Ade et al. *Afr. J. Clin. Exper. Microbiol.* 2022; 23 (2): 168 - 173 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Apr 2022; Vol.23 No.2
AJCEM/2166. https://www.ajol.info/index.php/ajcem

Original Article **Open Access**

Prevalence of Macrolide-Lincosamide-Streptogramin-B resistance among clinical *Staphylococcus aureus* isolates in University of Ilorin Teaching Hospital, Ilorin, Nigeria

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Abstract:

Background: Inducible antibiotic resistance among Gram-positive cocci is a significant public health challenge that is grossly underreported within Africa, especially Nigeria. Hence, the aim of this study was to determine the prevalence of macrolide-lincosamide-streptogramin-B (MLS$_B$) resistance among clinical isolates of *Staphylococcus aureus* at University of Ilorin Teaching Hospital, Ilorin, Nigeria.
Methodology: Clinical isolates were presumptively identified by Gram's stain reaction and conventional biochemical tests such as catalase, coagulase, DNase, and mannitol fermentation. Phenotypic MLS$_B$ resistance was determined by placing clindamycin and erythromycin discs within 15 mm of each other and observing for a D-zone. Antibiotic sensitivity testing to selected antibiotics including cefoxitin for detection of methicillin resistance, was done using the modified Kirby-Bauer disc diffusion method.
Results: Of the total 112 *S. aureus* isolates tested in the study, 31 (27.7%) were MLS$_B$-resistant. MS phenotype (16.1%) was the most prevalent phenotype followed by constitutive MLS$_B$ (cMLS$_B$) resistance (6.2%), and inducible MLS$_B$ (iMLS$_B$) resistance (5.4%). All MLS$_B$-resistant and sensitive *S. aureus* isolates were susceptible to linezolid, rifampin, tigecycline, and mupirocin while resistance rates of the MLS$_B$ resistant isolates (n=31) to other antibiotics were; tetracycline (58.1%), ciprofloxacin (48.4%), fusidic acid (41.9%), gentamicin (38.71%), cotrimoxazole (35.5%), fosfomycin (29.0%), and cefoxitin (70.9%). Comparatively, resistance rates of the MLS$_B$-sensitive isolates (n=81) to other antibiotics are; tetracycline (70.4%), ciprofloxacin (39.5%), fusidic acid (22.2%), gentamicin (45.7%), cotrimoxazole (46.9%), fosfomycin (18.5%) and cefoxitin (34.6%). There was no significant difference in the antibiotic resistance rates between MLS$_B$ resistant and MLS$_B$ sensitive strains to the antibiotics (p>0.05) except to fusidic acid (p=0.0369) and cefoxitin (p<0.0001). There was also no significant difference in antibiotic resistance rates with respect to the three MLS$_B$ resistance phenotypes (p>0.05), except for fusidic acid which was significantly higher in cMLS$_B$ than other phenotypes (p=0.007).
Conclusion: The introduction of MLS$_B$ resistance detection among Gram-positive cocci in routine microbiological practice can play an important role in monitoring inducible resistance and thereby preventing therapy failure.

Keywords: *Staphylococcus aureus;* D test; constitutive MLS$_B$; inducible MLS$_B$; MS phenotype; resistance

Received Dec 19, 2021; Revised Mar 04, 2022; Accepted Mar 05, 2022

Prévalence de la résistance au macrolide-lincosamide-streptogramine-B parmi les isolats cliniques de *Staphylococcus aureus* à l'hôpital Universitaire de l'Université d'Ilorin, Ilorin, Nigeria

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Abstrait:

