



Methicillin and Inducible Clindamycin-resistant *Staphylococcus aureus* Isolates from Clinical Samples in Abia State

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Authors' contributions

This work was carried out in collaboration among all authors. Author ACI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ESA and CIC managed the analyses of the study. Author RNN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Staphylococcus aureus is a major bacterial pathogen that causes different community and hospital-acquired infections. *S. aureus* resistant to methicillin has become a big and expanding problem of concern in many developing countries. Clindamycin has also been discovered to be a preferred therapeutic alternative for the treatment of both methicillin susceptible and resistant staphylococcal infections. This study examined the prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA) in clinical samples of patients in Abia state, Nigeria using standard recommended procedures. A total of 750 clinical specimens of blood and urine samples, wound, ear, nasal, high vaginal and ear swabs were collected from three major health facilities in Abia state, Nigeria. Each sample was cultured for bacterial isolates and examined for colonial and cellular morphology while biochemical identification was performed. Antimicrobial susceptibility test was performed on Mueller-Hinton agar (MHA) by disc diffusion method and MRSA screening was done using cefoxitin disc. A total of 265 (35.3%) *S. aureus* isolates were recovered, out of which 126(47.5%) were from males

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and 139(52.5%) were from females, however there was no association between the prevalence and gender (p-value = 0.05) and also prevalence and age (p-value = 0.52). Of the 265 *S. aureus* isolates recovered, 164(61.9%) were MRSA. All 100% of the MRSA were susceptible to vancomycin, 120(73.2%) to clindamycin, 92(56.1%) to gentamycin. All 100% were resistant to ceftazidime, 157(95.7%) to cloxacillin, 146(89.0%) to augmentin, 136(82.9%) to ceftriaxone and 103(61.6%) to erythromycin. The MRSA strains showed much higher resistance rate than their MSSA counterparts to all tested antibiotic except clindamycin. 64(39.0%) of the MRSA were resistant to 4 classes of antibiotics indicating multi drug resistance (MDR). The overall prevalence of inducible clindamycin resistance among methicillin resistant isolates was 29(17.7%). This implies that 17.7% could have been misidentified as clindamycin susceptible by Kirby-Bauer disk diffusion method. In conclusion prevalence of MRSA was high and it is important to routinely carry out the D-test for detection of inducible clindamycin resistance if clindamycin is considered as a treatment option.

Keywords: MRSA; MDR; inducible clindamycin-resistance.

1. INTRODUCTION

Staphylococcus aureus is a Gram positive, non-spore forming, facultative anaerobe that often colonizes the skin, skin glands and mucous membranes especially the anterior nares of healthy individuals [1]. The adverse effect of colonization is that it increases the risk of subsequent infection since those with *S. aureus* infections are usually infected with strains found on them [2].

S. aureus has been a leading cause of human infection throughout history. From 1997-1999, it was reported as the most abundant cause of skin and soft tissue, bloodstream and lower respiratory tract infections in the United States, Canada, Europe, Latin America and Western Pacific Coast (Diekema, et al. 2001). Other infections associated with *S. aureus* include endocarditis, mastitis, meningitis, osteomyelitis, phlebitis, pneumonia as well toxic shock syndrome and food poisoning [3,4,5].

The pathogenesis of infection caused by this organism is attributed to the expression of an array of virulence determinants. Reports from different authors have assigned over 50 potential virulence factors that include toxins and enzymes to these organisms and these are carried either on the chromosomes or on mobile genetic elements found in the organisms [6].

Methicillin was introduced for the treatment of infections caused by penicillin-resistant *Staphylococcus aureus* in 1959 and by 1961 there were reports from the United Kingdom of isolates of *S. aureus* that had acquired resistance to methicillin (methicillin-resistant *S. aureus*, MRSA). Thereafter MRSA isolates were recovered from other European countries and

later from Japan, Australia and the United States [7].

Methicillin-resistant *Staphylococcus aureus* has become a leading cause of hospital acquired infections worldwide accounting for more than 60% of *S. aureus* isolates in hospitals in the United States [8]. *S. aureus* becomes resistant to methicillin when it acquires the gene *mecA* which encodes for the altered protein PBP2a which is not inactivated by methicillin [9,10]. MRSA is of concern not only because of its resistance to methicillin but also because it is generally resistant to many other chemotherapeutic agents such as the quinolones, aminoglycosides [11], and a low level resistant to vancomycin [12]. The acquisition of such resistance does not necessarily cause the organism to be more intrinsically virulent than other strains of *S. aureus* that have no antibiotic resistance, but it does make MRSA infections more difficult to treat with standard types of antibiotics and thereby more dangerous [13].

