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Prevalence and Antibiotic Resistance Profiles of Methicillin-Resistant *Staphylococcus aureus* Isolated from Clinical Specimens in Anyigba, Nigeria

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) is a major public health concern, and it is responsible for both hospital and community associated infections globally. In this study, we aimed at determining the prevalence and pattern of resistance of MRSA to commonly used antibiotics in Anyigba, Nigeria. This was a hospital based, cross-sectional study conducted between August 2017 and February 2018. One hundred and fifty routine clinical specimens were collected from selected health facilities in Anyigba for laboratory analyses. Standard laboratory methods were employed in the identification of the isolates. Methicillin-resistant Staphylococcus aureus (MRSA) was confirmed using Oxacillin Resistance Screening Agar Base (ORSAB) supplemented with 2g/l of Oxacillin. Screening to determine the antibiotic resistance profiles of all confirmed MRSA isolates was by disc diffusion method. A total of 124 (82.7%) isolates of Staphylococcus aureus were recovered from clinical samples obtained. Of these isolates, 28 (22.6%) were methicillin resistant. The percentage distribution rate of MRSA was highest (50.0%) in urine samples. Majority of these isolates were resistant to at least four of the six antibiotics tested. Most of the isolates recovered from urine samples were resistant to Gentamicin (92.9%), Amoxicillin (100.0%) and Cotrimoxazole (85.7%). Our study showed a significant presence of MRSA isolates in the clinical specimens collected, with a relatively high rate to gentamicin, Amoxicillin and Cotrimoxazole antibiotics. This study highlights the need for monitoring of antimicrobial use considering the lack of innovation in the development of new antimicrobials which lessens efforts at combating infections caused by antibiotic-resistant pathogens.

Keywords: Staphylococcus aureus, MRSA, Antibiotic resistance, Clinical specimens

INTRODUCTION

Staphylococcus aureus is a Gram-positive, spherical, non-spore forming, non-motile facultative anaerobic bacterium common associated with skin, skin glands and mucous membrane particularly in the nasal passages of healthy individuals with approximately 25 - 40% of the population colonized with it (Konrad *et al.*, 2009; Frana *et al.*, 2013). The bacterium is one of the most studied and characterised species of staphylococci, and one of the most significant human pathogens causing both nosocomial and community acquired infections (Harris *et al.*, 2002; Fang and Hedin, 2003).

This bacterium is also responsible for various infections ranging from mild conditions, such as skin and soft tissue infection, to severe, life threatening debilitation such as pneumonia, bacteraemia, meningitis, sepsis and pericarditis (Lowy, 1998; Waldvogel, 2000; Frana *et al.*, 2013). Its cells form grape-like clusters and produce staphylococcal enterotoxins (SE). It is responsible for almost all staphylococcal food poisoning which is commonly associated with human and animals (Le Loir *et al.*, 2003; Konrad *et al.*, 2009). Infections caused by this bacterium have resulted in significant morbidity and mortality rates in both community and hospital settings (Turner *et al.*, 2019).

Antibiotics resistance in *Staphylococcus aureus* was almost unknown when penicillin was first introduced in 1943. However, in the year 1950, 40% of hospital *Staphylococcus aureus* were resistant to penicillin and by 1960 this had risen to 80% (Chambers, 2000). The treatment of patient with *Staphylococcus aureus* infection has become a major concern since the emergence of antimicrobial resistant *Staphylococcus aureus* (Kumar *et al.*, 2011).

Methicillin-resistant *Staphylococcus aureus* (MRSA) were first detected in the early 1960s shortly after methicillin came into clinical use (Chamber, 1997; Islam *et al.*, 2011). It was first reported in England, but it is now widely spread, particularly in the hospital settings (Islam *et al.*, 2011).

The wide spread of this resistant strain of *Staphylococcus aureus* may be due to clonal dissemination between different hospitals, cities, countries and even continents causing infections worldwide (Enright *et al.*, 2002; Oliveira *et al.*, 2002).

Methicillin-resistant *Staphylococcus aureus* carries the *MecA* gene that codes for an alternative penicillin binding protein known as PBP-2a, with low binding affinity to all beta-lactams. These strains were first described in hospital setting after the introduction of beta-lactamase insensitive penicillin into the medical practice and they continue to be a serious problem in healthcare due to their ability to acquire multidrug resistance determinants (Konrad *et al.*, 2009; Kurlenda *et al.*, 2009).