Contexte: La résistance inductible aux antibiotiques chez les cocci à Gram positif est un défi de santé publique important qui est largement sous-déclaré en Afrique, en particulier au Nigeria. Par conséquent, le but de cette étude était de déterminer la prévalence de la résistance au macrolide-lincosamide-streptogramine-B (MLS$_B$) parmi les isolats cliniques de *Staphylococcus aureus* à l'hôpital universitaire d'Ilorin, Ilorin, Nigeria.
Méthodologie: Les isolats cliniques ont été identifiés par présomption par la réaction de coloration de Gram et des tests biochimiques conventionnels tels que la catalase, la coagulase, la DNase et la fermentation du mannitol. La résistance phénotypique au MLS$_B$ a été déterminée en plaçant des disques de clindamycine et d'érythromycine à moins de 15 mm l'un de l'autre et en observant une zone D. Les tests de sensibilité aux antibiotiques pour certains antibiotiques, y compris la céfoxitine, pour la détection de la résistance à la méthicilline, ont été effectués à l'aide de la méthode de diffusion sur disque de Kirby-Bauer modifiée.
Résultats: Sur les 112 isolats de *S. aureus* testés dans l'étude, 31 (27,7%) étaient résistants à la MLS$_B$. Le phénotype MS (16,1%) était le phénotype le plus répandu, suivi de la résistance constitutive au MLS$_B$ (cMLS$_B$) (6,2%) et de la résistance inductible au MLS$_B$ (iMLS$_B$) (5,4 %). Tous les isolats de S. aureus résistants et sensibles au MLS$_B$ étaient sensibles au linézolide, à la rifampicine, à la tigécycline et à la mupirocine, tandis que les taux de résistance des isolats résistants au MLS$_B$ (n=31) à d'autres antibiotiques l'étaient; tétracycline (58,1%), ciprofloxacine (48,4%), acide fusidique (41,9%), gentamicine (38,7%), cotrimoxazole (35,5%), fosfomycine (29,0%) et céfoxitine (70,9%). Comparativement, les taux de résistance des isolats sensibles au MLS$_B$ (n=81) à d'autres antibiotiques sont; tétracycline (70,4%), ciprofloxacine (39,5%), acide fusidique (22,2%), gentamicine (45,7%), cotrimoxazole (46,9%), fosfomycine (18,5%) et céfoxitine (34,6%). Il n'y avait pas de différence significative dans les taux de résistance aux antibiotiques entre les souches résistantes au MLS$_B$ et les souches sensibles au MLS$_B$ aux antibiotiques (p>0,05) sauf à l'acide fusidique (p=0,0369) et à la céfoxitine (p<0,0001). Il n'y avait pas non plus de différence significative dans les taux de résistance aux antibiotiques par rapport aux trois phénotypes de résistance MLS$_B$ (p> 0, 05), à l'exception de l'acide fusidique qui était significativement plus élevé dans cMLS$_B$ que les autres phénotypes (p=0,007).
Conclusion: L'introduction de la détection de la résistance MLSB parmi les coques Gram-positifs dans la pratique microbiologique de routine peut jouer un rôle important dans la surveillance de la résistance inductible et ainsi prévenir l'échec du traitement.

Mots clés: *Staphylococcus aureus*; essai D; MLS$_B$ constitutif; MLS$_B$ inductible; phénotype SEP; la résistance

Introduction:

Macrolide, lincosamide, and streptogramin B (MLS$_B$) are a group of chemically distinct antibiotics that function primarily by inhibiting bacterial protein synthesis (1). The macrolides contain 14–16 membered lactone rings, the lincosamides are alkyl derivatives of proline that lack a lactone ring, and streptogramin B antibiotics are cyclic peptide compounds composed of two distinct factors (A and B) possessing synergistic inhibitory and bactericidal activity (2). MLS$_B$ antibiotics are clinically used as alternative drugs for the treatment of some *S. aureus* infections such as skin and soft tissue infections, especially in penicillin-allergic patients (3). However, widespread use of these antibiotics have selected for the development of resistant strains (4).

