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Multidrug resistance of *Staphylococcus aureus* strains isolated from medical centers of Batna (north-east Algeria)

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ABSTRACT: The emergence of resistant strains of *Staphylococcus aureus* is a major public health problem mainly in hospitals around the world and in Algeria in particular. This work aims to assess the resistance of Staphylococcus aureus in the University Hospital Center of Batna and the Hematology Unit of the Anti-Cancer Center using conventional standardized methods during a study period of four months. A total of 70 strains of *S. aureus* were isolated and their antibiotic susceptibility study showed significant resistance to β-lactam especially to penicillin (95.71%) and 61.43% to tobramycin. The methicillin-resistant strains (MRSA) formed 30%. Resistant strains to macrolide-lincosamide streptogramin B (MLSB) and aminoglycosides (KTG) classes presented 17.14% and 21.43% respectively. These results require a control plan by compliance with the hygiene conditions and the organization of the prescription of antibiotics and other molecular and epidemiological studies.

Keywords: *Staphylococcus aureus*; MRSA; MLSB; KTG; University Hospital of Batna; Hematology Unit of the Anti-Cancer Center.

1. INTRODUCTION

Staphylococcus aureus is a Gram-positive coccus acting as a commensal as well as a major pathogen. It is known to exist as normal flora in the skin of an estimated 20% of the world population without causing any harm and is persistently carried and in the upper respiratory tract [1, 2]. However, it could be an opportunistic pathogen for humans and animals when it enters the bloodstream and tissue [3]. Practically, it becomes infectious only when it can enter into the skin or mucous membrane through a penetrating object and can cause both minor skin infections, including mild skin and soft tissue infections, impetigo, boils, folliculitis, furuncles carbuncles, abscesses and life-threatening diseases like meningitis septicemia, infective endocarditis, osteomyelitis, bacteremia, and fatal pneumonia [4]. It can initiate community-acquired and hospital-acquired

infections and is the second most common bacterial agent in healthcare-associated infections in the Mediterranean region (12.5% in Algeria) [5].

Antibiotic therapy is critical in controlling *S. aureus* infections. However, excessive use of antibiotics has resulted in the development of resistant *S. aureus* strains [6]. It exemplifies the adaptive evolution of bacteria in the antibiotic era better than any other human pathogen, with its unique and rapid ability to respond to each new antibiotic with the development of a resistance mechanism, beginning with penicillin and methicillin and progressing to the most recent, linezolid and daptomycin [7]. Resistance mechanisms include penicillinase and aminoglycoside-modification enzymes inactivating the antibiotic [8], target alteration disabling the binding of the antibiotic (penicillin-binding protein 2a of methicillin-resistant *S. aureus* and D-Ala-D-Lac of peptidoglycan precursors of vancomycin-resistant strains), trapping (for daptomycin and vancomycin) and efflux pumps (tetracycline and fluoroquinolones) [7].

Methicillin-resistant Staphylococcus aureus (MRSA) may be transmitted from person to person by physical contact and in rare cases, through the air. MRSA has rapidly emerged as the most regularly occurring resistant pathogen found in many parts of the world, including Europe, the United States, North Africa, the Middle East and East [9]. MRSA strains have been classified as “high priority 2 pathogens”, by the World Health Organization (WHO) due to their great threat to human and animal health [10]. MRSA infections account for 20-80% of all nosocomial *S. aureus* infections in many hospitals around the world [11] and are associated with increased mortality, morbidity hospital stay and costs [12]. Additionally, the mortality rate of MRSA infection has exceeded that of acquired immune deficiency syndrome (AIDS), Parkinson’s disease and murder based on the Centers for Disease Control (CDC) in the USA [13].

S. aureus antibiotic resistance is evolving and studying his phenomenon becomes an emergency; therefore, the purpose of this work was to report the state of the antibiotic resistance and the main emergent mechanisms of *S. aureus* clinical isolates recovered from the university hospital and the central laboratory of the Anti-Cancer Center of a medium-sized city (Batna, North-Eastern Algeria).

2. MATERIAL AND METHODS

2.1. Bacterial isolates

During the period of four months (January to May 2016), 158 non-redundant positive cultures of *Staphylococcus sp.* were recovered from different pathological samples (throat swab, blood, urine, cerebrospinal fluid, pleural fluid, pus, ascites and others) obtained from hospitalized patients and outpatients consulting the University Hospital Center of Batna (Northeastern Algeria) a structure of 635 beds and the hematology unit of the Anti-Cancer Center a structure of 240 beds. The isolates were presumptively identified by routine tests; colony morphology, Gram’s staining, isolation on mannitol salt agar (MSA), catalase test, free coagulase production, and API 20Staph System (bioMérieux SA, Marcy-l’Etoile, France).