Methicillin-resistant *Staphylococcus aureus* is one of the important antibiotic-resistant pathogens and a leading cause of hospital-associated and community-associated infections worldwide (Lee *et al.*, 2018). The World Health Organization (WHO) recently included MRSA as one of the indicators for antimicrobial resistance in the monitoring framework of the Sustainable Development Goals connected to the health target 3.d (strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks) (WHO, 2021).

The prevalence of MRSA infection in developed and developing nations varies. In 2014, the prevalence of invasive MRSA isolates in Europe ranged from 0.9% in the Netherlands to 56% in Romania (ECDC, 2015). In Africa, MRSA prevalence has been reported to be heterogenous within and across countries. National data from 9 African countries show MRSA rates to approximate between 12 and 80%, with some countries exceeding 82% (Falagas *et al.*, 2013; CDDEP, 2015; Garoy *et al.*, 2019). Reports on methicillin resistance in *Staphylococcus aureus* have also been documented to have exceeded 20% in all World Health Organization (WHO) regions and above 80% in some regions (WHO, 2014). Available evidence demonstrated that the prevalence of MRSA infection in Nigeria has increased. The rate was reported as 18.3% in 2009, 16.5% in 2010, 42.3% in 2013, 46.9% in 2020 and 48.9% in 2021(Shittu *et al.*, 2011; Shittu *et al.*, 2012; Alli *et al.*, 2015; Adeiza *et al.*, 2020; Medugu *et al.*, 2021). These data indicate that MRSA infection rate has increased from 18.3% in 2009 to 48.9% by 2021.

Methicillin-resistant *Staphylococcus aureus* especially hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) is at present not only associated with mortality but with long hospital stays and imposes a serious economic burden on scarce healthcare resources worldwide (Kong *et al.*, 2016). The health burden attributable to MRSA has been summarised in the WHO antimicrobial resistance report as significant increased all-cause, bacterium-attributable and intensive care unit mortality (WHO, 2014).

In Nigeria, surveillance data that describes the trend of MRSA in clinical isolates over a period of time is not enough (Abubakar and Sulaiman, 2018) despite established facts that MRSA is a major clinical problem globally. This study on the prevalence and antibiotic resistance profiles of Methicillin-resistant *Staphylococcus aureus* in Anyigba has, therefore, become necessary because of the pathogens' potential for high morbidity and mortality especially in resource-poor settings.

MATERIALS AND METHODS

Study Design and Area

This hospital-based cross-sectional study which was carried out between August 2017 and February 2018 was conducted in Anyigba, a community in Dekina Local Government of Kogi State, Nigeria. The community has a population estimated to be about 130,000 inhabitants and lies between latitude 7°15'-7°29' north and longitude 7°11'-7°32' east. The major occupation of these inhabitants is farming (Omatola *et al.*, 2019).

Ethical Clearance

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of Kogi State University Teaching Hospital (KSUTH), Anyigba in accordance with the ethical code of the World Medical Association Declaration of Helsinki. Study participants gave their consent to take part in the study.

Sample Collection

A total of 124 consecutive and non-duplicate *Staphylococcus aureus* isolates were recovered from routine clinical specimens obtained from patients attending three public health facilities in Anyigba, Nigeria, Kogi State University Teaching Hospital (KSUTH), Grimard Catholic Hospital (GCH) and Maria Goretti Hospital (MGH). These clinical specimens were collected from inpatients and included urine, high vaginal swabs (HVS), wound swabs, catheter, skin swabs, and nasal swabs. Information on sex and age of participants were obtained from patients' hospital records.

Isolation and Identification of *Staphylococcus aureus*. All clinical specimens were inoculated into 5ml Nutrient broth (Oxoid, UK) and incubated at 37ºC for 24 hours. A loopful of the broth culture was streaked on to Mannitol Salt Agar (Oxoid, UK) and incubated for 24-48 hours at 37ºC. Isolates with characteristic yellow colonies were Gram stained and further characterized by conventional microbiological methods such as catalase test, coagulase (both slide and tube methods) test, indole test and methyl red test. All observed isolates were stored at 4ºC on Nutrient Agar slants for further screening for methicillin resistance.

