*A genes). These data show that monitoring studies related to *Staphylococcus aureus* infections remain essential to identify resistance and inform policy on resistance.

Explorando o *Staphylococcus aureus* em pacientes infectados em um hopital universitário terciário: resultados de um estudo de coorte retrospectivo

Estabelecer uma linha de base de conhecimentos sobre terapia inadequada, virulência e r esistência em uma coorte de pacientes infectados com *S. aureus*. Estudo de coorte retrospectivo em hospital universitário de atendimento terciário foi empregado para avaliar os fatores de risco e o impacto da terapia inadequada entre pacientes com infecções por *Staphylococcus aureus*, resistência e virulência. Para avaliar a presença dos genes foi realizado PCR. Pacientes com MRSA eram mais velhos e hospitalizados 17 dias a mais do que aqueles com infecção por MSSA, que estavam em UTI com infecção na corrente sanguínea. 50,0% receberam antibioticoterapia inadequada e encontramos fatores de virulência associados ao MRSA (genes *mec*A, *Luk*S, *fnb*B e *clf*A). Esses dados mostram que os estudos de vigilância relacionados às infecções por *Staphylococcus aureus* permanecem essenciais para identificar a resistência e informar as políticas sobre resistência.

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Introduction

The epidemiology of S*taphylococcus aureus* is dynamic and has been presenting significant changes in recent years (OLIVEIRA; FARIA; LEVYAND, et al. 2001; AÑÓN; RODRÍGUEZ; TINAJAS, et al. 2004; PARKER, 2017; KOECH; COMO-SABETTI; BOXRUDE, 2019). Although Gram-negative bacteria are the most common source of nosocomial infections, *S. aureus* infections are still a substantial source of morbidity and mortality because they have the ability to induce inflammation and are responsible for superficial and invasive infections PELEG; HOOPER, 2010; SCHWEIZER.; EBER; LAXMINARAYAN, et al. 2011).

The treatment of infections caused by this microorganism is complicated by the high prevalence of multidrug-resistant strains, selected by the indiscriminate and inappropriate use of antibiotic, mainly associated with horizontal transfer of genes of resistance (HEGGERNDORNN; GOMES; SILVA, et al. 2016).

S. aureus still presents an arsenal of virulence factors that contribute to its survival and development, and it is responsible for the onset of clinical manifestations and severity of infections RICARDO-CALDERA; BUELVAS-DORIA; ESCOBAR-PÉREZ, et al. 2015). Although resistance plays an important role in the worsening of these infections, the pathogenic capacity of this microorganism is the result of the combined effect of the production of virulence factors, such as enzymes and toxins, and the ability to form biofilm, multiplication and dissemination in tissues and organs, besides its invasive capacity (CHAMBERS; DELEO, 2009; STEFANI; GOGLIO, 2010; BIMANAND, L.; TAHERIKALANI; JALILIAN, et al. 2018).

Reports of methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the 1960s, and currently, MRSA isolates are estimated with a prevalence of 25 of 50% or more in some hospitalization areas (INDRAWATTANA; SUNGKHACHAT; SOOKRUNG, et al. 2013; SANTAJIT; INDRAWATTANA, 2016). In recent years, due to the increased rate of detection of MRSA, empirical antibiotic treatment has become even more difficult, additionally, when the prescription occurs inappropriately, there is an increase in hospital stay, treatment costs and risk of death (PAUL; SHANI; MUCHTAR, et al. 2010; WEISS; FITZGERALD; BALAMUTH, et al. 2014; ZHANG; MICEK; KOLLEF, 2015; LI; LI; ZHANG, et al. 2019).

We aim to establish a baseline of knowledge regarding about inappropriate therapy, virulence and resistance in a cohort of patients infected with *S. aureus.*

Materials and methods

Patients, settings and study design

The data base at our clinical microbiology laboratory was reviewed to identify patients with *Staphylococcus aureus* infections from November/2015 to April/2016 at Uberlandia University Hospital (Brazil), a 533-bed tertiary-care university hospital. For comparison between patients with Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA), only the first episode was analyzed.

A retrospective cohort study was employed to evaluate the risk factors and the impact of inappropriate therapy among patients with *Staphylococcus aureus* infections. During the surveillance period, 80 episodes of *S. aureus* infection were recovered from 55 patients. The main outcome was in hospital mortality and the procedure also assessed secondary outcomes, including the duration of hospital stays, admission to the Intensive Care Unit (ICU) and the use of central venous catheter and mechanical ventilation.

