Phenotypic characterization of antimicrobial drug resistance of *Staphylococcus aureus* and *S. epidermidis* strains isolated from various community infections in Oum El Bouaghi city, Algeria

AMINA RAHMANI*, LAAREM MERADI, KARIMA MALAWI, FATMA KHANFOUF

Department of Natural and Life Sciences, Laboratory of Biotechnology of Natural Substances and Applications Larbi-Ben-Mhidi University of Oum El Bouaghi 040000, Algeria. Tel.: +213-542898529, *email: aminarahmani311@gmail.com*

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Abstract. Rahmani A, Moradi L, Malawi K, Khanfouf F. 2021. Phenotypic characterization of antimicrobial drug resistance of *Staphylococcus aureus* and *S. epidermidis* strains isolated from various community infections in Oum El Bouaghi city, Algeria. Biodiversitas 22: 2665-2671. In Algeria most community infections caused by *Staphylococcus aureus* and *Staphylococcus aureus* present resistance to several antibiotics and induce therapeutic failures. The aim of this study is the characterization and the comparison of antimicrobial resistance of *Staphylococcus aureus* strains isolated from community infection in Oum El Bouaghi city, Algeria. Species identification was realized by conventional biochemical tests and the determination of antibiotics susceptibility pattern was realized by using the agar disk diffusion method, according to the recommendations of the French Society for Microbiology (FSM, 2019). A total of 102 *Staphylococcus* strains were obtained from clinical samples, with a frequency of isolation of 57.8% for *S. epidermidis* and 42.2% for *S. aureus*, both strains present a resistance for most used antibiotics, the higher resistance was found for oxacillin in both strains with 25.6% for *S. aureus* and 42.4% for *S. epidermidis*. Multidrug-Resistance (MDR) phenotype was detected in 37.3% of *S. epidermidis* and 14% in *S. aureus* strains. In Algeria, new control policies should be adopted to prevent the further spread of antimicrobial-resistant strains, especially in the community.

**Keywords**: Antimicrobial resistance, community-infection, MDR, *Staphylococcus aureus*, *S. epidermidis*

**INTRODUCTION**

Overuse of antibiotics in human medicine is the contributor of the apparition of antimicrobial resistance, it’s now recognized as a global health problem and has enormous economic and health impacts (Li and Webster 2018) and has led to the emergence of resistant bacterial strains (Safarpoor et al. 2017). *Staphylococcus* isolates are opportunistic facultative pathogens widely distributed worldwide, ubiquitous, found as normal flora of the skin, nasopharynx, anterior nares, and mucous membranes of humans (Ceballos et al. 2019) and also in several environments. Based on their coagulase plasma, staphylococci is divided into two main groups, coagulase-positive *Staphylococci* (CoPS) include *Staphylococcus aureus* and the coagulase-negative *Staphylococci* (CoNS) (more than 30 species) such as: *Staphylococcus haemolyticus* and *S. epidermidis* (Becker et al. 2014).

The increasing prevalence of antimicrobial-resistant *S. aureus* has received much attention, in recent decades (Castro et al. 2016), it constitutes a serious public health problem because of its high colonizing and infectious capacity to cause a wide variety of suppurative infections in humans (Bassetti et al. 2017). Diseases caused by *S. aureus* depend on the host's immunity, age, normal flora and drug consumption (Kandi 2018). Nearly 30% of the human population is asymptptomatically colonized with *S. aureus* (Saleem et al. 2018). The CoNS were considered harmless skin commensal bacteria prior to the 1970s (Contreras et al. 2003) but in recent years, CoNS have been recognized as important opportunistic pathogens including: *Staphylococcus epidermidis*, *S. saprophyticus*, *S. haemolyticus*, and *S. lugdunensis* (Becker et al. 2014).

While traditionally, CoNS considered as less pathogen than CoPS (Fišarová et al. 2019). The dissemination of multidrug resistance in *Staphylococcus* spp. (Virdis et al. 2010) and Methicillin-resistant *S. aureus* (MRSA) is a serious health concern (Castro et al. 2016). It has acquired resistance to several families of antibiotics, often detected in hospitals and communities (John et al. 2019). The evaluation of the antimicrobial susceptibility of *Staphylococcus* spp. isolates determine which antibiotics should be administrated for monitoring the spread of resistant strains in community (Morency-Potvin et al. 2017).

