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Research article

Prevalence of methicillin and clindamycin resistant *Staphylococcus* species at a tertiary hospital in Tanzania: Implications for antibiotic stewardship and infection management

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Abstract
Methicillin and clindamycin resistance (constitutive and inducible) pose a common clinical challenge in treating Staphylococcal infections. This cross-sectional study, conducted at Muhimbili National Hospital (MNH) in Tanzania from April to June 2023, to assess the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and clindamycin-resistant *Staphylococcus (S.)* species by using a cefoxitin disk (30 μg) and the D-test method as per CLSI 2022 guidelines. Of the 361 clinical samples, 125 (34.6%) were culture-positive. Among *Staphylococcus* spp., *S. aureus* was 6% (12/125), while 33.6% (42/125) were coagulase-negative staphylococci (CoNS). Among the isolated *S. aureus,* 75% were resistant to methicillin, while 66.7% of the CoNS were resistant to methicillin. Further, 92% (11/12) of the *S. aureus* isolates were resistant to erythromycin, and 50% (6/12) were resistant to clindamycin. Among the CoNS, 83% (35/42) were resistant to erythromycin, and 52% (22/42) were resistant to clindamycin. The proportion of inducible macrolides lincosamide streptogramin B resistance (iMLSB), constitutive macrolides lincosamide streptogramin B resistance (cMLSB), and macrolides lincosamide streptgramin B methicillin susceptible (MS) phenotypes among *S. aureus* isolates was 16.7%, 41.7%, and 33.3%, respectively, and among CoNS was 19%, 35.7%, and 28.6%, respectively. The overall prevalence of iMLSB and cMLSB phenotypes was 18.5% (10/54) and 37% (20/54), respectively. Comparatively, MRSA had more resistance to ciprofloxacin than methicillin-susceptible *S. aureus* (MSSA) (88.9% vs. 33.3% p = 0.027), while methicillin-resistant coagulase-negative staphylococci (MR-CoNS) had significantly higher resistance to gentamicin (35.7% vs. 7.1% p= 0.005), and trimethoprim-sulfamethoxazole (78.6% vs. 50% p= 0.007) than methicillin-susceptible coagulase-negative staphylococci (MS-CoNS). The high prevalence of methicillin and inducible clindamycin resistance in this study points out a potential rise in treatment failures, prolonged hospitalization, and limited treatment options. Thus, emphasizes the importance of antibiotic stewardship and laboratory-guided antibiotic decisions. To address the growing challenge of antibiotic resistance in Tanzania, it is advisable to implement stringent public health measures, including monitoring antibiotic usage, conducting educational initiatives, and raising awareness among patients and healthcare professionals.

Keywords: Antibiotic resistance, methicillin-resistant *Staphylococcus aureus*, MRSA, Inducible clindamycin resistance, D-test, Antibiotic stewardship

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Introduction

Globally, *Staphylococcus (S.)* spp., particularly *S. aureus* and *S. epidermidis* have been recognized as significant contributors to both healthcare and community-associated infections (Eladli et al., 2019; Salgueiro et al., 2019; Antimicrobial Resistance Collaborators, 2022). The unrestricted use of antibiotics has resulted in the development of anti-microbial resistance in *Staphylococcus* spp., consequentially lowering the potency of anti-microbial agents and leading to treatment failures, prolonged hospitalization, higher treatment costs, and mortality rates (Teeraputon et al., 2017; Paul et al., 2019; Antimicrobial Resistance Collaborators, 2022).

