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Linezolid and Methicillin Resistances in *S. aureus* Isolated from the Anterior Nares of Apparently Healthy Undergraduates of the Niger Delta University, Nigeria

Abdulrasheed Abdu[1*] and Adebayo Lamikanra[2,3]

[1]Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Amassoma, Bayelsa-State, Nigeria.
[2]Department of Pharmaceutics, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Nigeria.
[3]Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun-State, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author AL designed the study and wrote the protocol. Author AA performed the statistical analysis and wrote the first draft of the manuscript and managed literature searches. Author AL managed the review of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Background: The carriage of *Staphylococcus aureus* in the anterior nares of subjects in the study environment has not been carried out before and this study is thus a reference study against which future studies can be compared. The isolates obtained were also tested against frequently used antibiotics as well as linezolid, an antibiotic which is of considerable importance in the treatment of Methicillin Resistant *Staphylococcus aureus* (MRSA).
Methods: A total of 400 nasal swabs were collected from anterior nares of apparently healthy subjects aseptically using a sterile swab sticks. The antibiotic susceptibilities of isolates of

**Corresponding author: E-mail: abdulsoul@gmail.com;*

S. aureus obtained against eight different antibiotics including Linezolid were determined using the disc-plate method.
Results: The results showed that 91 (22.8%) of the subjects tested are nasal carriers of *S. aureus*. The incidences of resistance observed with each of the antibiotics tested were as follow: Erythromycin 83(91.2%), Tetracycline 79(86.8%), Co-trimoxazole 78(86.8%), Cefoxitin 77(84.6%), Linezolid 72(79.1%), Ciprofloxacin 70(76.9%), Augmentin 49(53.8%) and Gentamycin 39 (42.9%).
Conclusion: Treatment of *S. aureus* infections within the study environment should be based on the results of *in vitro* susceptibility testing of the isolates. Gentamicin promises to be the best antibiotic for the treatment of disorders associated with Staphylococci in the study area. This is of special importance in an environment within which a very substantial proportion of the isolates are resistant to methicillin and linezolid.

Keywords: Staphylococcus aureus; anterior nares; opportunistic infection; antibiotic resistance; linezolid and methicillin resistance; apparently healthy.

1. INTRODUCTION

Staphylococcus aureus is an opportunistic pathogen often carried asymptomatically on human skin, especially in the anterior nares. The nasal carriage of this organism is significant because carriers are often infected post-surgically with the same organisms which are found in their nose. This being the subject of several studies from different parts of the world including Nigeria. The results of these studies showed that the nasal carriage of *S. aureus* is affected by location, sex and age of the subjects studied. In the studies carried out in Nigeria, Paul et al. [1], Lamikanra et al. [2], Abdulhadi et al. [3], Nworie et al. [4] and Nsofor et al. [5] have reported carriage rates of 52.5%, 56.4%, 39%, 23% and 56.3% respectively. Lamikanra et al. [2] have also reported the nasal carriage of encapsulated *S. aureus* in the anterior nares of Nigerian school children. Another interesting aspect of the nasal carriage of *S. aureus* is the incidence of Methicilin resistant organisms. Methicillin-resistant *S. aureus* (MRSA) strains have acquired a gene that makes them resistant to all *beta-lactam* antibiotics and Hospital-associated strains of this organism are serious nosocomial pathogens that have become resistant to most common antibiotics making the treatment of infections caused by these very challenging [6,7]. Also, Community-associated MRSA strains occur in people who have not been hospitalized or recently had invasive procedures. They first appeared in high-risk populations (e.g., intravenous drug users, people with chronic illnesses), but are now found even in healthy children. Until recently, community-associated strains were susceptible to many antibiotics other than *beta-lactams*; however, resistance seems to be increasing, and multiple antibiotic resistant strains have started to emerge. Human-adapted MRSA can be transmitted to animals in close contact, which can sometimes act as carriers and re-infect people [8-10].

The aims of this study are to evaluate the nasal carriage rate of *S. aureus* isolated from the anterior nares of apparently healthy Medical and Nursing students of the Niger Delta University, Bayelsa State, Nigeria. In addition, the isolates were examined for their sensitivity to some of the most frequently prescribed antibiotics within the study area and to highlight the prevalence of MRSA as well as linezolid resistance in these students. The choice of this antibiotic is due to the fact that it is recognized as one of the few drugs that have been reported to be effective in the treatment of infections caused by MRSA, although there are no indications of its use within the study area. This study is the first to be carried out in the study area and it will serve as preliminary baseline data for nasal carriage rate and LRSA antimicrobial profile of *S. aureus* for the region.

2. MATERIALS AND METHODS

2.1 Sampling Area

The study was carried out in Amassoma, a semi urban settlement in the Niger Delta and is home to the Niger Delta University with a student population of about 20,000. It is located on Latitude 4°59’ 09’’ N and longitude 6°06’ 34’’ E. Its land area is 2,682 Km^2 (1,036 sq miles) at an elevation/altitude of 9 metres. It is in an area of high humidity (mean: 300C) and temperature (average: 26.7°C with annual rainfall of about 1777 mm.

