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PREVALENCE OF METHICILLIN-RESISTANT *Staphylococcus aureus* COLONIZATION AMONG HOSPITAL PATIENTS OF TEBESSA REGION IN EAST ALGERIA

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ABSTRACT

***Staphylococcus aureus* is a human pathogen of clinical importance related to a variety of infections. The objective of this study was to analyze the epidemiological characteristics of *S. aureus* obtained from the patients of several hospitals in Tebessa area (East Algeria). This study was made as per the microbiological methods based on morpho-physio-biochemical characters. *S. aureus* samples (1200) were analyzed, and 250 strains were identified, representing the 20.83% of population. An antibiogram accompanied by screening on oxacillin (6 µg mL^{-1}) made it possible to detect β-lactam resistant strains. Seventy eight (31.2%) methicillin-resistant *Staphylococcus aureus* (MRSA) strains were isolated. The study revealed that the risk factors like age, nature of sampling and use of β-lactams antibiotics by patients have a relationship with MRSA infection. On the other hand, the presence of MRSA has no relationship with sex factor of hospitalized patients. By comparison with previous studies, it is inferred that in Algeria the carriage of MRSA in the city is worrying. It is necessary to control the diffusion of these strains for the control of epidemics with multi-resistant germs.**

Keywords: Algeria, antibiogram, epidemiology, methicillin-resistant strains, *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is a Gram-positive and coagulase positive bacterium (Chemsi *et al.,* 2014). This bacterium is considered opportunistic pathogen causing infections like pneumonia **(**Subba Rao *et al.,* 2020; Jouzeau *et al.,* 2022**)**, skin infections (Nhan *et al.,* 2012), osteomyelitis and endocarditis **(**Michael *et al.,* 2017), etc**.** The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals varies considerably from one country to another. For instance, in USA MRSA were isolated from up to 59% of patients with community acquired infections (Moran *et al.,* 2006). It is responsible for several extremely varied diseases, which can be infection suppurative, localized or systemic, but also syndromes related to the action of toxins **(**Shoaib *et al.,* 2022**)**. These infections are a real public health problem both in terms of the virulence of bacteria than by the emergence of multidrug-resistant strains **(**Mitevska *et al.,* 2021**)**. However, since 1990 the MRSA infections have increased in adults and children with none of the risk factors for acquiring MRSA already described. These are MRSA infections of hospital origin (Bahareh *et al.,* 2021). The emergence of *S. aureus* resistant to current antibiotics and the prevalence of MRSA are important obstacles in the therapeutic profile of infections with multidrug-resistant bacteria (Huang and Chen, 2015). This bacterium became resistant to many antibiotics, using different mechanisms. Acquisition of mobile genetic resistance elements by horizontal gene transfer, mutations of antibiotic targets, and over-expression of endogenous efflux pumps are among the most important mechanisms (Arkwright *et al.,* 2002)**.** The objective of this study was to determine the prevalence of MRSA in hospital environment in eastern Algeria, in the patients between 2018 and 2020, antibiotic susceptibility pattern, risk factors associated with MRSA and to get an idea on the resistance of *S. aureus* to other antibiotics.

MATERIALS AND METHODS

Study setting

A total number of 1200 were collected from various pathological samples (pus, urine and vaginal samples) from several hospitals in the wilaya of Tebessa; a region located in the east of Algeria next to the Tunisian border. The samples were collected during January 2018 to April 2020. The present work was carried out in the Applied Microbiology Research Laboratory, University of Larbi Tebessi, Tebessa, Algeria.