Resistance of staphylococci to erythromycin was first reported in 1956, a few years after its introduction (5). Bacterial resistance to macrolides occurs via at least three different mechanisms including target modification, enzyme hydrolysis, and efflux pump (5, 6,7). The *erm* methylase gene mediates target modification by altering a site in the 23S rRNA, a common binding site for macrolides, lincosamides, and streptogramin B. Modification of the 23S rRNA confers cross-resistance to MLS$_B$ antibiotics. Hydrolytic enzymes such as erythromycin esterases (encoded by *ereA* and *ereB*) have been reported in *S. aureus* that lyses the lactone ring of the macrocyclic nucleus and phosphotransferases, consequently with introction of a phosphate on the 2'-hydroxyl group of the amino sugar. Macrolide efflux pumps which are ATP transporters (encoded by *msrA* and *msrB*) have also been reported in *S. aureus*. Expression of MLS$_B$ resistance in staphylococci may be constitutive or inducible. Constitutively resistant isolates are resistant to all macrolides, lincosamides, and streptogramin-B type antibiotics. Inducibly-resistant isolates, when tested individually, are only resistant to 14- and 15-membered macrolides, while 16-membered macrolides, commercially available lincosamide and streptogramin antibiotics remain active (5).

Staphylococcus aureus is a clinically significant bacterial pathogen that causes a vast array of diseases in humans and animals alike. *S. aureus* diseases range from mild skin and soft tissues infections to severe and life-threatening infections such as septicaemia, toxic shock syndrome, endocarditis, and pneumonia (8-9). Inducible clindamycin resistant *S. aureus* is a concern in clinical settings as they are not readily detected by routine laboratory methods. However, data on this antibiotic cross-resistance among clinical isolates of Gram-positive cocci in Nigeria are inadequate. Hence, this study was conducted to determine the prevalence of MLS$_B$ resistance among clinical isolates of *S. aureus* in the University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria.

Materials and method:

Study setting and ethical approval

University of Ilorin Teaching Hospital (UITH) is a tertiary healthcare centre located in Ilorin, Kwara State, North Central, Nigeria. The hospital renders its services to patients from various states including, Kwara, Kogi, Niger, Oyo, Osun, Ekiti, Lagos, and Kebbi, as well as the Federal Capital Territory (FCT) (10). Ethical approval for the study was obtained from the Ethical Review Board (ERB) of the UITH.

Study design

The study is a laboratory-based design that used clinical isolates of *S. aureus* recovered from clinical specimens submitted to the Department of Medical Microbiology and Parasitology of UITH.

Culture isolation and identification of *S. aureus*

Clinical specimens, including wound specimens, aspirates, eye swabs and ear swabs were inoculated directly on sheep blood and MacConkey agar plates. Bact/Alert-positive blood specimens were cultured on sheep blood, chocolate, and MacConkey agar plates. Inoculated plates were incubated aerobically while chocolate agar plates were incubated in microaerophilic environment in candle extinction jar. All culture plates were incubated at 37^{o}C for 18-24 hours. Isolates on culture plates were identified morphologically by Gram's stain reaction and standard biochemical tests that included catalase, coagulase, DNase and mannitol fermentation tests. Isolates that were Gram-positive cocci in clusters, catalase-positive, coagulase-positive, DNAse-positive, and mannitol-fermenters were identified as *S. aureus*.

Antibiotic sensitivity test (AST) of *S. aureus*

Antibiotic sensitivity testing (AST) was carried out on each *S. aureus* isolate using the modified Kirby-Bauer disc diffusion method. Bacterial inoculum was standardized to 0.5 McFarland standard before inoculating the surface of freshly prepared Mueller-Hinton agar (MHA) plates. The isolates were tested against the following antibiotics (Oxoid, UK); tetracycline (30µg), cotrimoxazole (1.25/ 23.75µg), mupirocin (5µg), linezolid (30µg), erythromycin (15µg), tigecycline (15µg), fusidic acid (10µg), fosfomycin (50µg), clindamycin (2µg), ciprofloxacin (5µg), rifampin (5µg), gentamicin (10µg) and cefoxitin (30 µg). *Staphylococcus aureus* ATCC 25923 was used as control strain for AST while *S. aureus* ATCC 43300 was used as control strain for cefoxitin disc test.

The diameters of zone of inhibition were measured with a calibrated ruler and interpretation of each isolate as sensitive, intermediate or resistant to the antibiotics was done using the Clinical and Laboratory Standards Institute (CLSI) breakpoints (11). Isolates with diameter of zone of inhibition ≤ 21 mm were classified as methicillin resistant (MRSA) and those with diameter ≥ 22 mm as methicillin sensitive (MSSA).