2.2. Antibiotic susceptibility

Antibiotic susceptibility testing was performed according to the recommendations of the Clinical Laboratory Standards Institute [14] using the disk diffusion method on Mueller Hinton agar. Twenty one antimicrobial agents were tested including; penicillin (10 µg), oxacillin (5 µg), cefoxitin (30 µg), tetracyclin (30 µg), erythromycin (15 µg), clindamycin (2 µg), pristinamycin (15 µg), teicoplanin (30 µg), vancomycin, trimethoprim + sulfamethoxazole (1.25/23.75 µg), ofloxacin (5 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), gentamicin (10 µg), kanamycin (30 µg), tobramycin (30 µg), chloramphenicol (30 µg), fosfomycin (50 µg), fusidic acid (10 µg), rifampicin (5 µg) (Oxoid/ Thermo Fisher Scientific, Basingstoke, UK). The plates were

inoculated with a 1/100 dilution of 0.5 McFarland suspension and incubated at 37ºC for 24 hours and the diameters of zones of inhibition were compared to reference values to determine the susceptibility or resistant pattern of the isolates. *S. aureus* ATCC 25923 was used as a wild-type for quality control.

2.3. Phenotypic detection of MRSA

The MRSA isolates were confirmed phenotypically using cefoxitin disc (30 µg) as recommended by CLSI. *S. aureus* with zone diameter of 21 mm or less with cefoxitin disc was phenotypically confirmed as MRSA [14].

2.4. Phenotypic detection of inducible clindamycin resistance (iMLSB phenotypes)

Erythromycin resistant and intermediate to susceptible clindamycin *S. aureus* isolates were tested for inducible resistance to clindamycin by the D-zone test as described in CLSI. The erythromycin disc (15 µg) was placed at a distance of 15 mm from the clindamycin disc (2µg). Resistance to both erythromycin (zone diameter ≤13 mm) and clindamycin (zone diameter ≤14 mm) was phenotypically considered as iMLSB (inducible MLSB), resistance to erythromycin (zone diameter ≤13 mm) and susceptibility to clindamycin (zone diameter ≥21 mm) with a D-shaped zone was considered as cMLSB phenotype (constitutive MLSB); and resistance to erythromycin (zone diameter ≤13 mm) without D-shaped zone was considered as MS (moderately sensitive) [14].

2.5. Data analysis

Frequencies of *S. aureus* isolates recovered from different wards were calculated as the percentage of the number of isolates to the total of surveyed patients hospitalized in different units. Pearson's Chi-squared test ($\chi 2$) was used to determine the statistical significance of group differences, with statistical significance defined as $P < 0.05$. Microsoft Excel 2013 was used to record the laboratory data.

3. RESULTS

3.1. Isolation

Of 2186 samples, 559 (25.57%) samples were culture positive, 125 (5.72%) of contaminated culture and 1502 (68.71%) of negative culture. The genus *Staphylococcus* was detected in 158 samples while *S. aureus* was identified in 70 ones.

3.2. Antibiotic susceptibility

The results of the antimicrobial susceptibility patterns of the total clinical isolates are summarized in (Table 1). Various resistance levels to β-lactam tested drugs were noted including penicillin (95.71%), oxacillin and cefoxitin (30%). The aminoglycosides resistance rates ranged from 61.43% for tobramycin to (34.28%) for kanamycin and (21.43%) for gentamicin. Moderate to low resistance rates towards macrolides and quinolones where erythromycin and ofloxacin presented the highest resistance levels with 28.58% and 24.28% respectively. Whereas rifampicin, chloramphenicol, vancomycin, pristinamycin, trimethoprim + sulfamethoxazole and ciprofloxacin were categorized as the effective molecules on the tested strains. Multidrug-resistant strains formed 48.57% of the total isolates.

The results showed that twenty-one isolates (30%) of *S. aureus* presented an MRSA profile resistance. MRSA isolates were found to be highly resistant to penicillin and cefoxitin (100%), oxacillin (95.24), to tetracyclin (66.67%), gentamycin (66.67%), tobramycin (71.43%), kanamycin (76.2%) and ofloxacin (71.43%) (Table 1). No resistance was recorded against rifampicin.