Microbiology assay

The isolates were identified as *S. aureus* based on their morphology, microscopic examination, catalase, coagulase test and Vitek test. Antimicrobial susceptibility test was performed by using disk diffusion method in Muller Hinton agar (Bio-Rad) (CA-SFM/ EUCAST, 2020). Antibiogram typing involved the comparison of isolates' susceptibilities to a range of selected antibiotics. This test is traditionally performed by disk diffusion or broth micro-dilution tests of an antibiotic (Daoudi, 2008). Testing of susceptibility to oxacillin, cefoxitin, kanamycin, gentamicin, erythromycin, tetracycline, pristinamycin, ofloxacin, chloramphenicol, trimethoprim/sulfamethoxazole and vancomycin was determined as recommended by the CA-SFM (CA-SFM/ EUCAST, 2020). After 18-24 h incubation, the diameter of inhibition zone around each disc antibiotic was measured. The areas of inhibition of each antibiotic were interpreted as "sensitive", "intermediate" or "resistant"; in accordance with the guidelines of CA-SFM (2020). The isolates with intermediate sensitivity were considered "resistant". All the isolated *S. aureus* were stored at -4°C in nutrient broth supplemented with 15% glycerol for further testing (Ficca *et al.,* 2006). The methicillin resistance phenotypes were identified using 30 µg cefoxitin disc (Bio-Rad). The strains of *S. aureus* susceptible to cefoxitin were considered as methicillin-susceptible *S. aureus* (MSSA), while those resistant to cefoxitin were considered resistant to methicillin (MRSA) (Kalambry *et al.,* 2022). Cefoxitin inhibition diameter of < 22 mm is characteristic of the presence of the *mec* A gene; the strain is, therefore, considered resistant to all β-lactams (include oxacillin, cefoxitin) (Dufour *et al.,* 2002).

Oxacillin MRSA screening

MRSA screening was performed on Mueller Hinton medium supplemented with 4% NaCl and containing an initial concentration of oxacillin of 6 µg mL^{-1} (NCCLS, 2000). The Petri-dishes were divided into 4 quadrants; one quadrant inoculated with test strain, two quadrants with the reference strains [*S. aureus* ATCC 29213 (oxacillin sensitive strain), and *S. aureus* ATCC 43300 (oxacillin resistant strain)] and the fourth quadrant kept uninoculated. The plates were incubated at 37°C for 18 h and the growth monitored. The growth of more than one colony of the test strain was sufficient to indicate the resistance to oxacillin (Felten *et al.,* 2002).

Epidemiological analysis

The characteristics recorded in epidemiological database were gender, age, type of sample collected and diagnosis. Written informal consent to participate in the study was obtained from the patients or nurses from hospitals.

Statistical analysis

Risk factors were analyzed using χ^2 test and 5% probability analysis regression test, while descriptive statistics were applied for antibiotic susceptibility data using a SPSS computerized statistical program (version 20).

RESULTS AND DISCUSSION

Prevalence of S. aureus and MRSA strains isolated from hospital patients

Based on the morpho-physio-biochemical characteristics, the present study revealed the presence of 250 strains of *S. aureus,* isolated from 1200 pathological samples, thus representing 20.83% of the population. The antibiogram (Fig. 1), and screening test on oxacillin detected 78 SARM (31.2%).

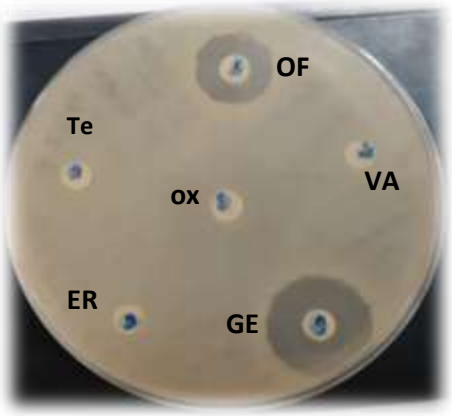

Fig. 1: Antibiogram of MRSA strain

These finding are close to the averages of 43% reported from Pakistan (Tayyabur *et al.,* 2020), 26.7% from Europe (Garau *et al.,* 2013), and 31% from Colombia (Reyes *et al.,* 2009). However, our findings differ from the higher prevalence of reported 52% reported from France (Thiolet *et al.,* 2007) and 68.3% from Colombia (Valderrama *et al.,* 2019). Contrary to the findings of Ficca *et al.* (2006) in France eleven methicillin-resistant strains were detected among the 254 carriers (4.33%), which represented 1% of the total population studied. Overall, MRSA in present study was 31.2% (78/250) with non-significant difference in prevalence in several hospitals in the wilaya of Tebessa (East Algeria). There were considerable variations in the prevalence of MRSA between hospitals, regions, and countries. These variations can be attributed to the existence of epidemic strains, the moment of study, the presence of patients at risk, the transfer of patients during various services, the practice of infection control policy, and the reliability of laboratory methods used in detection of MRSA.