In Algeria antimicrobial resistance, especially in *S. aureus*, represents one of the most important human health-threatening, in addition, investigations on the resistant patterns of *S. epidermidis* are very limited, for these reasons the aim of this study is to determine phenotypic characterization of antimicrobial drug resistance of *S. aureus* and *S. epidermidis* strains isolated from various community infections in Oum El Bouaghci city, Algeria.

**MATERIAL AND METHODS**

Sources of clinical samples

The investigation of *Staphylococcus* strains included 980 clinical samples, during January-October 2020 in Oum...
El Bouaghi (Algeria). A total of 102 strains were isolated from many pathological samples (blood, pus, vaginal swab, sperm culture, skin sample, urine, breast sampling, and vulvar puncture) in the community medical analysis laboratory at Oum El Bouaghi (Algeria). All samples were transported to the laboratory in iceboxes at 4°C and were analyzed within 1 to 2 hours after sampling.

Microbiological isolation and identifications
To isolate strains, clinical samples were cultured 24H on Mannitol salt-agar (Chapman Agar) at 37°C. Isolates were grown and confirmed after culture as Staphylococcus aureus and S. epidermidis by microscopic characters such as bacterial morphology, mobility, Gram-stain and biochemical tests: catalase, oxidase, coagulase, hemolysis, DNase, mannitol fermentation tests (Quinn et al. 1994), and API STAPH-IDENT System (Wesley et al. 1982).

Antibiotic susceptibility tests
A total of 102 isolates were tested, after 24H at 37°C of incubation, and antibiotic susceptibility testing was performed using the standard disk diffusion method according to the recommendations of the Antiogram Committee of the French Microbiology Society (http://www.sfnn-microbiologie.org/). From each isolate, bacterial inoculums (~0.5 Mac Farland) were swabbed on Muller-Hinton agar.

The 12 drugs tested and their concentrations are cefoxitin (30µg), oxacillin (1µg), imipenem (10µg), vancomycin (30µg), ciprofloxacin (5µg), gentamycin (10µg), cotrimoxazole (25µg), erythromycin (15µg), lincomycin (2µg), spiramycin (15µg), pristinamycine (15µg) and fosfomycin (200µg). The plates were incubated at 37°C for 24H. The zone of growth inhibition around antibiotic discs was evaluated according to FSM (2019). Isolates were designated as resistant, sensitive, or intermediate after the measured zone of inhibition around antibiotic discs according to FSM (2019). The isolates were distinguished as MRSA (Methicillin-resistant Staphylococcus aureus) and MSSA (Methicillin sensitive Staphylococcus aureus) respectively by Oxacillin Disk Diffusion Method, and strains exhibiting resistance to three or more classes of antibiotics were defined as multidrug-resistant (MDR).

Statistical analysis
The data analysis was done using SPSS version 20, and Values were expressed as the percentages of the variables. In order to evaluate the difference in antibiotic resistance of the clinical strains obtained (S. aureus and S. epidermidis) the Pearson’s Chi-square (X²) test was performed, with 95% as confidence intervals, so a P-value less than 5% were considered statistically significant.

RESULTS AND DISCUSSION
Staphylococcus aureus is a gram-positive bacterium that has a greater impact on human health by causing various diseases (Mahendra et al. 2020). In this study, a total of 102 Staphylococcus isolates obtained from 980 samples were identified giving an overall prevalence of 10.4% (102/980) which is almost similar to the results of a study by Gahamanyi et al. (2017) in Rwanda with a prevalence of 10%, but lower than that observed in Nigeria (24.5%) (Chijioke et al. 2016). Among the 102 Staphylococcus infections, the prevalence of S. aureus was 42.2%, which is higher than the rate obtained in Algeriers 38% (Antri et al. 2011) and in Eastern Algeria 19.6% (Alioua et al. 2014). S. epidermidis is the most commonly reported CoNS species implicated in infections (Asante et al. 2020; Zatout et al. 2020). In worldwide, the prevalence of S. epidermidis in human infections varied from 6% to 68% (Asante et al. 2020), in this study this prevalence presents a rate of 57.8%, which is higher than that found in another study conducted in Algeria 43.9% (Zatout et al. 2020), in Iran 46% (Chabi and Montaz 2019), and in Nigeria 1.1% (Shittu et al. 2012).