Phenotypic detection of MLS$_B$ resistance

Freshly prepared Mueller-Hinton agar (MHA) plates were inoculated with standardized (0.5 McFarland) inoculum of the test organisms using a sterile cotton swab. Inducible clindamycin resistance was detected by placing erythromycin (15µg) and clindamycin (2µg) (Oxoid, UK) within 15-20 mm of each other, and incubating the plates aerobically at 37^{o}C for 24 hours. The diameters of zone of inhibition were measured with a calibrated ruler and interpretation of the result of each isolate was done with the Clinical and Laboratory Standards Institute (CLSI) breakpoints (11).

Resistance of the test isolate to both erythromycin (zone diameter of inhibition ≤ 13mm) and clindamycin (zone diameter of inhibition ≤ 14 mm) discs was reported as constitutive resistance (cMLS$_B$), resistance to erythromycin alone with the formation of a D-shaped zone of inhibition between the two discs was reported as inducible resistance (iMLS$_B$; D-test positive), while resistance to erythromycin alone with no appearance of a D-zone was reported as MS phenotype (D-test negative) (11).

Statistical analysis

Statistical analysis was done using IBM SPSS version 21.0. Fisher exact test (with Odds ratio and 95% CI) was used to determine association between methicillin resistance and MLS$_B$ resistance as well as between MLS$_B$ resistance and antibiotic resistance. The Chi square test was used to measure significant difference between MLS$_B$ resistance phenotypes and antibiotic resistance. P value less than 0.05 was considered to be statistically significant.

Results:

A total of 112 clinical isolates of *S. aureus* were recovered from clinical specimens. Of these, 31 (27.7%) were MLS$_B$-resistant. The prevalence of the MLS$_B$ resistance phenotypes were MS phenotype (16.1%, n=18), cMLSB (6.2%, n=7), and iMLSB (5.4%, n=6). A total of 50 (44.6%) isolates were methicillin resistant (MRSA) while 62 (55.4%) were methicillin sensitive (MSSA) isolates (Table 1).

Table 1: Prevalence of MLS$_B$ resistance in MRSA compared to MSSA isolates

***S. aureus* strain**	**MLSB resistance n (%)**	**MLS$_B$ sensitive n (%)**	**Total n (%)**	**OR**	**95% CI**	**p-value**
MRSA	22 (70.9)	28 (34.6)	50 (44.6)	4.627	1.88-11.388	0.000526*
MSSA	9 (29.1)	53 (65.4)	62 (55.4)			
Total	**31 (27.7)**	**81 (72.3)**	**112 (100)**			

MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin sensitive *Staphylococcus aureus*; MLS$_B$ = macrolide-lincosamide-streptogramin B; OR=Odds ratio; CI = Confidence interval; n = number of isolates; *= statistically significant

Table 2: Univariate analysis of antibiotic resistance phenotypes of MLS$_B$-resistant *Staphylococcus aureus*

Antibiotics	**cMLS$_B$ (%) (n=7)**	**iMLS$_B$ (%) (n=6)**	**MS phenotype (%) (n=18)**	**Total (%) (n=31)**	**X^2**	**p-value**
Tetracycline	3 (42.9)	6 (100.0)	9 (50.0)	18 (58.1)	5.479	0.0646
Cotrimoxazole	3 (42.9)	1 (16.7)	7 (38.9)	11 (35.5)	1.185	0.5528
Ciprofloxacin	2 (28.6)	5 (83.3)	8 (44.4)	15 (48.4)	4.147	0.1258
Gentamicin	2 (28.6)	3 (50.0)	7 (38.9)	12 (38.7)	0.6259	0.7313
Fusidic acid	6 (85.7)	0	7 (38.9)	13 (41.9)	9.912	0.007*
Fosfomycin	2 (28.6)	2 (33.3)	5 (27.8)	9 (29.0)	0.06834	0.9664
Cefoxitin	5 (71.4)	3 (50.0)	14 (77.8)	22 (70.9)	1.686	0.4304

cMLS$_B$ = constitutive macrolide-lincosamide-streptogramin B; iMLS$_B$ = inducible macrolide-lincosamide-streptogramin B; MS = macrolide sensitive; X^2 = Chi square; n = number of isolates; * = statistically significant