Table 1. Antibiotic susceptibility patterns of *S. aureus* isolates.

Antibiotic susceptibility (%)						
Antibiotics	**Total *S. aureus* (N=70)**			**MRSA (N=21)**		
	R	I	S	R	I	S
Penicillin (PEN)	95.71	0	4.29	100	0	0
Oxacillin (OXA)	30	0	70	95.24	0	4.76
Cefoxitin (FOX)	30	0	70	100	0	0
Tetracyclin (TE)	44.28	1.43	54.29	66.67	4.76	28.58
Erythromycin (ERY)	28.58	5.71	65.71	47.61	14.29	38.1
Clindamycin (CLI)	11.43	4.29	84.28	19.05	0	80.95
Pristinamycin (PRI)	2.86	0	97.14	4.76	0	95.24
Teicoplanin (TEC)	1.43	0	98.57	4.76	0	95.24
Vancomycin (VAN)	2.86	0	97.14	4.76	0	95.24
Trimethoprim + sulfamethoxazole (SXT)	7.14	5.71	87.15	23.81	9.52	66.67
Kanamycin (KA)	34.28	2.86	62.86	76.2	4.76	19.04
Tobramycin (TOB)	61.43	0	38.57	71.43	0	28.57
Gentamicin (GEN)	21.43	0	78.57	66.67	0	33.33
Chloramphenicol (CHL)	1.43	1.43	97.14	4.76	4.76	90.48
Rifampicin (RIF)	0	2.86	97.14	0	9.52	90.48
Fusidic acid (FUS)	30	0	70	47.61	0	52.39
Ofloxacin (OF	24.28	4.29	71.43	71.43	4.76	23.81
Levofloxacin (LEV)	14.29	7.14	78.57	42.85	19.05	38.1
Fosfomycin (FOS)	11.43	0	88.57	9.52	0	90.48
Ciprofloxacin (CIP)	7.14	4.29	88.57	19.05	0	80.95
Multidrug-resistance pattern (resistance to ≥3 drug classes)						
Total *S. aureus* (N=70), n (%)				MRSA (N=21), n (%)		
34 (48.57)				19 (90.48)		

S - susceptible, R - resistant, I - intermediate.

Among 70 *S. aureus* isolates, iMLSB, cMLSB, MS resistance was found in 9 (12.85%), 3 (4.29%) and 7 (10%) respectively. Four (19.05%) of MRSA strains were iMLSB (Figure 1 D), and one strain presented MRSA-KTG phenotype (Table 2, Figure 1 C).

Table 2. Phenotypes of *S. aureus* antibiotic resistance.

Phenotypes	**MRSA n (%)**	**MRSA-KTG n (%)**	**MRSA-MLSB n (%)**	**Total *S. aureus* n (%)**	**p-value**
MLSB	4	1	0	12	>0.01
MS (ERY R)	6	4	4	7	
KTG	14	0	1	15	
Total	24 (100)	5 (100)	5 (100)	34 (100)	

MLSB - macrolide lincosamide-streptogramin B class phenotype (iMLSB + cMLSB), MS - moderate sensitive phenotype, ERY R – erythromycin-resistant phenotype, KTG - kanamycin-tobramycin-gentamycin resistance phenotype.

The total MLSB strains showed high resistance (from 77.78% to 100%) to penicillin, tetracycline, erythromycin, clindamycin, kanamycin and tobramycin and were intensively susceptible (100%) to pristinamycin, teicoplanin, vancomycin and trimethoprim + sulfamethoxazole (Figure 1 B).

Resistance to all aminoglycosides was defined as the KTG phenotype that forms 15 (21.43%) of all the isolates. One strain showed KTG phenotype only, when the other strains presented an association to MRSA and MRSA-MLSB phenotype (Table 2, Figure 1 C and E). The total KTG isolates were all resistant (100%) to tobramycin, kanamycin, and gentamycin and extremely resistant (100%) to penicillin and cefoxitin, oxacillin (93.75%), tetracyclin (87.5%), and ofloxacin (81.25%); meanwhile these strains were noticeably susceptible (100%) to ciprofloxacin, vancomycin, teicoplanin and chloramphenicol (92.86%) (Figure 1 A).