A notable resistance displayed by *Staphylococcus* spp. to methicillin has limited the treatment options for infections caused by methicillin-resistant *S. aureus* (MRSA). As a result, a macrolide Lincosamide-Streptogramin B (MLSB) antibiotic has emerged as a preferred choice for managing MRSA infections (Assefa, 2022). However, extensive use of MLSB has led to the acquisition of resistance to MLSB by *Staphylococcus* (El-Said et al., 2019; Abdullahi et al., 2022; Kariuki et al., 2022). A notable resistance to MLSB is mediated by target site modification regulated by *erm* genes, which may be constitutive (cMLSB) or inducible (iMLSB) (El-Said et al., 2019). The constitutive resistant phenotype (cMLSB) *Staphylococcus* spp. exhibits resistance to both erythromycin and clindamycin (Thapa and Sapkota, 2016), while inducible resistant phenotypes (iMLSB) *Staphylo-*

coccus spp. show resistance to erythromycin and susceptibility to clindamycin *in-vitro* (El-Said et al., 2019).

The Clinical and Laboratory Standards Institute (CLSI) employs the D-test as a means to assess the presence of inducible clindamycin resistance among *Staphylococcus* spp. (CLSI, 2022). The inability to perform D-tests routinely in the laboratory causes inadequate treatment of infections by *Staphylococcus*, which can cause treatment failures, leading to the development of a constitutive resistance (Khashei et al., 2018). Globally, there is a significant variation in the rates of inducible clindamycin resistance in different regions(Adhikari et al., 2017; Mzee et al., 2021).

In Tanzania, very few reports have been published regarding the prevalence of inducible clindamycin-resistant *S. aureus* in clinical specimens (Mzee et al., 2021). This study was conducted at Muhimbili National Hospital (MNH), the largest referral hospital in Tanzania, to determine the prevalence of inducible clindamycin resistance in clinical isolates of *Staphylococcus* spp. and their potential association with methicillin resistance.

Material and Methods

Ethics approval and consent to participate

Ethical approval of this study was obtained from the Senate Research and Publication Committee of Muhimbili University of Health and Allied Sciences (MUHAS) with reference number DA.282/298/01L/204. After that, permission to conduct the study was granted by the Muhimbili National Hospital administration. Participants who consented were requested to sign an informed consent form before study enrollment. We excluded, without any prejudice, all patients who did not consent.

Study design, duration, and setting

The present study was a cross-sectional analytical investigation conducted at the Microbiology Unit of the Central Pathology Laboratory (CPL) of the Muhimbili National Hospital (MNH) Dar es Salaam, Tanzania, from April to June 2023. MNH is the largest tertiary hospital in Tanzania, with a capacity of 1500 beds, and serves around 2,000 outpatients daily.

Study population and data collection

This study included clinical samples from patients with clinical features of systemic infections, including fever and system-specific symptoms for infections as per hospital guidelines, from whom blood specimens, urine, cerebral spinal fluid (CSF), ascitic, and pleural fluid were collected for culture according to standard microbiological guidelines in sterile, labeled leakproof containers and processed at CPL. A structured data collection tool was used to record blood, urine, CSF, ascitic, and pleural fluid microbiological results. Colonial morphology, Gram stain characteristics, bacterial identification, and anti-microbial susceptibility test results were also recorded in the tool. Additionally, demographic characteristics, including age, sex, and patient information were recorded.

Laboratory procedures

Culture and bacterial identification

Blood was collected into blood culture bottles for adults (BD BACTEC Plus Aerobic/F Culture bottles, Becton Dickinson and Company; New Jersey, United States) and pediatrics (BD BACTEC^{TM} Ped Plus^{TM}/F Culture bottles, Becton Dickinson and Company; New Jersey, United States). Blood culture bottles were incubated in the laboratory into BD BACTEC^{TM} FX40 analyzer for a maximum of 5 days (Mahon et al., 2015).

Blood agar (BA) and chocolate agar (CA) (Oxoid Ltd, Hampshire, UK) were used for blood, CSF, and ascitic and pleural fluid. CLED agar (cysteine-, lactose-, and electrolyte-deficient) (Oxoid Ltd, Hampshire, UK) was used for urine samples. Cultured plates were incubated at 37°C with 5-10% CO_2 for blood agar (BA) and chocolate agar (CA) and examined for growth after 24–48 hr. Bacteria were identified by colonial morphology and Gram stain. Gram-positive cocci in clusters were further identified by catalase, coagulase (Remel Europe Ltd, Dartford, UK), and Mannitol Salt Agar (Oxoid Ltd, Hampshire, UK) for further identification of *S. aureus* (Mahon et al., 2015).