Data of Table 1 showed that S. epidermidis is more frequently isolated from infections than S. aureus, as demonstrated by other studies (Oliveira et al. 2017), this high occurrence of S. epidermidis is may be due to the presence of various virulence factors which can be considered as the main reasons to cause infections (Otto 2009), and probably persistent carriage of this germ could act as a reservoir for infection (Archana et al. 2014), contrary to other results obtained in several countries showing that S. aureus is more frequent than S. epidermidis such as in Nigeria (Shittu et al. 2012) and in China (Yang et al. 2020).

Staphylococcus aureus is one of the most common causes of infections and it’s also a normal flora of skin that can enter the body through abrasion, cracks, burn, surgical incisions, cuts and causes pyogenic infections (Sangita et al. 2019). This study has revealed that S. aureus is the most predominant micro-organism from pus samples, as earlier studies have indicated (Onemu and Ophori 2013), with the occurrence of 72.7% which is almost similar to the finding in the study conducted in Algeria 64.28 % (Benyagoub et al. 2020), but its higher than results obtained in Egypt 38% (Abdeen et al. 2021) and in Maroc 19% (Benouda and Elhamzaoui 2009). For S. epidermidis the highest occurrence was identified from urine with the rate of 91.4%, probably this is primarily related to the contamination of urine by the commensal flora (Frédéric et al. 2008), and according to Longauerova (2006) CoNS have emerged as a principal cause of UTIs, especially S. epidermidis (Nanoukon et al. 2017).

Table 1. Staphylococcus aureus and S. epidermidis prevalence according to samples types

| Samples    | Prevalence of Staphylococcus aureus strains according origin n (%) | S. aureus prevalence n (%) | S. epidermidis prevalence n (%) |
|------------|---------------------------------------------------------------|-----------------------------|---------------------------------|
| Urine      | 35 (34.3%)                                                    | 3 (8.6%)                    | 32 (91.4%)                      |
| Skin       | 1 (1%)                                                       | 0 (0%)                      | 1 (100%)                        |
| Vaginal    | 3 (3%)                                                       | 0 (0%)                      | 3 (100%)                        |
| Pus        | 44 (43.1%)                                                   | 32 (72.7%)                  | 12 (27.3%)                      |
| Mammary    | 8 (7.8%)                                                     | 2 (25%)                     | 6 (75%)                         |
| Sperm culture | 9 (8.8%)                                                   | 5 (55.6%)                   | 4 (44.4%)                       |
| Blood      | 1 (1%)                                                       | 1 (100%)                    | 0 (0%)                          |
| Vulvar     | 1 (1%)                                                       | 0 (0%)                      | 1 (100%)                        |
| Total      | 102                                                          | 43 (42.2%)                  | 59 (57.8%)                      |
Data in Table 2 show the variation of the prevalence of *S. epidermidis* and *S. aureus* according to the gender of patients. According to the Chi-square test, there is a significant difference in the distribution of *S. epidermidis* and *S. aureus* between males and females (p-value < 0.05). The rate of isolation in *S. epidermidis* is higher in females (66.1%) than in males (33.9%), contrary to *S. aureus* which is more frequent in males (55.8%) than in females (44.2%), according to a study by Gahamanyi et al. (2017) in Rwanda males (63.3%) had more *S. aureus* than females (36.7%). The Chi-square test shows that there is no difference between the two strains at each age group (p-value > 0.05) (Table 3). The highest isolation rate of *S. aureus* and *S. epidermidis* are in the age category between 30-59 years old. The result for *S. aureus* is also in agreement with another Algerian study (Benyagoub et al. 2020), probably the factors associated with colonization by *S. aureus* were age group (Archana et al. 2014).