Antibacterial resistance

In present study, a total number of 78 MRSA were characterized which corresponds to the prevalence of 6.5% among 1200 samples. A strain is considered sensitive when the MIC of antibiotic is close to 6 µg mL^{-1} (CA-SFM, 2020). The resistance of *S. aureus* to cefoxitin was 79.49% (Table 1). This cross-resistance corresponding to bacteria that develop resistance to antibiotics in the same family, by the same mechanism. The choice of using oxacillin screening method to get 31.20%; that oxacillin is the good marker of resistance to the methicillin for staphylococci; critical diameter valid for determining susceptibility/resistance to the molecule but also as a marker of methicillin resistance for which the cefoxitin test is not recommended due to the strong risk of false negative (CASFM, 2020). The MRSA isolated from hospital samples showed resistance to other families of antibiotics; the tetracycline family with a percentage of 79.49%, the macrolide family (erythromycin) with 51.28%, and giving them resistance to certain aminoglycosides (amikacin and vancomycin) with 53.85 and 52.56%, respectively (Fig. 2). However, the resistant percentages of the isolates against gentamicin, chloramphenicol, pristinamycin, triméthoprim and oflaxacin were 3.85, 14.10, 24.36, 26.92 and 32.05%, respectively (Fig. 2).

Table 1: Antibiotics tested on *S. aureus* according to CA-SFM 2020

Antibiotics	Disk load (µg)	Critical diameters (mm)	
		S* ≥	RI**<
Erythromycin	15	21	21
Oxacillin	05	20	20
Céfoxitin	30	22	22
Pristinamycin	15	22	22
Amikacin	30	18	18
Chloramphénicol	30	18	18
Gentamicin	10	18	18
Vancomycin	30	17	17
Tétracyclin	30	19	19
Trimethoprim	05	14	14
Oflaxacin	05	20	20

S*: Sensitive strain. RI**: Resistant or Intermediate strain

The antibiotic resistance profile of MRSA isolates in this study was mainly restricted to the β-lactams, tetracycline, erythromycin, vancomycin and amino-glycosides antibiotics. This profile was almost like that found in Germany (Fessler *et al.,* 2011). The tetracycline resistance phenotype observed in this study could be explained by the presence of *tetK* and *tetM* genes in the microarray (Zarfel *et al.,* 2013). The high percentage of resistance (79.49%) as well as perilous when compared with those obtained by Azzouzi (2018) in Morocco which is down with tetracycline which is explained by the crier development by this bacterial species at the level of their mechanism of resistance against tetracycline.

Erythromycin resistance is widespread among methicillin-resistant strains (37 out of 43). This can be explained by cross-resistance to macrolides by methylation of 23S ribosomal RNA (Nhan *et al.,* 2012). There were 96.6% MRSA strains sensitive to gentamicin, as per the which agrees with the report of university hospital center (CHU) of Angers. Regarding the sensitivity to trimethoprim