Anti-microbial susceptibility testing

Kirby–Bauer's disk diffusion method was used to test anti-microbial susceptibility as per CLSI guidelines (CLSI, 2022). The following standard antibiotic disks (OXOID UK, Liofilchem™ Italy) were used, penicillin (10 μg), trimethoprim-sulphamethoxazole (1.25/23.75 μg), tetracycline (30μg), gentamicin (10 μg), erythromycin (15 μg), clindamycin (2 μg), ciprofloxacin (5 μg), cefoxitin (30 μg), nitrofurantoin (300 μg), and chloramphenicol (30 μg). Inhibition zones were measured in millimeters and interpreted as susceptible, intermediate, or resistant according to the 2022 CLSI guidelines (CLSI, 2022).

Phenotypic detection of MRSA

A cefoxitin disk (30 μg) was used to test for MRSA according to the Clinical and Laboratory Standards Institute (CLSI) 2022 guidelines (CLSI, 2022). An inhibition zone diameter of $\leq$21 mm around the cefoxitin disk was considered MRSA. The *S. aureus* ATCC BAA-977 D test positive and *S. aureus* ATCC BAA-976 D test negative ATCC®, Virginia, USA) were used as the controls.

Phenotypic detection of inducible clindamycin resistance (iMLSB phenotypes)

Inducible clindamycin resistance (iMLSB) was detected using the D-test method as per CLSI 2022 guidelines (CLSI, 2022), whereby an isolate was positive for iMLSB when it was resistant to erythromycin but susceptible to clindamycin with a flattened D-shaped zone of inhibition of clindamycin adjacent to the erythromycin disk. Resistance to both clindamycin and erythromycin was recorded as constitutive resistance (cMLSB), while an isolate that was resistant to erythromycin and susceptible to clindamycin without a flattened D-zone was recorded as macrolide and streptogramin B (MS) phenotype. The *S. aureus* ATCC BAA-977 D test positive, and *S. aureus* ATCC BAA-976 D test negative were used as the controls.

Data analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were summarized as median and interquartile range (IQR), whereas percentages and proportions were used to describe categorical variables. To test the difference in categorical variables, *Chi-square* test was used.

Results

Demographic features and clinical information for all samples

A total of 361 specimens (243 blood, 98 urine, 10 ascitic fluids, 5 CSF, and 5 pleural fluids) were collected for processing. A total of 42 CoNS and 12 *S. aureus* were isolated from the cultured specimens. A high *S. aureus* positivity rate was obtained from blood cultures (91.7%), followed by urine cultures (8.3%). All the CoNS (100%) were isolated from blood cultures and none from other samples (Table 1).

Rate of methicillin resistance and inducible clindamycin resistance

A Majority (75%) of isolated *S. aureus* were resistant to methicillin, while 66.7% of the isolated CoNS were resistant to methicillin. Furthermore, among isolated *Staphylococcus* spp., 92% (11/12) of the *S. aureus* isolates were resistant to erythromycin, and 50% (6/12) were resistant to clindamycin. Among the CoNS, 83% (35/42) were resistant to erythromycin, and 52% (22/42) were resistant to clindamycin. The proportion of iMLSB, cMLSB, and MS phenotypes among *S. aureus* isolates was 16.7%, 41.7%, and 33.3%, respectively, and among CoNS was 19%, 35.7%, and 28.6%, respectively (Table 2).

Table 1: Distribution of *Staphylococcus* spp. isolated from clinical specimens according to age, sex, ward, and specimen type.