Overuse and misuse of antibiotics in clinical setups have led to the emergence of resistance in bacteria (Ji et al. 2018) in the community. Much less is known about the epidemiology of CoNs in health care facilities compared to MRSA (methicillin-resistant *Staphylococcus aureus*) (Becker et al. 2014). Methicillin resistance among *Staphylococci* may be due to the expression of the mecA gene (Zong et al. 2011). This study provides important data on methicillin resistance, we found 68% the rate of resistance of methicillin (oxacillin), including 42.4% in *S. epidermidis* and 25.6% in *S. aureus*, the rate of MRSA is higher than that shown by Alioua et al. (2014) in Algeria (7.6%), but its lower than the rate observed in another study in Algeria 40.5% (Antri et al. 2010), and as reported by the World Health Organization (WHO) that in some African regions, 80% of *S. aureus* and *S. sp* infections are methicillin-resistant (Kaasch et al. 2014). In developed countries, the prevalence of MRSA has reached a disturbing level within the past few years (Altaf et al. 2019).

Based on the antimicrobial susceptibility patterns thirty two *Staphylococcus* strains were MSSA (Table 4), most of MSSA isolates were susceptible to nearly all antimicrobial agents used in this study, in contrast, for the MRSA strains, the most prevalent resistances were for cefoxitin and oxacillin (25.6%) respectively, others studies showed that the resistance to β-lactam is more than 50% in *S. aureus* strains (John et al. 2019). Among the MRSA obtained, one strain (9.1%) presents resistance to lincosamides associated with macrolides susceptibility (ERY<sub>3</sub>-LIN<sub>8</sub> phenotype) which is more frequent among MRSA isolates of animal origin but is very unusual among MRSA of human origin (Schwarz et al. 2018). We found only 2.3% of MRSA are resistant to imipenem and 11.6% were resistant to fluoroquinolones and lincosamides this resistance is probably due to the use of these antibiotics to treat several community infections caused by *S. aureus* (Massanari et al. 1988), thus this resistance may induce clinical failure as has been reported by Siberry et al. (2003). But these resistance rates are lower than the results obtained in the study conducted by Ceballos et al. (2019) in Spanish hospitals which indicates that resistance to fluoroquinolones is 67% and 50% for lincosamides. The antibiotic resistance pattern of MRSA showed lower resistance rates to some family of antibiotics including aminoglycosides (4.7%), antifolates (11.6%), and macrolide (20.9%) compared to results of a previous study in Algeria (Achek et al. 2018).
The finding of multiple antimicrobial resistance in CoNs is alarming (Nascimento et al. 2015). Data in Table 4 shows that in *S. epidermidis*, the highest resistance is being to both oxacillin and cefoxitin (42.4%), this work demonstrated that resistance to aminoglycosides is to 22%, macrolides (32.2%), and antifolates (35.6%). Our results are higher than those found by Achek et al. (2018). According to literature, aminoglycoside resistance is also frequent in Staphylococcal species (Nemeghaire et al. 2014), these species can harbored aacA-D gene-encoded resistance to aminoglycosides, which is more prevalent and diffused in staphylococci of human origin (Johler et al. 2011), and probably the strains may express enzymes mediating gentamicin resistance, such as gentamicin phosphotransferase and aminoglycoside 60-N-acetyltransferase (Eladli et al. 2019). *S. epidermidis* strains have acquired resistance to other antibiotics such as rifamycin, fluoroquinolones, gentamicin, tetracycline, chloramphenicol, erythromycin, clindamycin, sulfonamides, and streptogramins because the overuse of antibiotics has led to the emergence of infectious bacteria resistant to a wide antimicrobial agent (Otto 2009; Rogers et al. 2009).