The increasing prevalence of methicillin resistance among staphylococci is becoming a huge problem [14]. This situation has led to the renewed interest in the usage of macrolide-lincosamide-streptogramin B (MLSB) antibiotics to treat *S. aureus* infections with clindamycin being the preferred option due to its excellent pharmacokinetic properties [15]. However, the wide spread use of MLSB antibiotics has led to an increase in the number of staphylococcal strains acquiring resistance to MLSB antibiotics [16]. Resistance to MLSB occurs by two different mechanisms notably an active efflux mechanism known to be encoded by the *msrA* gene (macrolides Streptogramin B resistance) and ribosomal target modification encoded by the *erm* gene (MLSB resistance) [17]. The

expression of the MLSB phenotype can be constitutive or inducible in the presence of low levels of inducers, such as the antibiotic erythromycin. *erm* genes encode enzymes that confer inducible or constitutive resistance to MLS agents via methylation of the 23S ribosomal RNA, thereby reducing binding by MLS agents to the ribosome [18].

In Nigeria, it has been reported that the prevalence of MRSA varies between 34.7% and 71.2% [19,20,]. The current prevalence of MRSA and inducible clindamycin resistance is not precisely known in Abia state. This study was carried out to determine the methicillin and inducible clindamycin-resistant *S.aureus* from clinical samples in Abia state.

2. MATERIALS AND METHODS

The study was carried out at three tertiary hospitals in Abia state, Nigeria, between April 2016 and August 2018. The samples came from three senatorial zones; Umuahia, Aba and Isikwuato. Presumptive *Staphylococcus* spp. isolates from routine clinical samples submitted to the medical microbiology laboratory of the hospitals within this period were included in this study. Identification of all isolates both morphologically and biochemically was done using standard laboratory methods [Cheesbrough, 2000]. Briefly, all Gram-positive cocci in clusters that were positive to catalase, and coagulase tests were tentatively identified as *S. aureus*. They were confirmed by a positive result with mannitol fermentation and DNase tests. Susceptibility testing was carried out on Mueller Hinton Agar (MHA) plates using the modified Kirby-Bauer disc diffusion technique (CLSI, 2009). The following antibiotic discs from Oxoid were used: cefoxitin (30 µg), cloxacillin (5 µg), clindamycin (2 µg), erythromycin (15 µg), gentamycin (30 µg), ciprofloxacin (5 µg), azithromycin (15 µg), levofloxacin (5 µg), vancomycin (30 µg) and ceftazidime (30 µg), cefuroxime (30 µg), ceftriaxone (30 µg), ofloxacin (5 µg) and augementin(30 µg) from Rapid lab.

Following this technique, a sterile cotton swab stick was used to inoculate the test organism onto the entire surface of MHA plate with the suspension of the test isolates equivalent to a 0.5 McFarland standard and then incubated at 35°C for 18–24 h. The diameter of the zone of inhibition of each isolate to the tested antibiotics was measured in millimeters with a ruler and compared to the Clinical Laboratory and

Standards Institute guideline for interpretation [21]. The isolates were considered methicillin resistant if the diameters of the zones of inhibition for cefoxitin were ≤ 21 mm and susceptible if ≥ 22 mm.

Clindamycin inducible resistance was detected as described by Adebayo, et al. [22]. Erythromycin (15 µg) and clindamycin (2 µg) (OXOID UK) discs were placed 15-20 mm apart edge to edge. Appearance of flattened clindamycin zone between clindamycin and erythromycin forming a D shape with erythromycin resistance was considered as positive clindamycin inducible resistant (iMLSB). Resistance to both discs was recorded as constitutive resistance (cMLSB) and resistance to erythromycin alone was taken as MS phenotype (D-Test negative). Interpretation of the diameters of zone inhibition was as follows: Erythromycin (E)-sensitive (S) = ≥ 23 mm, E-resistance = ≤ 13 mm; Clindamycin (DA)-S= ≥ 21 mm, DA-R = ≤ 14 mm [23,21].

3. RESULTS

3.1 Collection of Samples

A total of 750 samples collected from different clinical samples were screened for the presence of *S. aureus*. A total of two hundred and sixty five clinical isolates of *S. aureus* were recovered from the various clinical specimens of patients submitted during the study. 126 (47.5%) isolates were recovered from males, while 139 (52.5%) were from females. 13 (4.9%) were from the age group of 0–11 years, 28 (10.6%) from the age group of 11–20 years and 59 (22.3%) from the age group of 21-30, 58 (21.9%) from 31-40, 56 (21.1%) from 41-50, 28 (10.6%) from 51-60 and 23 (8.7%) from >60 years (Table 1).