Variable	Frequency	Percent (%)	*S. aureus* (%)	CoNS[a] (%)
Age group (years)[b]				
< 2 years	107	29.6	4 (1.1)	21 (5.8)
2 -17	75	20.8	1 (0.3)	4 (1.1)
18 – 40	85	23.5	3 (0.8)	6 (1.7)
41 – 60	53	14.7	1 (0.3)	6 (1.7)
>61	41	11.4	3 (0.8)	5 (1.4)
Sex				
Male	166	46.0	7 (1.9)	28 (7.8)
Female	195	54.0	5 (1.4)	14 (3.9)
Ward				
ICUs	60	16.6	3 (0.8)	8 (2.2)
Medical ward	67	18.6	2 (0.6)	3 (0.8)
Neonatal ward	60	16.6	2 (0.6)	9 (2.5)
Pediatric ward	87	24.1	3 (0.8)	13 (3.6)
Surgical ward	21	5.8	1 (0.3)	2 (0.6)
Others[c]	66	18.3	1 (0.3)	7 (1.9)
Specimen type				
Ascitic fluid	10	2.8	0 (0.0)	0 (0.0)
Blood	243	67.3	11 (91.7)	42 (100)
CSF	5	1.4	0 (0.0)	0 (0.0)
Pleural fluid	5	1.4	0 (0.0)	0 (0.0)
Urine	98	27.1	1(8.3)	0 (0.0)

[a]CoNS= coagulase-negative staphylococci.
[b]The median age was 17 years with an interquartile range (IQR) of 43 years.
[c]Others: outpatient department, oncology ward.

Table 2: Proportion of MRSA and inducible clindamycin resistance among *Staphylococcus* species.

Susceptibility pattern (phenotype)	*S. aureus (%)*	CoNS (%)
Methicillin susceptible	3 (25)	14 (33.3)
Methicillin-resistant	9 (75)	28 (66.7)
ERY-S, CL-S	0 (0.0)	5 (12)
ERY-R, CL-R (cMLSB)	5 (41.7)	15 (35.7)
ERY-R, CL-S (D-test positive, iMLSB)	2 (16.7)	8 (19)
ERY-R, CL-S (D-test negative, MS)	4 (33.3)	12 (28.6)
ERY-S, CL-R	1(8.3)	7 (16.7)

KEY: CoNS= methicillin-resistant coagulase-negative staphylococci, CL– clindamycin, ERY– erythromycin, cMLSB- constitutive macrolides lincosamide streptogramin B resistance, iMLSB- inducible macrolides lincosamide streptogramin B resistance, MS- macrolides lincosamide streptogramin B; R– resistant; S– susceptible.

Distribution of inducible clindamycin resistance among MRSA, MSSA, MR-CoNS, and MS-CoNS

Among MRSA isolates, 22.2% showed inducible MLSB phenotype (iMLSB), while 33% showed constitutive MLSB (cLMSB) phenotype and 44% were MS phenotype. Sixty-seven percent of MSSA isolates were cLMSB phenotype, and 33% were susceptible to erythromycin and clindamycin. None of the MSSA isolates showed iMLSB and MS phenotypes. Among the MR-CoNS, iMLSB, cLMSB, and MS phenotypes were detected in 25.0%, 36.0%, and 32.0%, respectively. While among MS-CoNS, iMLSB accounted for 7%, cMLSB accounted for 36%, and MS accounted for 21% (Table 3).

Anti-microbial susceptibility pattern

There was significant resistance to ciprofloxacin (88.9% vs. 33.3% p= 0.027) among MRSA compared to MSSA, while among CoNS, there was significant resistance to gentamicin (35.7% vs. 7.1% p = 0.005) and trimethoprim-sulfamethoxazole (78.6% vs. 50% p= 0.007) among the MR-CoNS compared to MS-CoNS (Table 4).