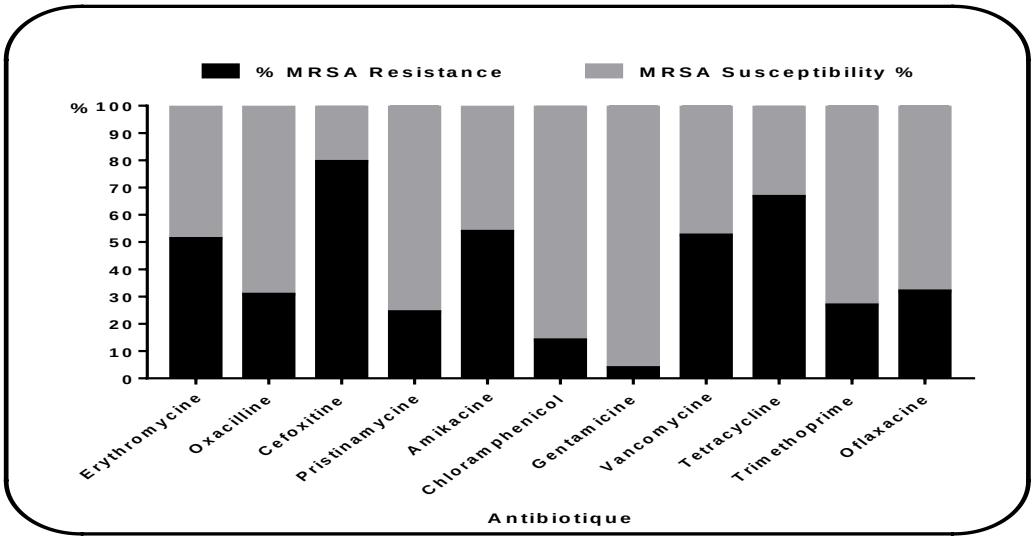

Fig. 2: Resistance profile of *S. aureus* strains against 11 antibiotics tested

of MRSA strains; it was too high (73.08%) because we noted a sensitive percentage between 95 and 98% (ONERBA, 2009).

Association of risk factors with acquisition of MRSA

Several factors were found associated with a higher risk for nosocomial acquisition of MRSA, such as prolonged hospitalization, care in an intensive care unit, prolonged antimicrobial therapy, and proximity to a patient in the hospital who is infected or colonized with MRSA. A total number of 250 *S. aureus* were isolated [110 from women (44%) and 140 from men (46%)]. Identification of MRSA revealed 78 positive samples (31.2%) against 68.8% non-positive samples (Table 2). Among the positive samples, 43 were women (55.13%) and 35 men (44.87%), with male/female sex ratio of 0.81. The factors linked to patient's gender, of which the majority have found that the rate of *S. aureus* is higher in males than in females. Our study reports the same dominance (55% men and 45% women), but is contrary to the finding of Davido (2018) who found a female sex 60% and men 40%. The study revealed that sex can be a risk factor. Gender male is not considered to be a significant risk factor for ISO in general.

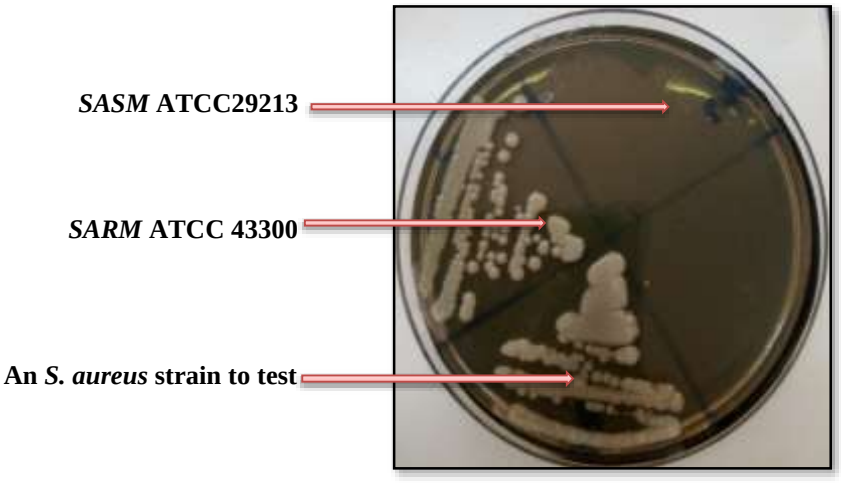

Fig. 3: Oxacillin screening test of a MRSA strain

Of the 250 patients affected by *S. aureus*; 74 were adults (29.6%), 159 old (63.6%) and 17 child (6.8%) patients. Among the MRSA positive samples; 71.8% were procured from old patients, 19.23% from adult patients and 9.15% from child, respectively (Table 2). The difference between the average ages in infected and uninfected patients was statistically significant with $p = 0.04$. The elderly people are always exposed to the risk of infection (Chadi *et al.*, 2016) which confirm our finding. Higher prevalence was found in elderly people; with 71.8% prevalence in elders, which corroborates with Davido (2018) who found 100% carriers of *S. aureus* in old patients in France. These results confirm that advanced age is linked to the onset of chronic diseases like diabetic, which creates immune alterations and makes the body susceptible to colonization of *S. aureus* or other bacteria (Chadi *et al.*, 2016), establishing a relationship between age and MRSA infection.