All the 265 isolates were sensitive to vancomycin, 181 (68.3%) were susceptible to gentamycin, and 177 (66.8%) to clindamycin. All 265 (100%) of the isolates were resistant to ceftazidime, 203 (76.6%) to cloxacillin, and 195 (73.6%) to augmentin (Table 3). While 165 (61.9%) of the 265 isolates were cefoxitin resistant (MRSA), while 101(38.1) were cefoxitin susceptible (MSSA) (Table 3).

A total of 65 (%) of the MRSA isolates were from samples of urine, 38 (%) from wound swab, 31 from high vaginal swab (HVS) etc (Table 2). All the 165 MRSA isolates were sensitive to vancomycin, 120 (73.2%) to clindamycin and 92

(56.1%) to gentamycin. All were resistant to ceftazidime, 157 (95.7%) to cloxacillin, 146 (89.0%) to augmentin and 136 (82.9) to ceftriaxone (Table 2).

High rates of multidrug resistance were observed among isolates with 115(70.1%) being designated as such having expressed resistance to four or more classes of the antibiotics tested,

also no isolate was fully susceptible to all the tested antibiotics (Table 4).

Out of the 265 *S. aureus* isolates, 150 (56.6%) of them were erythromycin resistant. These isolates when subjected to D test, 73 (27.5%) isolates showed resistance to erythromycin and clindamycin indicating constitutive MLSB phenotype. Out of the 177 isolates that showed

Table 1. Prevalence of *S. aureus* among various age groups and gender

Age group	Overall		<i>S. aureus</i> no (%)	MRSA no (%)
	Male no (%)	Female no (%)		
<11	5	8	13(4.9)	3(1.8)
11-20	14	14	28(10.6)	14(8.5)
21-30	24	35	59(22.3)	29(17.7)
31-40	25	33	58(21.9)	42(25.6)
41-50	31	25	56(21.1)	39(23.8)
51-60	16	12	28(10.6)	20(12.2)
>60	11	12	23(8.7)	17(10.4)
Total	126	139	265	164

Table 2. Distribution of staphylococcal isolates obtained from different clinical samples

Sample type	<i>S. aureus</i>	MRSA	MSSA
	No (%)	No (%)	No (%)
Wound and abscess	62(23.4)	38(23.1)	24(23.8)
Blood culture	4(1.5)	1(0.6)	3(2.9)
Urine	113(42.6)	65(39.6)	48(29.3)
Ear swab	6(2.3)	4(2.4)	2(2.0)
Nasal	4(1.5)	3(1.8)	1(1.0)
High vaginal swab	43(16.2)	31(18.9)	12(11.9)
Urethral swab	33(12.5)	22(13.4)	11(10.9)
Total	265(100)	164(61.9)	101(38.1)

Table 3. Antibiotic sensitivity profile of *Staphylococcus aureus* isolates

Antibiotics	MSSA (N=101)		MRSA (164)		Total (265)	
	S	R	S	R	S	R
Levofloxacin	73(72.3)	28(27.7)	35(21.3)	129(78.7)	108(40.8)	157(59.2)
Vancomycin	101(100)	0(0)	164(100)	0(0)	265(100)	0(0)
Ciprofloxacin	61(60.4)	40(39.6)	26(15.9)	138(84.1)	87(32.8)	178(67.2)
Azithromycin	53(52.5)	48(47.5)	40(24.4)	124(75.6)	93(35.1)	172(64.9)
Cloxacillin	55(54.5)	46(46.5)	7(4.3)	157(95.7)	62(23.4)	203(76.6)
Gentamycin	89(88.1)	12(11.9)	92(56.1)	72(43.9)	181(68.3)	84(31.7)
Erythromycin	54(53.5)	47(46.5)	61(37.2)	103(61.6)	115(43.4)	150(56.6)
Cefoxitin	101(100)	0(0.0)	0(0.0)	164(100)	101(38.1)	164(61.9)
Ceftazidime	0(0)	101(100)	0(0)	164(100)	0(0)	265(100)
Cefuroxime	66(65.3)	35(34.7)	37(22.6)	127(77.4)	103(38.9)	162(61.1)
Ceftriaxone	62(61.4)	39(38.6)	28(17.1)	136(82.9)	90(34.0)	175(66.0)
Ofloxacin	64(63.4)	37(36.6)	34(20.7)	130(79.3)	98(37.0)	167(63.0)
Augmentin	52(51.5)	49(48.5)	18(11.0)	146(89.0)	70(26.4)	195(73.6)
Clindamycin	57(56.4)	44(43.6)	120(73.2)	44(26.8)	177(66.8)	88(33.2)

MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin - sensitive *Staphylococcus aureus*, S: Susceptible; R: Resistant

Table 4. Prevalence of multiple-drug resistance among MRSA isolates

Parameter	Frequency of multi-drug resistance	
	Number	(%)
Fully sensitive	-	-
Resistant to 1 class	3	1.8
Resistant to 2 classes	14	8.5
Resistant to 3 classes	32	19.5
Resistant to 4 classes	64	39.0
Resistant to 5 classes	33	20.1
Resistant to 6 classes	18	11.0
Resistant to 7 classes	-	-

Table 5. Susceptibility patterns of *S. aureus* isolates against erythromycin and clindamycin

Susceptibility pattern (Phenotype)	MRSA No (%)	MSSA no (%)	Total (%)
ERY-S,CL-S	57(34.8)	52(51.5)	109(41.1)
ERY-R,CL-R(constitutive <i>mls_B</i>)	45(27.4)	28(27.7)	73(27.5)
ERY-R,CL-S, D-test positive(<i>lms_B</i>)	29 (17.7)	3(3.0)	32(12.1)
ERY-R,CL-S(D-test negative <i>ms</i>)	33(20.1)	18(17.8)	51(19.2)
Total	164(61.9)	101(38.1)	265

Key: Ery – erythromycin, Cl – clindamycin, S – sensitive, R – resistant, *lms_B* - inducible *mls_B* phenotype, *Ms* - *ms* phenotype, Constitutive *mls_B* = constitutive *mls_B* phenotype

clindamycin sensitivity, 32 (12.1%) isolates showed positive D test indicating inducible MLSB phenotype, while 51 (19.2%) showed true sensitivity to clindamycin (D test negative indicating MS phenotype).

In MRSA, 57(34.8)% had the susceptible phenotype (E-S, CL-S). Constitutive MLSB phenotype was 45(27.4%) and the inducible MLSB phenotype was 29 (17.7%), while in methicillin sensitive Staphylococcal isolates (MSSA), the constitutive MLSB phenotype was 28 (27.7%) and the inducible MLSB phenotype was 3(3.0%). The E-S and CL-S phenotype predominated over the inducible resistance phenotype and constitutive resistance phenotype among MRSA and MSSA isolates. The percentage of inducible and MS resistance was higher amongst MRSA isolates when compared with MSSA isolates (Table 5).

4. DISCUSSION

Staphylococcus aureus is a well-known nosocomial pathogen with an alarmingly increasing level of developing resistance to many available antimicrobial agents [24]. The overall prevalence of *S. aureus* from clinical samples obtained in this study is 35.3%. A total of 265 (35.3%) *S. aureus* isolates were recovered, out of which 126(47.5%) were from males and 139(52.5%) were from females, however there was no association between the prevalence and

gender (p-value = 0.05) and also prevalence and age (p-value = 0.52).

Though MRSA does not show a predilection for any particular age or sex, no age is exempt from these infections [25]. In the present study, it was found that highest rate of MRSA was observed in age group of 31-40 years showing a prevalence rate of 25.6% while age group <11 had the least prevalence of MRSA with 1.8%.

The overall MRSA prevalence of 61.9% of *S. aureus* isolates in this study may be considered high although it falls within the range determined in previous reports from some other parts of the country. Onomu and Ephori [26] recorded 79% from Benin city and a study in Nigerian women recorded 71.2% [20]. Some centers however have reported lower rates of 26.9%, 47.8% from Abuja and Oshogho respectively [27,28]. Different studies from other countries have recorded variations of MRSA prevalence, 23.6% in Australia to over 61% in Taiwan and Singapore and more than 70% in Japan and Hongkong. Differences in the length of study period, number of study sites, sample size, sample type and laboratory procedures employed are attributed as factors that may cause variations in prevalence rate of MRSA [29].

Some years back, cloxacillin was highly recommended in treatment of Staphylococcal infections in view of the excellent *in vitro*

sensitivity results. This could be seen from the reports obtained at Ilorin Nigeria [30] with 78% sensitivity and at Owerri, Nigeria [31] with 85.4% sensitivity. However, these results are at variance with current trends in MRSA susceptibility to cloxacillin as could be seen from the results of the present study and others conducted from various parts of the country [32,33,34]. The high level of resistance could be associated with earlier exposure of these drugs to isolates which may have enhanced development of resistance.