Identification of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) was confirmed using Oxacillin Resistance Screening Agar Base (ORSAB; Oxoid, UK) supplemented with Oxacillin (2g/l). All isolates identified as *Staphylococcus aureus* from a normal saline suspension adjusted to 0.5 McFarland standard were streaked onto ORSAB plates and incubated at 37ºC for 24 hours. Cultures were identified based on formation and colour of colonies. Blue-coloured colonies indicated the presence of MRSA (Becker *et al.*, 2002).

Antibiotic Susceptibility Test

Susceptibility testing of confirmed MRSA isolates was performed using disc diffusion method. Discrete colonies of freshly grown MRSA isolates were suspended into normal saline and the turbidity of the suspension was adjusted to 0.5 McFarland standard. The suspension was inoculated onto Mueller Hinton Agar (MHA) by streaking the surface of the agar while rotating the plate approximately 60ºC to ensure even distribution bacterial suspension. Plates were allowed to dry before aseptically introducing antibiotic discs to the surface of the agar and then incubated for 18hrs at 37ºC (Arjyal *et al.*, 2020). The following antibiotics were used; Ceftriaxone (30 ¤g), Gentamicin (10 µg), Ciprofloxacin (5 µg), Amoxicillin+Clavulanic acid (30 µg), Amoxicillin (30 µg) and Cotrimoxazole (25 µg). Results were interpreted as resistant or susceptible based on the interpretative standard chart of the Clinical and Laboratory Standards Institute (CLSI, 2016) manual.

RESULTS

From a total of 150 samples collected from selected hospitals, 124 isolates of *Staphylococcus aureus* (82.7%) were confirmed. Of these isolates, 90 (72.6%) were recovered from females (Table 1) while 42 (33.8%) of patients within the age group 26 – 35 years were most affected (Table 2).

Results from the detection of methicillin resistance showed that 28 (22.6%) of the 124 *Staphylococcus aureus* isolated were methicillin resistant (Figure 1). The distribution of MRSA isolates against various clinical samples showed a high frequency of MRSA in urine samples (50.0%). Six (21.4%) of the MRSA isolates were from Nasal swabs, 4 (14.3%) from high vaginal swabs and 2 (7.1%) from the skin (Table 3).

The pattern of resistance of MRSA isolates from the various sample types against a number of antibiotics is shown in Table 4. Majority of the isolates were found to be resistant to at least four of the six antibiotics tested. Resistance to Ciprofloxacin acid and Amoxicillin accounted for 60.7% and 85.7% respectively. Of the 28 MRSA strains isolated, 25(82.1%) were sensitive to Amoxicillin+Clavulanic acid and the remaining (17.9%) were resistant.

Methicillin-resistant *Staphylococcus aureus* isolates recovered from urine samples were highly resistant to Gentamicin (92.9%), Amoxicillin (100%) and Cotrimoxazole (85.7%). A 100% resistance to Ciprofloxacin and Amoxicillin+Clavulanic acid was observed in isolates recovered from catheter and wounds while resistance to 5 of the 6 antibiotics tested against isolates recovered from high vaginal swabs ranged between 25% to 75%.

Table 1: Sex distribution of patients with *Staphylococcus aureus* infection

Sex	No. Examined (%)	No. Positive (%)
Male	39 (26.0)	34 (27.4)
Female	111 (74.0)	90 (72.6)
Total	**150 (100.0)**	**124 (100.0)**

Table 2: Age distribution of patients with *Staphylococcus aureus* infection

Age group (Years)	No. Examined (%)	No. Positive (%)
<16	14 (9.3)	12 (9.7)
16 - 25	35 (23.3)	28 (22.6)
26 - 35	47 (31.3)	42 (33.8)
36 - 45	32 (21.3)	24 (19.4)
46 - 55	09 (6.0)	06 (4.8)
56 - 65	02 (1.3)	02 (1.6)
>65	11 (7.3)	10 (8.1)
Total	**150 (100.0)**	**124 (100.0)**