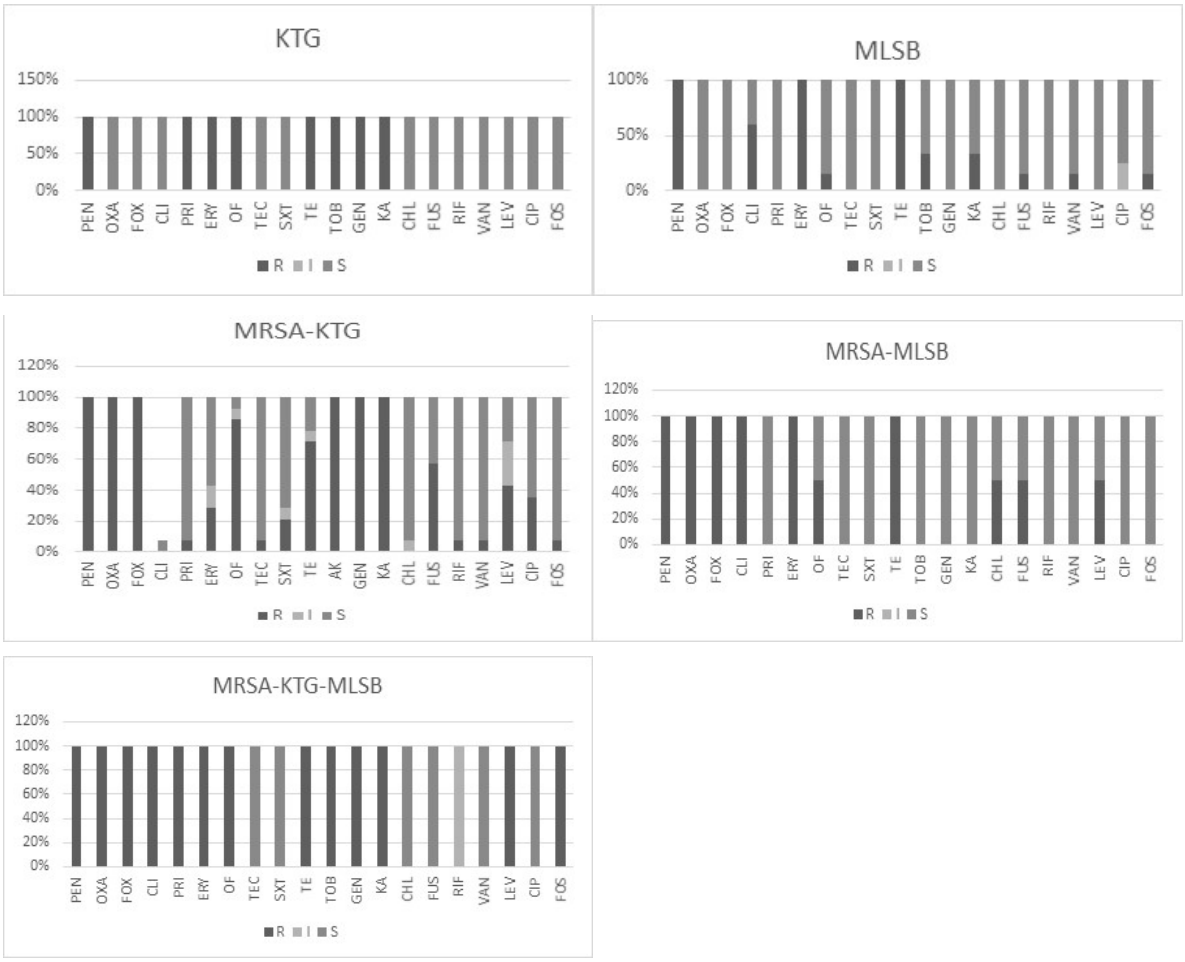

Figure 1. Antibiotic susceptibility patterns in resistance phenotypes. A) KTG phenotype antibiogram (kanamycin-tobramycin-gentamycin resistance), B) MLSB phenotype antibiogram (iMLSB + cMLSB macrolide licosamide-streptogramin B class), C) MRSA-KTG phenotype antibiogram (MRSA methicillin-resistant *Staphylococcus aureus*), D) MRSA-MLSB phenotype antibiogram, E) MRSA-KTG-MLSB phenotype antibiogram.

4. DISCUSSION

The relatively low rate of positive cultures (25.53%) attests that aseptic conditions were respected during the bacteriological analysis. Our results are consistent with those of Boukhatem et al. [15] where negative cultures presented 74.83% versus 22.73% of positive cultures.