The data and the samples analyzed in the present study were obtained in accordance with the norms and approved by the Federal University of Uberlandia Ethics Committee (UFU), through license number 36601814.7.0000.5152 and 60374516.6.0000.5152.

Definitions

Hospital infection is acquired after the admission of the patient and it is manifested during hospitalization or after discharge, when it may be related to the hospitalization or hospital procedures (BRASIL, 1998). Inappropriate empirical therapy is the antimicrobial treatment with agents that did not have "*in vitro*" activity and/or treatment performed over 48 hours (DAIKOS; TSAOUSI; TZOUVELEKIS, et al. 2010).

Hospital mortality is an evolution of patient's condition to death in 30 days after diagnosis of infection (LODISE; PATEL; KWA, et al. 2007).

Identification of species, antimicrobial susceptibility and molecular testing

Microbial identification and antimicrobial susceptibility testing were performed on a VITEK®II automated system (bioMérieux). To assess the presence of the *mec*A gene, *Luk*S gene, *fnb*B and clfA genes in *Staphylococcus aureus* strains, a polymerase chain reaction (PCR) was performed, as described previously by Kondo et al. (2007), Said Salim et al. (2005) and Tristan et al. (2003), respectively. All PCRs were carried in a mastercycler personal (Eppendorf). To perform the PCR, only 38.8% of the isolates were chosen, due to the costs of molecular techniques. The criteria for selecting these were based on the antibiogram as follows: samples with the highest resistance profiles (in the cases of groups R1 and R2) and samples only with resistance to methicillin (in the case of group R3)

Statistical analysis

The evaluate of quantitative variables were performed by Student's T-Test. Categorical variables were expressed as mean and standard deviation. The statistical significance was defined by a value of $P \geq 0,05$, using the statistical program GraphPad Prism 5.01.

Results and Discussion

Fifty-five patients (147 episodes with infection) were selected hospital-wide during surveillance period, *S. aureus* was the most common species (54.4%), of which 29.9% were oxacillin resistant followed by Gram-negative bacilli (38.8%). Most of this isolated (32.6%) were detected from patients on the ICU. A predominance of bloodstream infection (40.9%) among MRSA, and pneumonia (33.3% and 31.5%, respectively) among MSSA and Gram-negative bacilli was observed (Table 1).

Table 1- Episodes of hospital bacterial infection from November/2015 and April/2016 second according to isolation site and clinic/ sector.

Isolation site/ Clinic	TOTAL N= 147 (%)	MRSA N= 44 (%)	MSSA N= 36 (%)	p	OTHERS GRAM-POSITIVE COCCI[1] N= 10 (%)	GRAM-NEGATIVE BACILLI[2] N= 57 (%)
Isolation site						
Lung	41 (27.8)	11 (25.0)	12 (33.3)	0,4126	0	18 (31.5)
Blood/ Catheter tip	47 (31.9)	18 (40.9)	10 (27.7)	0,2473	8 (80.0)	11 (19.2)
Wound	31 (21.0)	13 (29.5)	11 (30.5)	1,0000	2 (20.0)	5 (8.7)
Urine	18 (12.2)	1 (2.2)	2 (5.5)	0,5855	0	15 (26.3)
Outhers[3]	10 (6.8)	1 (2.2)	1 (2.7)	1,0000	0	8 (14.0)
Clinic/ Sector						
Medical clinic	44 (29.9)	22 (50.0)	6 (16.6)	0,0002	1 (10.0)	1 (1.7)
ICU[5]	48 (32.6)	11 (25.0)	8 (22.2)	0,7985	3 (30.0)	35 (61.4)
Cirurgical clinic	17 (11.5)	7 (15.9)	2 (5.5)	0,1749	3 (30.0)	10 (17.5)
Others[6]	38 (25.8)	4 (9.0)	20 (55.5)	0,0001	3 (30.0)	11 (19.2)

[1]*Staphylococcus haemoyticus, Staphylococcus hominis, Staphylococcuss aprophyticus, Staphylococcus epidermidis, Staphylococcus caprae, Streptococcus pyogenes, Streptococcus spp.*
[2]*Stenotrophomonas maltophilia, Serratia marcenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii*
[3]Eyes, soft parts, bone
[4]Intensive-care unit
[5]Emergency room, pediatric, nursery, gynecology and obstetrics

Table 2 - Relationship between antimicrobial resistance profile, isolation site and resistance and virulence profile of the clinical samples of sensitive and resistant *Staphylococcus aureus* and infection episodes used in the study.