Table 3: Univariate analysis of antibiotic resistance of MLS$_B$-resistant and MLS$_B$-sensitive *Staphylococcus aureus*

Antibiotics	**MLS$_B$-sensitive (%) (n=81)**	**MLS$_B$-resistant (%) (n=31)**	**Total (%) (n=112)**	**OR**	**95% CI**	**p-value**
Tetracycline	57 (70.4)	18 (58.1)	75 (61.5)	1.715	0.7271-4.047	0.2631
Cotrimoxazole	38 (46.9)	11 (35.5)	49 (40.2)	1.607	0.6829-3.780	0.2961
Ciprofloxacin	32 (39.5)	15 (48.4)	47 (38.5)	0.6966	0.3026-1.603	0.4022
Gentamicin	37 (45.7)	12 (38.7)	49 (40.2)	1.331	0.5720-3.099	0.5314
Fusidic acid	18 (22.2)	13 (41.9)	31 (25.4)	0.3956	0.1632-0.9588	0.0369*
Fosfomycin	15 (18.5)	9 (29.0)	24 (19.7)	0.5556	0.2133-1.447	0.3027
Cefoxitin	28 (34.6)	22 (70.9)	50 (44.6)	4.627	1.88-11.388	0.000526*

MLS$_B$ = macrolide-lincosamide-streptogramin B; OR=Odds ratio; CI = Confidence interval; n = number of isolates; * = statistically significant

All the MLS$_B$-resistant and MLS$_B$-sensitive isolates of *S. aureus* were sensitive to linezolid, rifampicin, mupirocin, and tigecycline. The resistance rates of the MLS$_B$-resistant isolates (n=31) to other antibiotics are; tetracycline (58.1%), ciprofloxacin (48.4%), fusidic acid (41.9%), gentamicin (38.7%), cotrimoxazole (35.5%), fosfomycin (29.0%), and cefoxitin (70.9%) (Table 2). Comparatively, resistance rates of the MLS$_B$-sensitive isolates (n=81) to other antibiotics are; tetracycline (70.4%), ciprofloxacin (39.5%), fusidic acid (22.2%), gentamicin (45.7%), cotrimoxazole (46.9%), fosfomycin (18.5%) and cefoxitin (34.6%) (Table 3).

Discussion:

The rapid spread of antibiotic resistant strains of *S. aureus* has complicated treatment options for infections, especially in low- and-middle-income countries. This seeming difficulty due to antibiotic resistance led to the prominence of clindamycin, a MLS$_B$ antibiotic, for the treatment of skin and soft tissue infections caused by *S. aureus* and also for treatment in penicillin-allergic patients. Although rapid evolution of clindamycin resistance has been attributed to the use and misuse of clindamycin, inappropriate use of erythromycin can induce cross-resistance to clindamycin and streptogramin B antibiotics since all three antibiotics classes have a similar binding site. Hence, the inability to detect this resistance phenotype can lead to misuse of clindamycin, and consequently treatment failure (12-13).

MLS$_B$ resistance rate in this study was 27.7% which is comparable to 27.85% and 28.7% reported in Ethiopia and Nepal, India respectively (14–15). In a similar study, Ifediora et al., (16) reported 58.9% prevalence rate of MLS$_B$-resistant *S. aureus* in Abia State, Nigeria. Kishk et al., (17) reported a prevalence of 54.54% in Egypt while Lupinacci et al., (18) reported 68% in Sao Paulo, Brazil. In similar studies in India, Adhikari et al., (19) reported a prevalence of 54.4% in Nepal while Kavitha (20) reported a prevalence of 40.9% in Kilpauk. Furthermore, Sarrou et al., (21) reported a prevalence of 40.1% in Central

Greece, Goudarzi et al., (22) reported a prevalence of 42.16% in Tehran, Iran, and Jajajreh et al., (23) reported 60.6% in Jordan. Although, the prevalence of MLS_B-resistant *S. aureus* in our study seems lower compared to other locations, it still remains a significant cause of worry, especially in clinical settings.