The students sampled in this study were medical and nursing students of the university. They are of age: (range: 15-39, mean = 22), Sex: (Males: 124; Females: 276) and have stayed a period of 1 year minimum in the University.

2.2 Sampling

Anterior nares swabs were collected in accord to protocols described by Rongpharpi et al. [11]. A total of 400 nasal swabs were collected from anterior nares of apparently healthy subjects aseptically using a sterile swab sticks (Copan Diagnostics, Corona, CA, USA). Swabs were transported in Amies (Oxoid, England) transport medium to the Medical microbiology laboratory of the College of Health Sciences, Niger Delta University for bacteriological assay.

2.3 Isolation and Identification

In the laboratory, each swab was immediately inoculated onto Mannitol Salt Agar (MSA; Oxoid, England) plates and incubated at 37℃ for 24 h. The characteristic isolates were aseptically isolated and characterized using established microbiological methods that include colonial morphology, Gram stain characteristics, haemolysin production catalase, coagulase tests as well as DNase production [12]. The various isolates were identified to species level by employing standard microbiological methods [12,13]. Staphylococcus aureus isolates were confirmed through the use of the Staph identification 25 E (BioMeriux, France).

2.4 Antimicrobial Susceptibility Testing

The antimicrobial susceptibility pattern of all the isolates to Augmentin (30 g), Cefoxitin (30 g), Ciprofloxacin (5 g), Co-trimoxazole (25 g), Erythromycin (15 g), Gentamycin (30 g), Linezolid (30 g), and Tetracycline (30 g) all obtained from Oxoid (England) were determined using modified single disc diffusion technique in accordance to the guidelines of Clinical and Laboratory Standards Institute (CLSI, 2012) [14]. Briefly, standardized overnight culture of each isolate (containing approximately 10^6 cfu/ml) which was equivalent to 0.5 McFarland Standard was used to swab the surface of Mueller Hinton agar plates and excess drained off and dried while the Petri dish lid was in place. The standard antimicrobial discs were aseptically placed at reasonable equidistance on the inoculated plates and allowed to stand for I hr. The plates (prepared in duplicates) were then incubated at 37℃ for 18-24 h. The diameter of the zone of inhibition produced by each antimicrobial disc was measured with a ruler in millimeters. Breakpoints and interpretative for susceptibility/resistance was based on the CSLI criteria [14].

2.5 Statistical Analysis

Statistical analysis was done using SPSS (version 20) to determine frequency distribution, mean, harmonic mean, standard deviation, analysis of variance (ANOVA), Duncan Multiple Range and Pearson correlation coefficient.

3. RESULTS

As shown in Table 1, 227(56.8%) of the 400 studied subjects yielded Staphylococci growths. A total of 91(22.8%) of the isolates were Staphylococcus aureus.

Table 1. Age and sex distribution of the subjects and the isolation (Carriage) rate of Staphylococci spp. colonising anterior nares

Age	Male	Female	No (%) isolate
15-19	3	7	10(10.99)
20-24	24	39	63(69.23)
25-29	6	4	10(10.99)
30-34	0	4	4(4.40)
35-39	0	4	4(4.40)
Total	33	58	91(100)

Fig. 1, shows the antimicrobial susceptibility profile of the isolates. Overall, 83(91.2%) S. aureus showed resistance to Erythromycin whilst 39 (42.9%) of them were found to be resistant to gentamycin. The resistance profile to Tetracycline, Co-trimoxazole, Cefoxitin, Linezolid, Ciprofloxacin and Augmentin were 79(86.8%), 78(85.7%), 77(84.6%), 72(79.1%), 70(76.9%), and 49(53.8%) respectively.

The prevalence of multiple antibiotic resistance (MAR) of the isolates was investigated as shown by as show% (s)-55.2984(sh)-8.043362984(a)-8.0433(s)5(0s65(r)-13.1

susceptibility seen in this study may be that gentamycin appears to be infrequently used as it administered by injection, a dosage form which is far less amenable to self- medication than orally administered antibiotics in this locality [39].

The high percentage of Augmentin resistant *S. aureus* in this research as shown in Fig. 1 differs from the reports of various researchers Roopa and Biradar [40], Babafemi et al. [26], Fagade et al. [41] and Fadeyi et al. [42].

The antimicrobial resistance profile of *S. aureus* isolated in this study showed that 84.6%, of the isolates were resistant to Cefoxitin. This result is higher than earlier report made by Hummel et al. [24,25] and Roopa and Biradar [40] among the organisms isolated in their respective studies. Reports have documented that resistance to cefoxitin by disc diffusion can be used for the detection of MRSA strains in routine testing [43] because cefoxitin is regarded as a potential inducer of the system that regulates *mecA* gene [44]. For this reason, the resistant of our isolates which were found to be resistant to cefoxitin are considered resistant to methicillin.