The results of the antimicrobial susceptibility patterns of all isolated *S. aureus* showed various resistance levels to the tested drugs. Our data are comparable to those reported by Hailu et al. [16] with resistance rates of 7.9% to clindamycin, 34.6% to oxacillin, 42.6% to tetracycline, 23.1% to trimethoprim + sulfamethoxazole (SXT), 6.4% to chloramphenicol, 0% to ciprofloxacin, 14.1% to erythromycin and 65.4% to

penicillin. No resistance to rifampicin was detected among our isolates regarding its low prescription; it has been also reported according to Hasani et al. [17] that 8-17% of *S. aureus* isolates were resistant to rifampin.

The increased rate of hospital-acquired MRSA is due to the bacteria develop more resistance in the hospital environment and its spread between patients via the healthcare workers and the medical instruments [18]. MRSA has been associated mainly with nosocomial infections in a high occurrence as it develops resistance in the closed environments of hospitals and health care facilities, with the selection pressure and their convenience in spreading from patient to patient via the health care workers and the instruments, etc. The WHO reported different MRSA prevalences: 33-95% in Africa, 43-45% in America, 13-18% in Eastern Mediterranean Region, 27-50% in Europe, 2-80% in the South-East Asia region, and 4-84% in the Western Pacific Region [19].

Low ciprofloxacin resistance of total and MRSA isolates which is inconsistent with the results of Micek [20] who reported an exceptional resistance to ciprofloxacin of *S. aureus* isolates, nonetheless. Almost all strains including MRSA isolates in this study were highly susceptible to vancomycin, teicoplanin and fusidic acid which is in agreement with the study of Ohadian Moghadam et al. [18] reporting susceptible MRSA strains to these antibiotics. However, in Iran [21], one vancomycin-resistant isolate was recovered from clinical samples, and a study from Egypt reported that 17.4% of confirmed MRSA isolates were vancomycin-resistant [22]. Vancomycin has long been known as the last line of defense against infections caused by gram-positive cocci pathogens [20]. It has been considered as the most effective drug for treating severe MRSA infection, including both hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) [23]. Similarly to our finding, most MRSA strains were found to be resistant to gentamicin (86.8%) [24]. In an Algerian study, MRSA strains were 100% resistant to penicillin, 30.3-61.8% to aminoglycosides with resistance rates ranging from 55.75% and 12.12% to erythromycin and clindamycin respectively and 1.8% to vancomycin where the MIC values ranged from 16 µg/ml to 128 µg/ml [25]. The high aminoglycoside resistance indicates the ineffectiveness of these drugs against MRSA infections which is concordant with the study of Shokravi et al. [26]. The high rate of MDR-MRSA strains in comparison with total-MDR ones is similar to that reported by Jaradat et al. [27].

Che Hamzah et al. [28] reported that MLSB prevalence among 90 MRSA isolates was 46.7%, which is higher than our result; it is very clear that *Staphylococcus aureus* has a great ability to develop resistance to many antibiotics to which it has been exposed. Meanwhile, only cMLSB was detected in MRSA isolates [29]. The iMLSB phenotype is the unmostly important phenotype in the clinical environment. Lim et al. [30] found an iMLSB phenotype in 96% of MRSA strains. In this study, a significant correlation between resistance to methicillin and aminoglycoside resistance was noted as previously reported, the aminoglycoside-resistant MRSA-HA strains have spread widely. Rahimi [31] in his study, found that all the MRSA strains present a total resistance to aminoglycosides (KTG phenotype).

5. CONCLUSION

This study highlighted a serious public health concern regarding the multiresistance of *S. aureus* isolates. MRSA infection is still one of the most life-threatening infections in hospitals, thus regular surveillance of MRSA should be carried out in all hospital settings with the implementation of strict hygiene protocols. Furthermore, limiting the indiscriminate use of antibiotics may be an effective strategy against antibiotic resistance. Periodic surveillance studies will be critical in every hospital in order to fight MRSA-based hospital infections effectively and reduce resistance rates.

Author's contribution: MM: conceived the original idea, planned the experiment, analyzed the data and take the lead in writing the paper. NK and SK: carried out the experiments. AK-L: contributed to the analysis of the results. NH: analyzed the data, contributed to interpreting the results and wrote the paper. All authors read and approved the final version of the manuscript.

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