The current study reported a 5.4% prevalence of $iMLS_B$ which is lower than prevalence rates reported in Egypt (13.64%) and Ethiopia (24.1%) (15, 18). The reported $iMLS_B$ prevalence is also lower than 12.1% reported in a similar study carried out in Abia State, Nigeria (16). Similar studies in India have also reported higher prevalence rates including Nepal (11.48%, 15.2%) and Kilpauk (15.5%) (14, 19–20). In similar studies in Tehran, Iran, Khodabandeh et al., (23) and Goudarzi et al., (24) reported 22.9% and 14.2% $iMLS_B$ prevalence respectively. Similar studies have also reported higher $iMLS_B$ prevalence rates including Brazil (7.2%), Central Greece (11.48%) and Jordan (46.5%) (17, 21–22). The seemingly low prevalence of $iMLS_B$ among *S. aureus* is however not a call to complacency, but a call to a higher level of attention in the prescription of macrolides so as to keep this resistance low. Ultimately, the true prevalence of $iMLS_B$ among *S. aureus* is a function of accurate diagnosis, geographical variation, peculiar characteristics of the healthcare facility, and the population under study (23).

The current study reported a 6.2% prevalence of $cMLS_B$ *S. aureus* that is higher than prevalence rates reported in Ethiopia (2.53%) and India (4.6%) (14–15). This prevalence rate is however lower than 27.5% reported in Abia State, Nigeria (16). Similar studies have reported higher prevalence rates in Iran (56.2% and 23%), Egypt (38.64%), Brazil (60.8%), India (29.25% and 13.1%), Greece (26.44%), and Jordan (11.3%) (17–24). Lower prevalence of $cMLS_B$ *S. aureus* reported in this study can be attributed to the rational prescription and usage of macrolides, both within community and hospital settings which has not favoured the prominence of hyper-resistant strains and molecular types.

In our study, the 16.1% prevalence of MS phenotype of MLS_B resistance is comparable to prevalence rates in Iran (16.6%) and India (16.6%) (14, 24), but lower than 19.2% reported in Abia State, Nigeria (16). Similar studies have reported lower prevalence of the MS phenotype in Egypt (2.27%), Ethiopia (1.26%), India (13.7% and 12.3%), Greece (2.90%), Iran (4.9%), and Jordan (2.82%) (15, 18–23). Our study also reported significant association between MLS_B resistance and methicillin resistance in clinical isolates of *S. aureus.* The prevalence of MLS_B resistance was significantly higher among MRSA isolates than MSSA strains of *S. aureus*. This assertion is in tandem with the reports of Ifediora et al., (16) in Abia State, Nigeria and Kavitha (20) in Kilpauk, India. Similar studies have also reported higher MLS_B resistance among MRSA strains than MSSA strains (14–15,17–19,22–23). Furthermore, MRSA isolates have been globally reported to be multidrug resistant, especially the nosocomial strains. Hence, the spread of MRSA in clinical settings should be monitored to help thwart the possible evolution of MLS_B resistant strains of *S. aureus*.

Our study also reported varying antibiotic resistance patterns among MLS_B-resistant isolates, which is similar to reports of other studies on *S. aureus* (15,23). MLS_B resistance was associated with high resistance to fusidic acid in the study, however, there was no association between MLS_B resistance and resistance to other tested antibiotics. All MLS_B-resistant and sensitive *S. aureus* isolates in our study were susceptible to linezolid, rifampicin, tigecycline and mupirocin, hence, these antibiotics can be employed in the treatment of *S. aureus* infections in this region. However, caution should be taken in the administration of these antibiotics as antibiotic pressure can select for spontaneous evolution of resistant strains.

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