Discussion

The prevalence of MRSA varies worldwide and is higher in lower and middle-income countries (LMIC) (Klein et al., 2019; Gandra et al., 2020; Sulis et al., 2022). In our study, the proportion of MRSA was 75%, higher than the findings in the same hospital (Nkuwi et al., 2018) and other hospitals in Tanzania (Mzee et al., 2021). Furthermore, our study found that CoNS were highly resistant to methicillin, reaching 66.7%. These findings are parallel to findings from other studies whereby the proportion of MR-CoNS was 86.7% (El-Said et al., 2019). The high rate of methicillin resistance was seen in both *S. aureus* and CoNS in this hospital may be due to several factors, such as increasing misuse of antibiotics, lack of implementation of antibiotic stewardship, and the fact some patients might have used antibiotics before admission to the hospital because the study was conducted after the COVID-19 era (Kavanagh and Cormier, 2022).

In this study, inducible clindamycin resistance was prevalent in 41.7% of *S. aureus* isolates and in 37% among CoNS, which could be misinterpreted as clindamycin susceptible when solely assessed by the Kirby-Bauer disk diffusion method, causing treatment failure (Sasirekha et al., 2014). Among erythromycin-resistant isolates, 16.7% of *S. aureus* and 19% CoNS were inducible clindamycin resistance (iMLSB) phenotypes. Whereas among MRSA, there was a high rate of iMLSB (22%) compared to MSSA (0%), and these results were in line with findings in isolates from India (42.3%) (Aruna, 2013) but higher than the study in Brazil (7.2%) (Lupinacci et al., 2020) and in Egypt (20%) (El-Said et al., 2019). The variations in iMLSB resistance rates may be attributed to differences in clindamycin utilization patterns and the genetic diversity of the circulating *Staphylococcus* species, variations in infection prevention practices, and antibiotics prescription in different hospital settings (Vandana et al., 2009; Ambachew et al., 2022).

A high iMLSB resistance level indicates clinicians' need for cautious consideration when prescribing clindamycin. Antibiotic prescriptions should be guided primarily by laboratory results in such cases. The testing of inducible clindamycin resistance

Table 3: Proportion of inducible clindamycin resistance in *Staphylococcus species* isolated from clinical specimens.

Resistant phenotype	MRSA, no(%)	MSSA, no(%)	MR-CoNS, no(%)	MS-CoNS, no(%)
iMLSB	2 (22)	0 (0)	7 (25)	1 (7)
cMLSB	3 (33)	2 (67)	10 (36)	5 (36)
MS	4 (44)	0 (0)	9 (32)	3 (21)
Susceptible	0 (0)	1 (33)	2 (7)	5 (36)
Total (no.)	9	3	28	14

KEY: MRSA- methicillin-resistant *Staphylococcus aureus*, MSSA- methicillin-susceptible *Staphylococcus aureus*, MR-CoNS– methicillin-resistant coagulase-negative staphylococci, MS-CoNS– methicillin-susceptible coagulase-negative staphylococci, cMLSB- constitutive macrolides lincosamide streptogramin B resistance, iMLSB- inducible macrolides lincosamide streptogramin B resistance, MS- macrolides lincosamide streptogramin B.

Table 4: Antimicrobial resistance pattern of staphylococci species isolated from clinical specimens.

Antibiotics	MSSA (%)	MRSA (%)	*p-value*	MS-CoNS (%)	MR-CoNS (%)	*p-value*
Penicillin	3 (100)	9 (100)	-	14 (100)	28 (100)	-
Erythromycin	3 (100)	9 (100)	-	9 (64)	26 (92.9)	0.052
Clindamycin	2 (66.7)	3 (33.3)	0.061	6 (42.9)	10 (35.7)	0.653
Ciprofloxacin	1 (33.3)	8 (88.9)	0.027	5 (35.7)	8 (28.6)	0.639
Gentamicin	0 (0.0)	6 (66.7)	0.087	1 (7.1)	10 (35.7)	0.005
Trimethoprim-sulfamethoxazole	3 (100)	5 (55.6)	0.572	7 (50)	22 (78.6)	0.007
Chloramphenicol	0 (0.0)	0 (0.0)	0.157	2 (14.3)	7 (25)	0.144
Doxycycline	0 (0.0)	4 (44.4)	0.217	1 (7.1)	6 (21.4)	0.325