None of the strains has presented resistance to vancomycin, which is widely accepted as the most effective drug to treat staphylococcal infections (Holmes and Jorgensen 2008). Gentamicin, imipenem, and cotrimoxazole have preserved their activities; this is probably due to the low use of these antibiotics only in cases of severe infections caused by MDR organisms in human medicine (Kellie et al. 2019). The Chi-square test has indicated that there is no significant difference in resistance rates to all antibiotics used (*p*-value<0.05) between *S. aureus* and *S. epidermidis*, except for imipenem, gentamicin, and cotrimoxazole (*p*-value<0.05), these findings suggest that both strains can harbor antibiotic resistance genes but not expressing theses genes (Martineau et al. 2000; Duran et al. 2012). Overall, we found in this study that 22% of *S. epidermidis* were resistant to gentamicin compared to *S. aureus* with 4.7%. These observations are also in agreement with the findings of Martineau et al. (2000). Resistance to aminoglycosides such as gentamicin has increasingly been reported in CoNS species (Dubin et al. 1999).

Data of Tables 5, 6, and 7 delivers important information on current antimicrobial resistance, including multi-drug resistance (MDR) and Methicillin-Resistance (MR) for a collection of clinical isolates of *S. aureus* and *S. epidermidis* from community infections. It is alarming to have a high rate of MDR *Staphylococcus* in the community, especially in *S. epidermidis*, which is one of the CoNs recognized as a cause of nosocomial infections (Becker et al. 2014). Both strains present resistance between 3 to 7 different families of antibiotics (Table 6). However, the resistance mechanisms in CoNs are less well defined (Srinivasan et al. 2002), but multiresistant *S. epidermidis* is a potential source for transferring the mec gene and several genes encoding resistance to antibiotics between pathogenic Staphylococcal species (Shittu et al. 2012). So, this multi-resistance in developing countries is may be due to the not controlled use of antibiotics because several antibiotics are available without a doctor’s prescription (Kakai and Wamola 2002). The rise of resistance phenotype can be associated with auto-medication without prescription, lack of awareness in most of the people who stop antibiotics mid-way from fever, and a decline in the apparent symptoms (Saed et al. 2020).

### Table 5. Phenotype of MDR *Staphylococcus aureus* and *S. epidermidis*

| Type of strains | n (%) | Phenotype of bacteria MDR |
|-----------------|-------|---------------------------|
| *Staphylococcus epidermidis* (n=22) |       |                           |
| 1 (4.5%)         |       | CIP, GEN, SXT, ERY, LIN, PRI, FOS |
| 1 (4.5%)         |       | FOX, OXA, GEN, SXT, ERY, LIN, SPI, PRI, FOS |
| 1 (4.5%)         |       | FOX, OXA, CIP, GEN, SXT, ERY, SPI, PRI, FOS |
| 2 (9.1%)         |       | FOX, OXA, CIP, GEN        |
| 2 (9.1%)         |       | FOX, OXA, SXT, ERY        |
| 1 (4.5%)         |       | FOX, OXA, GEN, ERY, LIN, SPI |
| 1 (4.5%)         |       | FOX, OXA, ERY, LIN        |
| 1 (4.5%)         |       | FOX, OXA, CIP, GEN, SXT, ERY |
| 1 (4.5%)         |       | SXT, ERY, LIN, SPI, PRI, FOS |
| 2 (9.1%)         |       | FOX, OXA, SXT, ERY, LIN, SPI |
| 1 (4.5%)         |       | FOX, OXA, CIP, SXT, ERY, PRI |
| 2 (9.1%)         |       | FOX, OXA, CIP, GEN, SXT, ERY, LIN, PRI, FOS |
| 1 (4.5%)         |       | FOX, OXA, GEN, SXT, LIN |
| 1 (4.5%)         |       | FOX, OXA, SXT, ERY, LIN, SPI |
| 2 (9.1%)         |       | FOX, OXA, CIP, GEN, SXT, ERY, LIN, PRI, FOS |
| 1 (4.5%)         |       | FOX, OXA, SXT, ERY, LIN, SPI |
| 1 (4.5%)         |       | LIN, SPI, FOS |
| *Staphylococcus aureus* (n=6) |       |                           |
| 1 (16.7%)        |       | FOX, OXA, IMP, CIP, SXT, ERY, LIN, SPI, PRI, FOS |
| 1 (16.7%)        |       | FOX, OXA, SXT, ERY, LIN, SPI, PRI, FOS |
| 1 (16.7%)        |       | FOX, OXA, CIP, GEN, SXT, LIN |
| 1 (16.7%)        |       | FOX, OXA, CIP, SXT |
| 1 (16.7%)        |       | FOX, OXA, CIP, GEN, SXT, ERY, LIN, SPI, FOS |
| 1 (16.7%)        |       | ERY, LIN, FOS |
Table 6: Strains MDR to several families of antibiotics