EPISODES N= 80 (%)	RESISTANCE PROFILE	ANTIBIOTYPE	GENOTYPE (%)	ISOLATION SITE
15 (18.7)	CLI, ERY, RIF, PEN, MET	R1	*mec*A+/ PVL-/ *clf*A-/ *fnb*B- (46.6)	Wound (5); Blood/ Catheter tip (2)
			*mec*A+/ PVL-/ *clf*A+/ *fnb*B- (40.0)	Blood/ Catheter tip (3); Lung (2)
			NE	Lung (1)
			*mec*A+/ PVL-/ *clf*A+/ *fnb*B+ (6.6)	Lung (1)
			*mec*A-/ NE/ NE/ NE (6.6)	Wound (1)
24 (30.0)	CLI, ERY, PEN, MET	R2	*mec*A+/ PVL-/ *clf*A-/ *fnb*B- (25.0)	Wound (3); Blood/ Catheter tip (3)
			*mec*A+/ PVL-/ *clf*A+/ *fnb*B- (29.1)	Lung (4); Blood/ Catheter tip (2); Wound (1)
			*mec*A-/ NE/ NE/ NE (4.1)	Bone fragment (1)
			NE (41.6)	Blood/ Catheter tip (6); Wound (2); Lung (2)
2 (2.5)	PEN, MET	R3	*mec*A+/ PVL-/ *clf*A-/ *fnb*B+ (50.0)	Wound (1)
			NE (50.0)	Urine (1)
1 (1.2)	CLI, ERY, TET, PEN, MET	R4	NE (100.0)	Blood/ Catheter tip (1)
1 (1.2)	ERY, PEN, MET	R7	NE (100.0)	Blood/ Catheter tip (1)
1 (1.2)	CLI, ERY, MET, AMI, CIP	R8	NE (100.0)	Lung (1)
11 (13.7)	CLI, ERY, PEN	R9	NE (100.0)	Wound (5); Blood/ Catheter tip (3); Lung (2); Eyes (1)
5 (6.2)	CLI, ERY	R10	NE (100.0)	Lung (3); Blood/ Catheter tip (1); Wound (1)
2 (2.5)	ERY, PEN	R11	NE (100.0)	Wound (1); Bone fragment (1)
1 (1.2)	TET, PEN	R12	NE (100.0)	Lung (1)
13 (16.2)	PEN	R13	NE (100.0)	Blood/ Catheter tip (8); Wound (3); Lung (2); Eyes (1); Urine (1)
4 (5.0)	Susceptible	S	NE (100.0)	Lung (2); Wound (1); Urine (1)

CLI, Clindamycin; ERY, Erythromycin; RIF, Rifampicin; PEN, Penicillin; MET, Meticiline; TET, Tetracycline; AMI, Amicacina; CIP, Ciprofloxacin; NE, Not evaluated

Based on the antibiotic susceptibility test, 11 antibiotypes (R1-R11) were identified among isolates of *Staphylococcus aureus*. The most isolated were assigned antibiotype R2 (30.0%) and R1 (18.7%). In R2 strains presented predominantly the genotype *mec*A+/ PVL-/ *clf*A+/ *fnb*B- (29.1%), with more isolates in lung, while the R1, 46.6% strains presented the genotype *mec*A+/ PVL-/ *clf*A-/ *fnb*B- with more isolates in wound. (Table 2).

The table 3 shows the risk factors for *Staphylococcus aureus* infections. Although only the result of avera ge age presents significance, on what patients with MRSA had a mean age of 61.1 years and with MSSA, 37.7 years, other results showed important percentage differences. The majority of patients with resistant infection had ICU hospitalization (53.8%), made use of the inappropriate antibiotic therapy (50.0%) and used central venous catheter (61.5%), while the use of mechanical ventilation was higher in patients with sensitive infection (75.8%). The average hospitalization time and the average hospitalization time until diagnostic was also higher in patients with MRSA infection (44.5 days and 25.8 days, respectively).

Table 03 - Risk factors for Staphylococcus aureus with the resistance and sensitive phenotypes of hospitalized between November/2015 and April/2016.

