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Detection of Clindamycin-Resistant *Staphylococcus aureus* Isolated from clinical specimens in Baghdad

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Abstract

A total of 150 samples were collected from clinical sources in Baghdad. All samples were subjected to analyses and confirmed by VITEK2 system. As a result, 80 isolates were recognized as *S. aureus*. Disc diffusion method was used to test antibiotic susceptibility profile for the isolates towards 8 antibiotics. The results indicated that 12 isolates were multi-drug resistant (MDR), 11 isolates were extensively drug-resistant (XDR) and 8 were pandrug-resistant (PDR). Twenty-eight (35%) of the isolates were clindamycin resistant and 21 (26%) of these were constitutive clindamycin resistant as they show resistance towards erythromycin too; while 52 (65%) of the isolates were sensitive to both clindamycin and erythromycin and 7 isolates were reported to be erythromycin-sensitive but clindamycin-resistant. It is essential that all healthcare facilities should continuously monitor *S. aureus* to avoid treatment failures associated with induced lincosamide antibiotics resistance.

Keywords: Antibiotics, *Staphylococcus aureus*, VITEK 2 system, wounds, burns.

Introduction

Staphylococcus aureus is a ubiquitous Gram-positive bacterium, which may resident in various parts of body, especially skin and mucous membrane, as a human normal flora. In some cases, this bacterium can cause both community and nosocomial infections, including fatal pneumonia, bacteremia, osteomyelitis, infective endocarditis, mild skin and soft tissue infections [1–3].

Staphylococcus aureus has several virulence factors, including enzymes, proteins, toxins and others. In order to survive in various environmental conditions [4]. This bacterium is rapidly acquires resistance to antimicrobial drugs, making it a major contributor to the spread of diseases in healthcare settings [5].

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When compared to illnesses caused by susceptible strains of bacteria, those caused by antibiotic-resistant bacteria carry a higher risk of death and higher treatment costs [6]. Genomic mutations that change the target DNA-gyrase or decrease the number of proteins in the outer membranes can reduce drug absorption and so impart drug resistance [7,8].

Most antibiotics cannot kill Methicillin-resistant *S. aureus* bacteria, and some strains have even evolved resistance to drugs used as a last resort [9] .Resistance strains have regularly emerged shortly after new antibiotic were introduced to combat this infection. The most notable development is the rise in frequency of *S. aureus* isolates resistant to β-lactams. Therefore, efforts were focused on the use of clindamycin which is a lincosamide antibiotics that belongs to the macrolide-lincosamide-streptogramin B (MLS_B) antibiotic group [10]. The clindamycin was characterized by its pharmacokinetic properties as it inhibits toxin production through its ability to penetrate to the soft tissue, in addition to its availability in oral as well as parenteral formulation.However, the frequent and extensive use of this antibiotic has led to the development of resistance to it [11].

The resistance mechanism of clindamycin depends upon the ribosomal target site modification by the *23SrRNA* methylases that is mediated by one or more *erm* genes (*ermA, ermB, ermC, and ermF*) among which *ermA* and *ermC* are predominant genes [12]. This resistance mechanism could be either constitutive or induced in such a way that when the rRNA methylase is usually produced, the resistance phenotype is constitutive (cMLSB) but when an inducing agent such as erythromycin induced the production of methylase it said to be induced clindamycin resistance (iMLSB) [13]. The aims of this study was to determine the prevalence of constitutive and induced clindamycin resistance among multidrug resistant S. aureus isolates from different clinical samples.

Materials and Methods

Collection of clinical specimens

From November 2023 to January 2024, a total of 150 clinical samples were collected from individuals suffering from a range of infections. These samples included ear, nose, wound, burn swabs, urine, and blood samples. The samples were collected from Mahmoudiya Hospital and Al-Imamain AL-Kadhimain Medical City.

Bacterial isolation and identification

Blood agar and mannitol salt agar (MSA) were used as differential and selective media for cultivation of *Staph. aureus*. the samples were incubated at 37°C for 24 hours. For further identification of *Staphylococcus* to the species level, morphological, biochemical (coagulase, catalase, oxidase) and confirmed using VITEK2.