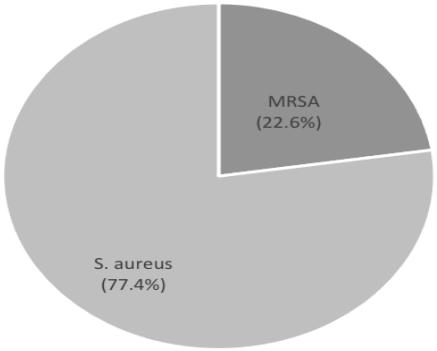

Figure 1: Occurrence of MRSA isolated from clinical specimens

Table 3: Distribution of *Staphylococcus aureus* (MRSA/MSSA) isolates in patients' clinical samples

Patients' sample type	MRSA (%)	MSSA(%)	Total (%)
Urine	14 (50.0)	46 (47.9)	60 (48.4)
Catheter	01(3.6)	01 (1.0)	02 (1.6)
Skin swabs	02 (7.1)	10 (10.4)	12 (9.7)
Nasal swabs	06 (21.4)	30 (31.3)	36 (29.0)
High vaginal swabs	04 (14.3)	06 (6.3)	10 (8.1)
Wound swabs	01 (3.6)	03 (3.1)	04 (3.2)
Total (%)	28 (22.6)	96 (77.4)	124 (100.0)

Table 4: Pattern of resistance of MRSA isolates from patients' sample types

Antibiotics	Urine No. of isolates (%)		Catheter No. of isolates (%)		Skin No. of isolates (%)		Nasal No. of isolates (%)		HVS No. of isolates (%)		Wounds No. of isolates (%)	
	R	S	R	S	R	S	R	S	R	S	R	S
CRO_{30}	08 (57.1)	06 (42.9)	-	01 (100.0)	02 (100.0)	-	02 (33.3)	04 (66.7)	03 (75.0)	01 (25.0)	-	01 (100.0)
CN_{10}	13 (92.9)	01 (7.1)	01(100.0)	-	01 (50.0)	01 (50.0)	03 (50.0)	03 (50.0)	03 (75.0)	01 (25.0)	-	01 (100.0)
CIP_5	10 (71.4)	04 (28.6)	01(100.0)	-	01 (50.0)	01 (50.0)	02 (33.3)	04 (66.7)	02 (50.0)	02 (50.0)	01 (100.0)	-
AMC_{30}	01 (7.1)	13 (92.9)	01(100.0)	-	-	02 (100.0)	02 (33.3)	04 (66.7)	-	04 (100.0)	01 (100.0)	-
AMX_{30}	14 (100.0)	-	-	01 (100.0)	01 (50.0)	01 (50.0)	06 (100.0)	-	03 (75.0)	01 (25.0)	-	01 (100.0)
COT_{25}	12 (85.7)	02 (14.3)	-	01 (100.0)	02 (100.0)	-	05 (83.3)	01 (16.7)	01 (25.0)	03 (75.0)	01 (100)	-

R: Resistant, **S:** Susceptible, **CRO_{30}**: ceftriaxone 30μg, **CN_{10}**: gentamicin 10μg, **CIP_5**: ciprofloxacin 5μg, **AMC_{30}**: amoxicillin+clavulanic acid 30μg, **AMX_{30}**: amoxicillin 30μg, **COT_{25}**: cotrimoxazole 25μg

DISCUSSION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major public health concern as it is responsible for both hospital and community associated infections worldwide (CDC, 2013; Falagas *et al.*, 2013; Chen and Huang, 2014). The health burden attributable to MRSA has been summarised as bacterium-related and intensive care unit mortality as well as post-infection and intensive care unit length of stay (WHO, 2014; Wangai *et al.*, 2019).

Surveillance of antibiotic resistance is necessary for the detection and monitoring of threats to public health. Our study addresses this goal by determining the prevalence and pattern of resistance of MRSA to commonly used antibiotics in Anyigba. In this study, we observed 22.6% methicillin-resistance rate amongst *Staphylococcus aureus* isolates from clinical samples obtained from the patients. This is comparable to 20.23% observed in a study by Ghebremedhin *et al.* (2009). This finding falls within the range determined in a previous report which put the prevalence in Nigeria at the range of 21% - 30% (Abdullahi and Iregbu, 2018). Furthermore, different studies have shown similar results in the prevalence rates of MRSA in different countries ranging from 23.6% in Australia (Diekema *et al.*, 2001) to 25% in England, Greece and France (Orrett, 1997). The reported proportion is however lower than previously reported values (28.6% - 50%) in Nigeria (Ikeh, 2003; Taiwo *et al.*, 2005; Nwankwo *et al.*, 2010). The observed prevalence of MRSA in this study calls for concern especially at this time where there is a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements (Ventola, 2015).