| Strains              | Number (n) and percentage (%) of isolates MDR to several families |
|----------------------|---------------------------------------------------------------|
|                      | Three | Four | Five | Six | Seven | Eight |
|----------------------|-------|------|------|-----|-------|-------|
| S. aureus (n=43)     | 2     | 33.3 | 0    | 0   | 1     | 16.7  |
|                      |       |      |      |     | 1     | 16.7  |
|                      |       |      |      |     | 2     | 33.3  |
|                      |       |      |      |     | 0     | 0     |
| S. epidermidis (n=59)| 6     | 27.3 | 0    | 0   | 9     | 40.9  |
|                      |       |      |      |     | 0     | 5     |
|                      |       |      |      |     | 22.7  | 2     |
|                      |       |      |      |     | 9.1   |       |

Table 7. resistance to methicillin and multi-drug resistance profile of S. aureus and S. epidermidis according to samples types

| Samples            | S. aureus | S. epidermidis |
|--------------------|-----------|----------------|
|                    | MRSA      | MDR            |
|                    | R to meth | MDR            |
| Urine              | 1 (9.1%)  | 1 (16.7%)      | 13 (59.1%) |
| Skin               | 0 (0%)    | 0 (0%)         | 1 (4.5%)   |
| Vaginal            | 0 (0%)    | 0 (0%)         | 1 (4.5%)   |
| Pus                | 7 (63.6%) | 4 (66.7%)      | 5 (20%)    |
| Mammary            | 2 (18.2%) | 0 (0%)         | 2 (8%)     |
| Spermculture       | 1 (9.1%)  | 1 (16.7%)      | 1 (4.5%)   |
| Blood              | 0 (0%)    | 0 (0%)         | 0 (0%)     |
| Vulvar             | 0 (0%)    | 0 (0%)         | 0 (0%)     |
| Total              | 11 (25.6%)| 6 (13.9%)      | 25 (42.4%) |
|                    |           | 22 (37.3%)     |            |

Results show that the rate of MDR and MR in S. epidermidis is higher than found among S. aureus, according to Cercenado (2010) and Morgenstern et al. (2016) most MR-CoNs isolates were multi-drug resistant, and that the rate of antibiotic resistance of CoNs isolated from different clinical infections is generally higher than CoPs-related infections. Thus, treatment of methicillin-resistant CoNs related infections is difficult to challenge (Biavasco et al. 2000).

From pus, the prevalence of MDR and Methicillin Resistance (MR) among S. aureus is to (66.7%; 63.6%) respectively, these rates are higher than that observed in S. epidermidis. However, from urine the antibiotic resistance of S. epidermidis is higher than that shown among S. aureus (Table 7), according to Muder et al. (2006) which indicate that S. aureus is a rare cause of urinary tract infections, accounting for only 0.5% to 6% of all positive urine cultures.

The present study determines the phenotypic analysis of antibiotic resistance of 43 S. aureus and 59 S. epidermidis strains isolated from human community infections samples in Oum El Bouaghi city (Algeria) and it indicates that S. epidermidis is more prevalent in community infection than S. aureus with high levels of resistance to commonly used antibacterials except for vancomycin. The presence of MDR in some S. epidermidis and S. aureus strains is due to the misuse of antibiotics in Algeria and should be considered as a serious health concern. In Algeria, regular surveillance of antibiotic prescriptions for human infections is essential in order to conserve the efficacy of the antibiotics and reduce the emergence of multi-drug resistant strains.

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