Antimicrobial susceptibility test

The Kirby-Bauer method, as specified in Clinical and Laboratory Standards Institute (CLSI) guideline [14] was utilized to test susceptibility profile for the isolates against the applied antibiotic using

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Muller Hinton agar as a culture media. The antimicrobial discs listed in (table1) were supplied by Himedia/India.

Table (1): The antimicrobial agents of this study.

Antimicrobial	Symbol	Disk content	Antimicrobial Class
Erythromycin	ERY	15 µg	Macrolides
Azithromycin	AZM	15 µg	Macrolides
Clindamycin	CL	2 µg	Lincosamide
Cefoxitin	CXN	30 µg	Cephamycin (2nd-generation)
Vancomycin	VA	30 µg	Glycopeptide
Gentamicin	GEN	10 µg	Aminoglycoside
Tetracycline	TE	30 µg	Tetracyclines
Ceftazidime	CAZ	30 µg	Cephalosporins (3rd-generation)

Results and Discussion

Based on used examination procedures; 80 samples (53%) were positively identified as *Staph. aureus* as they appear grape-like clusters under microscope forming golden yellow colonies on MSA and their mode of ß-hemolysis on blood agar in addition to their ability to produce catalase and coagulase enzyme while they were unable to produce oxidase enzyme and this was confirmed by the results of the VITEK 2 system. According to the isolation source; 47 (58.75%) the isolates were from skin samples that include epidermal (30%; n=24/80), wounds (20%; n=16/80) and burns (9%; n=7/80) followed urine (n=12; 15%), blood (n=10; 12%), nasal (n= 4; 5%), sputum (n= 3; 4%), ear (n=2; 2%), knee joint (n=2; 3%) as represented in figure (1).

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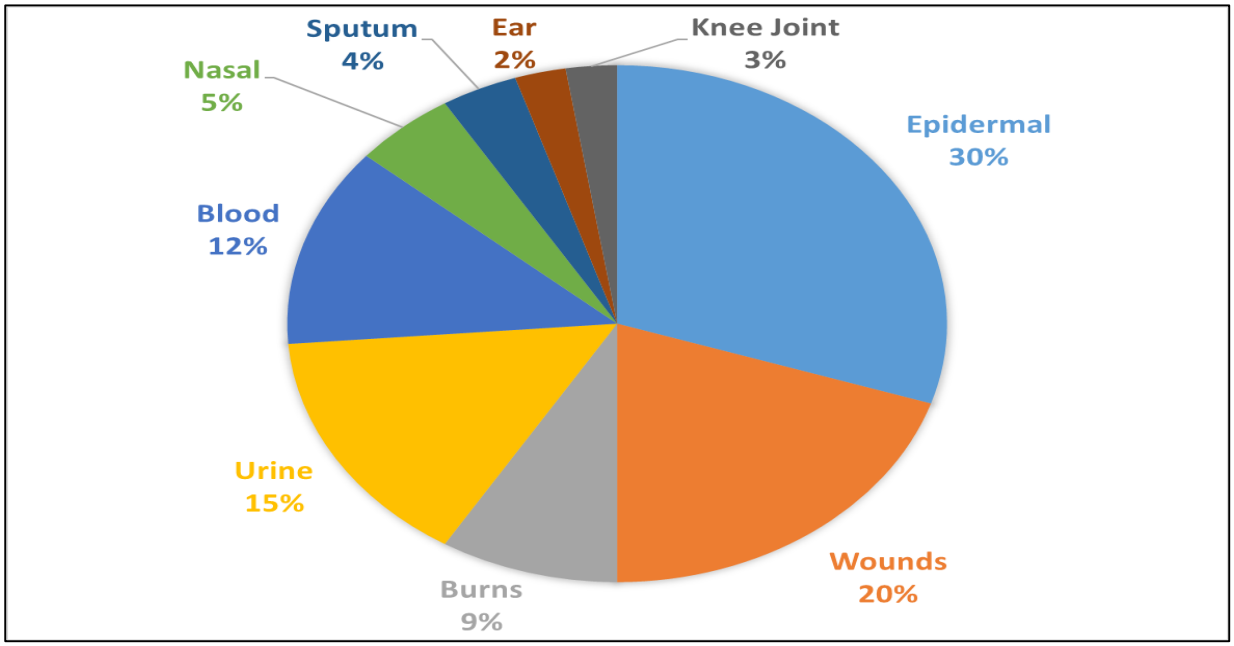