Resistance among the isolates to ceftazidime, cefuroxime and ceftriaxone (second generation cephalosporins), were (100%), (77.4%) and (82.9%) respectively. These drugs were very effective against *S. aureus* years ago but resistance may be because it is readily available with many cheap brands in the market. The Japanese experience cites the introduction of 2nd and 3rd generation cephalosporins in the early 1980s as playing a significant part in the emergence and spread of MRSA in Tokyo hospitals. The steady increase of MRSA in Italy, Europe and Britain has also been attributed to the use of cephalosporins [35].

High resistance of isolated MRSA strains to quinolone was observed; ciprofloxacin 133(84.1%), levofloxacin 129(78.7%) and ofloxacin 130(79.3%) while there was lower level of resistance among the MSSA counterparts (27.7%, 39.6% and 36.6%) respectively. This is consistent with other studies in other parts of the world [36,37]. Previous studies also have implicated fluoroquinolones as being culpable to MRSA acquisition even though the mechanisms responsible for this action have not been fully elucidated. It further revealed fluoroquinolone use as being significantly associated with MRSA but not MSSA acquisition [38].

The MRSA isolates in this study exhibited excellent susceptibility to vancomycin, and the finding is in line with results from previous studies in Nigeria, [39,40,41] however, there are some reports of the emergence of vancomycin-resistant *S. aureus* in some centers in Nigeria. [40,42]. The display of excellent susceptibility of these isolates to vancomycin, is good for therapeutic purposes. This drug is not commonly in use in many hospitals and so does not contribute significantly to selective pressure. It is also not readily available across the counter [28].

The high level of multiple drug resistance shown by the MRSA isolates obtained in this study is of

great concern. Majority of the MRSA isolates showed resistance to more than 4 antibiotic classes, indicating the presence of strong selective pressure from antibiotics used in the study area. One of the cities used in this study is a commercialized city with most inhabitants on high level of self-medication.

Clindamycin is indicated in the treatment of skin and soft-tissue infections caused by *Staphylococcus* species [43,44]. There is a risk of treatment failures when clindamycin or any non-inducer macrolide is used to treat infections caused by staphylococcal strains carrying inducible erm gene and so it is important to carry out a D Test to detect resistance [43].

The present study revealed that out of 265 isolated *S. aureus* tested for inducible clindamycin resistance, 32 (12.1%) were positive (D-test positive). This is comparable with a study conducted in Nigeria (11.2%) [44] and Bangalore, India (9.15%) [45], though higher studies have been observed in other places [46]. This difference or variability could be attributed to difference in geographical location, methicillin susceptibility of the *S. aureus* isolates and age group of the study subjects [47].

The overall prevalence of inducible clindamycin resistance among MRSA isolates was 29 (17.7%), whereas among MSSA, only 3 (3.0%) isolates showed inducible clindamycin resistance. This is similar to result obtained by Okojoku, et al. [48] in Jos. Some other investigators have however reported a higher incidence of iMLSB resistance while others indicated a lower incidence [49,50,44]. In reality, incidence of the MLSB phenotype of *S. aureus* depends on the patient population studied, the geographical region, the hospital characteristics and methicillin susceptibility (MRSA or MSSA) [45].

In the present study, 20.1% of erythromycin-resistant MRSA isolates showed true clindamycin susceptibility (MS phenotype) and this implies that patients with infections caused by such isolates can be treated with clindamycin without emergence of resistance during therapy.

5. CONCLUSION

It has been observed that there is a high level of self-medication in Nigeria and this indiscriminate use of antibiotics without prescription contributes to upsurge of drug resistant strains of microorganisms. This has rendered the

commonly used antibiotics completely ineffective in the treatment of different kinds of infections (Paul, et al. 1982). The present study has shown high prevalence of MRSA with high rates of resistance to commonly available and used antimicrobials, however it is encouraging to note that vancomycin resistance was not observed among the isolates. Vancomycin is currently the most effective agent against isolated MRSA strains with susceptibility rate of 100%. These data show that antimicrobial resistance is high among *S. aureus* strains in our locality. There is therefore the need to establish a routine antimicrobial susceptibility surveillance system to screen all clinical *S. aureus* isolates for methicillin resistance and to improve current infection control programs in our hospitals in order to prevent the spread of resistant microorganisms including MRSA.

Vancomycin should be used as the first empirical choice of treatment for serious MRSA infections in our environment, and to prevent resistance, its use should be limited to those cases where they are clearly needed and as determined by laboratory susceptibility testing and/or recommended by treatment guidelines. Whenever clindamycin is to be used as alternative, there should be a D-test conducted to avoid treatment failure.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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