In Africa, several studies have indicated that the prevalence of MRSA is between 25% - 50% (Vlieghe *et al.*, 2009; Falagas *et al.*, 2013). However, comparatively higher values have been reported in other settings in Africa (Garoy *et al.*, 2019). Higher frequency of MRSA has also been reported in other parts of the world including Peru (80%) and Colombia (Guzman-Blanco *et al.*, 2009; Jimenez *et al.*, 2012). Differences in study design, specimen type and laboratory methods have been linked to the intercountry variation in the prevalence rate of MRSA (Garoy *et al.*, 2019).

Among all infectious agents causing urinary tract infections (UTIs), *Staphylococcus aureus* is considered an important pathogen because of its high level of resistance against commonly used antibiotics (Hammer *et al.*, 2014; Yahaghi *et al.*, 2014). Findings in this study show that the proportion of *Staphylococcus aureus* isolates from urine samples is high (48.4%) when compared with other studies from Nigeria (20.8% - 32.4%) (Ekwealor *et al.*, 2016; Oladeinde *et al.*, 2011; Ayepola *et al.*, 2015). In general, high proportion of *Staphylococcus aureus* from Africa has been reported from UTIs and the reasons for this phenomenon are unknown (Ayepola *et al.*, 2015) but might be related to altered interplay of the host, the microorganism, and the environment (Schaumburg, 2014).

Accumulating evidence from previous studies has demonstrated that the mechanisms of resistance for MRSA are very complex making it resistant to many kinds of antibiotics. Hence, understanding the drug resistance of MRSA in a timely manner is of significance for the treatment of *Staphylococcus aureus* infection (Foster, 2017; Peterson and Kaur, 2018; Guo *et al.*, 2020). In our present study, we investigated the antibiotic resistance pattern of MRSA isolates to 6 antimicrobials, and a significant number of isolates showed high resistance to 4 or more antibiotics. This observation is similar to results from previous studies (Campanile *et al.*, 2015; Tadesse *et al.*, 2018; Kot *et al.*, 2020). Lower rate of resistance (17.9%) to Amoxicillin+Clavulanic acid was observed. This may be due to collateral sensitivity where resistance to one antibiotic increases sensitivity to another (Harrison *et al.*, 2019).

Our study revealed that the MRSA strains recovered from urine samples were generally multidrug resistant with increasing resistance to Gentamicin, Amoxicillin, and Cotrimoxazole. This finding is in line with previous studies (Rajaduraipandi *et al.*, 2006; Looney *et al.*, 2017; Singh *et al.*, 2019). These drugs are available as over-the-counter antibiotics and may have developed resistance due to selective pressure from inappropriate use (Abdullahi and Iregbu, 2018). The high resistance (100%) to Amoxicillin+Clavulanic acid observed in MRSA isolates from catheter and wound swabs may be due to the production of additional beta-lactamases by MRSA strains rendering them resistant to improved antibiotics such as Amoxicillin+Clavulanic acid (Osman *et al.*, 2018). Similar results from previous studies have been noted for Ciprofloxacin among strains in Kinshasa (Iyamba *et al.*, 2014), and Nigeria (Abdullahi and Iregbu, 2018). Melaku *et al.* (2012) had earlier in a study on antibiogram of nosocomial UTIs in Ethiopia, reported that most bacteria including *Staphylococcus aureus* were over 80% resistant to Amoxicillin + Clavulanic acid.

CONCLUSION

The prevalence rate of MRSA observed in this study (22.6%) calls for concern especially in this era of antimicrobial resistance. This study found that a significant number of isolates were resistant to multiple antibiotics at varying rates. Most of the MRSA strains recovered from urine samples were resistant to Gentamicin, Amoxicillin and Cotrimoxazole. Isolates recovered from catheter and wound swabs showed high resistance to Amoxicillin+Clavulanic.

RECOMMENDATION

We recommend that resistance in *Staphylococcus aureus* strains be monitored continuously in order to control antibiotic resistance as well as good infection control practices. Also, the use of antibiotics without prescription or inappropriate prescription should be discouraged as the overuse and misuse of antibiotics results in the emergence and spread of resistant strains.

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