Table 2: Distribution of MRSA infection as per the risk levels of gender, age, type of sample, and use of antibiotics

Risk factors	Positive (%)	Negative (%)
Gender		
a) Male	44.87	55.13
b) Feminine	55.13	44.87
c) Whole population	31.20	68.80
IC	18.17-33.87	
P-value	0.01	
Age		
a) Adult	19.23	80.77
b) Old	71.79	28.21
c) Child	9.15	90.15
IC	6.19-41.03	
P-value	0.04	
Type of sample		
a) Pus	74.35	25.65
b) Urine	21.79	78.21
c) Pre-vaginal	3.84	96.16
IC	16.05-37.79	
P-value	0.04	
Use of antibiotic		
a) β-lactamin	52.56	47.44
b) Other antibiotics	48.38	51.62
IC	25.33-40.40	
P-value	0.0001	

With respect to the type of samples, we found 197 pus samples (78.8%), 45 urine samples (18%) and 8 pre-vaginal samples (03.2%) (Table 2). Among the MRSA positive samples, 87.18% were from pus, 8.97% from urine and 3.84% from vaginal samples. The difference between the type of samples risk was statistically significant ($p = 0.04$). It is noted that the prevalence of rates of samples from patients which are contaminated by SARM were the pus which represented the high rate compared to other samples. The results corroborate with those of Daoudi (2008) who reported a rate of 77.34%. The sampling sites also influence the result. So, in pus we isolated the highest rate (74.35%). Pus came mainly from direct debits skin and soft parts (Elhamzaoui *et al.,* 2009). Our findings are in line with CA-SFM (2020) in Columbia where hospitalized patients were sampled for MRSA.

The use of antibiotics families of β-lactams as treatment was found higher in hospital environment (72%) as compared to the other families of antibiotics (28%). This showed a significant difference ($p = 0.0001$) between the use of β-lactams and the spread of MRSA strain (Table 2). In short, the over-use and misuse of antibiotics in clinics have become the major have become the major factors for fast development of resistance in bacteria (Hussain *et al.,* 2008). The most important cause of increased resistant phenotypes was the shortage of responsiveness, lack of understanding the effect of self-medication and excessive use of antibiotics by people. The variations in various studies exist due to various strain types at specific areas, hospital infection control plans, and other methods adopted to limit the use of antibiotics (Aqib *et al.,* 2020).

MRSA were resistant to two or more antibiotics as compare to the MSSA, indicating multi-resistance of certain isolated hospital strains (Arkwright *et al.,* 2002)**.** The most important causes of increased resistant phenotypes are lack of understanding about the effect of self-medication and excessive use of antibiotics in people. Differences in results of various studies exist due to various strain types at specific areas, hospital infection control plans, and other methods adopted to limit the use of antibiotics (Aqib *et al.,* 2020). The analysis of the resistance profile showed that MRSA strains have developed resistance to antibiotics used with emergence of new resistance phenotypes. This study shows the resistance profile of *S. aureus* in Algeria which could be a guide for the physician in the treatment of infections caused by this pathogen. Furthermore, molecular characterization could have provided better information on virulence factor associated with resistance.

Conclusion: The present study revealed high prevalence of MRSA in Eastern Algeria. All risk factors showed a significant association in the acquisition of MRSA. *In vitro* therapeutic efficacy indicated trimethoprim-sulfamethoxazol, oflaxacin, chloramphenicol, pristinamycin and gentamicin as highly efficacious against the MRSA strains isolated. The surveillance of nosocomial infection showed relationship with workload, type and severity of illnesses, consumption of antibiotics and bacterial resistance. Organizations need to be improved to fight against nosocomial infection and carry actions as per the priorities at national and local level.

Conflict of interest: The authors declare that they have no conflict of interest among them.

Ethical statement: The present work was conducted with proper permission and approval from the authorities in the University of Tebessi, Algeria and the concerned hospitals in wilaya of Tebessa.

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