One of our limitations during this susceptibility test was excluding Vancomycin, the drug of choice for MRSA, from the susceptibility test because we were unable to get the commercial disc. Nonetheless, Delorme et al. [45] reported the exclusion of vancomycin from their study because vancomycin may produce erratic results in disc diffusion susceptibility test [45]. However, even with the absence of vancomycin susceptibility test, the result of this study can be compared with the findings of several outcomes including [46-49] which established that linezolid is a drug that is as effective as vancomycin. Both antibiotics do not just have similar failure and success rates but adverse effects as well [47,50].

The high (75.8%) resistance to trimethoprim/sulfamethoxazole in this study is comparable to what has been reported by Ojulong et al. [51] and Stanley et al. [52] in Uganda and many other researchers, a finding correlated to that by Kumar et al. [53]. This could be due to the fact that this drug is very commonly available in our setting and is also indiscriminately used for prophylaxis by individuals with symptoms of Upper Respiratory Tract infections (URTI) and Urinary Tract Infections (UTI). The study by Paul et al. [1] showed zero resistance to trimethoprim/ sulfamethoxazole in Nigeria in 1985. This is worthy of mention and comparison. It shows that trimethoprim/sulfamethoxazole resistance has risen astronomically over the intervening years.

In order to combat the increase in mortality and morbidity due to therapeutic failures in the treatment of multidrug resistant *S. aureus* infections, particularly those that are methicillin and vancomycin resistant, the search for new efficacious therapeutic agents led to the discovery and introduction to clinical practice of the oxazolidinone antibiotic: Linezolid by FDA in 2000 as an alternative to vancomycin [46,54,55] of which resistance was already appearing. Within one year of its introduction into treatment regime for multidrug resistant Gram-positive organisms, however, some strains of *Enterococcus faecium*, were reported [56] and in the same year, Tsiodras et al. [57] reported the first Linezolid resistant *Staphylococcus aureus* in a patient in the USA. Since then, linezolid-resistant *S. aureus* have been detected in separate cases [58-60].

In the present study, 79.1% of *S. aureus* isolates were found to be linezolid resistant, making this finding one of the highest resistance rate recovered among *S. aureus* isolates anywhere as the incidence of linezolid resistance has remained low. For example, Hummuel et al. [24] in Zaira, northern Nigeria and Stanley et al. [52] in Uganda reported 0% resistance to linezolid respectively. Global surveillance studies report <1% of *Staphylococcus aureus* as linezolid resistant and the incidence of linezolid resistance has remained low even among MRSA as a study conducted by Baddour and colleagues [61] in Riyadh, Saudi Arabia, observed Linezolid resistance in about 4.1% of MRSA isolates. Another study conducted in South India by Rajaduraipandi and colleagues reported LRSA in 2% of MRSA [62]. Similarly, incidence of 2.2% was reported by Norma et al. [63] from Mexico. Harcharan et al. [64] however reported 20.3% LRSA in Rajasthan, northern India. Aamir et al. [65] also reported a resistance rate of 30.0% LRSA in a study carried out in Egypt. Nonetheless, consistent, though slightly higher with our findings, the resistance rates to linezolid was 85.7% in MRSA isolates as reported by Armin et al. [66] from Iran. The high incidence of linezolid resistance in the organisms isolated in this study is unexpected since this antibiotic is not normally used within the study environment and it is not clear how linezolid resistance is so high in isolates obtained from apparently healthy subject. It has been suggested by several workers that the high rate of resistance to many antibiotics in Nigeria is as a result of the uncontrolled use and ready availability of antibiotics in Nigeria [67] this is worrisome and is worthy of note. Particularly that linezolid is not routinely prescribed and administered in our locality. More so that the drug is very difficult, if available in our market, in other words, its availability for misuse or self-administration as reported among other antibiotics is not anticipated. So, this high resistance recorded must be of concern to practitioners and public health, since these organisms and their antimicrobial resistance have been documented to be associated with opportunistic infections and can be transferred from these individuals to the patients, hospital environments and the community [6,7,24,68-71] making it a life-threatening organism which may lead to increase mortality and morbidity, particularly among colonised individuals, immunocompromised persons and HIV patients. Staphylococcal resistance to linezolid is said to be mediated through ribosomal mutations (23S rRNA or ribosomal proteins L3 and L4) or through methylation of 23S rRNA by the horizontally transferred *Cfr* plasmid-borne ribosomal methyltransferase [72-74]. The mechanisms by which linezolid resistance develops and spread within the study environment needs to be investigated.

5. CONCLUSION

The study highlights that treatment of *S. aureus* infections within the study environment should be based on the results of *in vitro* susceptibility testing of the isolates. However, Aminoglycosides: Gentamicin promises to be the best antibiotic for the treatment of disorders associated with Staphylococci in the study area. This is of special importance in an environment within which a very substantial proportion of the isolates are resistant to methicillin and linezolid.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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