	TOTAL N=55 (%)	MRSA N=26 (%)	MSSA N=29 (%)	p	DEATH N=10* (%)
Average age, years(±SD)	48.8 (±24.46)	61.1 (±16.56)	37.7 (±26.24)	0.0009	53.6
Average hospitalization time, days (±SD)	37.0 (±38.48)	44.5 (±48.67)	27.5 (±25.62)	0.5550	25.0
Average hospitalization time until diagnostic, days (±SD)	17.1 (±27.34)	25.8 (±37.29)	9.3 (±8.146)	0.1785	16.0
Inappropriate antibiotic therapy	19 (34.5)	13 (50.0)	7 (24.1)	0.5251	5 (50.0)
ICU hospitalization	23 (41.8)	14 (53.8)	8 (27.5)	0.6610	8 (80.0)
Patients with CVC	29 (52.7)	16 (61.5)	12 (41.3)	0.8193	9 (90.0)
Patients with MV	38 (69.0)	16 (61.5)	22 (75.8)	0.8006	8 (80.0)

SD, Standart deviation; ICU, Intensive-care unit; CVC, Central venous catheter; MV, Mechanical ventilation
*50.0% MRSA

Analyzing and determining the importance of MRSA in research-limited countries is a great challenge, since today the study has demonstrated a more significant prevalence of Gram-negative bacilli as etiology of infections. However, our results agree with previous studies reporting a high burden of this phenotype among Staphylococcus aureus infection (ENRIGHT; ROBINSON; RANDLE, et al. 2002; WORLD HEALTH ORGANIZATION, 2015; FRIEDRICH, 2019).

Interestingly, in our assessment, MSSA was responsible for 33.3% of pneumonia and MRSA was predominant of bloodstream infection. Special attention was given to the Gram-negative bacilli, the main cause of pneumonia and urinary tract infection. This is particularly worrisome, since the literature shows that therapeutic options are scarce or ineffective to the multidrug-resistant organisms (ZARAGOZA; ARTERO; CAMARENA, et al. 2003; BASETTI; POULAKOU; RUPPE, et al. 2017).

MRSA is a well-recognized public health problem through the world (CIMOLAI, 2007; STRUELENS, 2009; CHESSA; HANAU; MAZZARELLO, 2015). From a hospital perspective, patients with MRSA tendent to be older, to have a longer hospital stay, to have a recent background of hospitalization, among others. The present study has detected and considered such factors, in which the patients with MRSA infection were significantly older and were hospitalized 17 days longer than those with MSSA infection, as well as in previous hospitalizations when the same comparison was made.

Empirical antibiotic therapy may appear to be a good treatment strategy before the microbiological result is available, however, as an inappropriate therapy can lead to increased antibiotic resistance (ZHANG; MICEK; KOLLEF, 2015; YOON; PARK; SOHN, et al. 2016). This phenomenon is more marked in countries where the level of consumption and antimicrobial resistance are higher and where multidrug-resistant pathogens spread rapidly (CIORBA; ODONE; VERONESI, et al. 2015; BRAGA; CAMPOS; BATISTÃO, et al. 2019). In our surveillance, 50.0% of patients with MRSA infection received inappropriate antibiotic

therapy. The literature shows that the delay in initiating appropriate therapy may lead to a higher mortality rate (WI; RHEE; KANG, et al. 2018). Due to the small number of patients, the data collected in this study did not allow the specific examination of the effect of appropriate antibiotic therapy. However, knowing the prescribing patterns of antibiotics for S. aureus infections in our institution, may justify the results of similar mortality rates between MRSA and MSSA in our cohort, which leads us to assume that empirical antibiotic therapy may have been more effective against MRSA during the study period.

S. aureus is also a versatile pathogen in the production of several types of virulence factors, with the objective of destroying the host cells and causing infections in different ways (FOSTER; GEOGHEGAN; GANESH, et al. 2013; OTTO, 2014; WI; RHEE; KANG, et al. 2018; JIANG; YIN; YOU, 2018). Although our sample size was small, we found important virulence factors associated with MRSA. The fnbB genes responsible for binder production of fribronectin and clfA (POWERS; WARDENBURG, 2014), responsible for cloning factor encoding were positive in 8.8% and 44.1%, respectively, in MRSA strains. The lukS, responsible for the production of the PVL toxin was not present in any of the strains evaluated (MORAN; KRISHNADASAN; GORWITZ, et al. 2006), this should be found to be more prevalent in community strains.

In conclusion, although Gram-negative bacilli are predominant in nosocomial infections in Brazil, *Staphylococcus aureus*, particularly those resistant and more virulent, is still present in the hospital environment in important frequencies especially in ICU. Our further results confirm previous report showing a high frequency of inappropriate antibiotic therapy among MRSA associated with a very long hospitalization time.

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