KEY: MRSA- methicillin-resistant *Staphylococcus aureus*, MSSA- methicillin-susceptible *Staphylococcus aureus*, MR-CoNS– methicillin-resistant coagulase-negative staphylococci, MS-CoNS– methicillin-susceptible coagulase-negative staphylococci.

phenotypes should be done routinely using the erythromycin-clindamycin disc approximation test (D-test), which has been found to have a sensitivity of 100% when compared with *erm* and *msr* genes detection by polymerase chain reaction (Steward et al., 2005; Juda et al., 2016). On the other hand, constitutive clindamycin resistance was seen in 33% of the MRSA isolates and in 36% of the MR-CoNS isolates, which, together with the finding of a high proportion of inducible clindamycin seen in this study, shows the immense use of the macrolides and lincosamides in treating different infections (Teeraputon et al., 2017).

The current study displayed very high resistance rates to erythromycin among both *S. aureus* (92%) and CoNS (83%) isolates, findings which are higher than those reported in other studies (Khashei et al., 2018; Poddighe and Aljofan, 2020; O'Neill, 2016). Several studies have indicated that during the COVID-19 pandemic, macrolides were highly used to treat and prevent bacterial infections (Pani et al., 2020; Poddighe and Aljofan, 2020; Sulis et al., 2022).

Our findings further show significant resistance to ciprofloxacin among the MRSA isolates and high resistance against gentamicin, trimethoprim-sulfamethoxazole, and erythromycin amongst the MR-CoNS, also seen in other studies (Almanaa et al., 2020). These findings can be explained by the carriage of a transposon Tn554, which contains the gene *ermA* mediating MLS resistance, resulting in a higher resistance rate to MLS anti-microbial agents (Blair et al., 2015). On the other hand, MS-CoNS exhibited higher resistance to ciprofloxacin (35.7% vs. 28.6%) and clindamycin (42.9% vs. 35.7%) compared to MR-CoNS, which could also be due to differences in *mecA* detection rates between the two groups (Marincola et al., 2021). The high prevalence of methicillin and clindamycin (inducible and constitutive) resistance, as well as associated resistance against several antibiotics such as erythromycin, gentamicin, trimethoprim-sulfamethoxazole, observed in this study, has serious implications on clinical outcomes (e.g., mortality, length of hospital stay), and an increased burden on healthcare resources and does limit treatment options (Wu et al., 2023).

Conclusion

In conclusion, our study revealed significantly higher rates of MRSA than previously reported and resistance in CoNS at a Tanzanian tertiary care hospital. The rise in resistance is attributed to multiple factors, including antibiotic misuse, inadequate antibiotic stewardship, and potential prior antibiotic use by patients, notably during the COVID-19 pandemic. Inducible clindamycin resistance was common among isolated *Staphylococcus* species, highlighting the need for laboratory-guided antibiotic treatment decisions. In this scenario, the erythromycin-clindamycin disc approximation test (D-test) is crucial to prevent treatment failures. High levels of erythromycin resistance may result from increased macrolide usage during the pandemic.

Resistance to ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole in MRSA and MR-CoNS indicate potential transposon-mediated resistance mechanisms, posing a major challenge in infection management and resource utilization. These findings point out potentially increased mortality rates, extended hospital stays, increased healthcare resource utilization, and limited treatment options due to antibiotic resistance in the management of bacterial infections in Tanzania. Hence, antibiotic stewardship, utilization of D-test, education and awareness in the health care providers and patients to avoid misuse of antibiotics at both ends, research and surveillance to monitor antibiotic resistance patterns and alternative therapies, as well as the development of strict public health policies are recommended to combat the rising problem of antibiotic resistance in these settings.

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