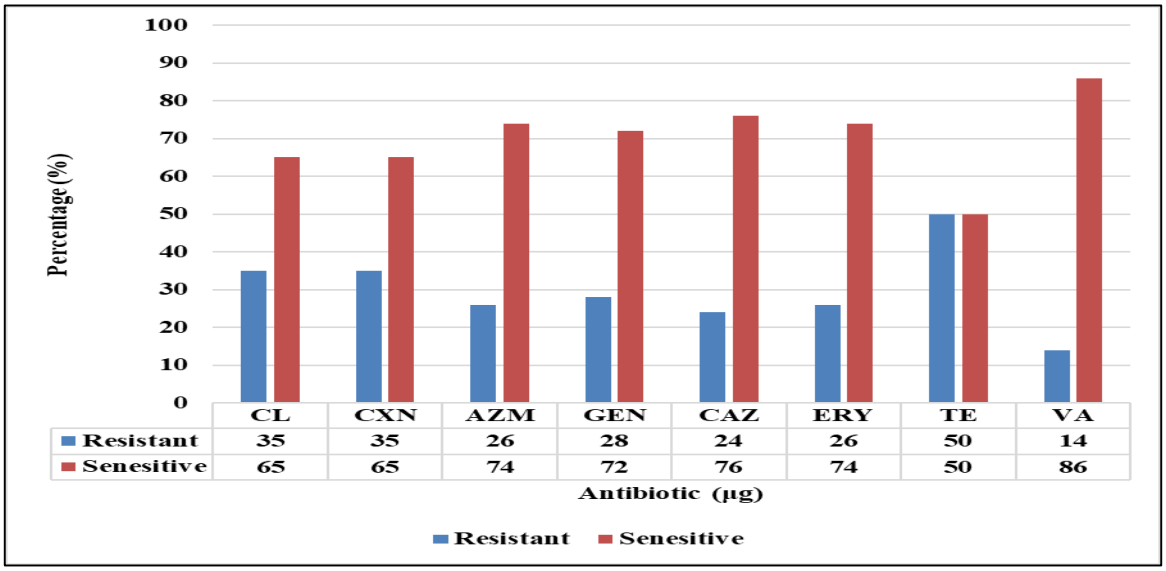

Figure (1): The distribution of *S. aureus* isolates among samples.

From these 80 isolates, resistance to both CL and CXN was (35%, n=28/80), for AZM (26%, n=21/80), for GEN (28%, n=22), for ERY (26%, n=21/80), for TE (50%; n=40/80), for CAZ (24%; n=19/80) and the lowest resistant ratio was recorded for VA (14% n=11/80), as represented in figure (2).

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Figure (2): Antibiotic resistance patterns of *S. aureus* isolates.

ERY=Erythromycin
CL=Clindamycin
CXN=Cefoxitin
AZM=Azithromycin
GEN=Gentamicin
CAZ=Ceftazidime
TE=Tetracycline
VA=Vancomycin

The antibiotic resistance categories were determined as MDR, XDR and PDR. Among 80 isolates, n=12/80 (15%) were MDR, n=11/80 (13.75%) were XDR and n=8/80 (10%) were PDR, while the rest of isolates (62.5%); n=50 being out these categories.

Table (2): The percentages of distribution for isolates among the categories of antibiotic resistance.

Category	Isolates	
	Number	Percentage (%)
MDR	12	15
XDR	11	13.75
PDR	8	10
Non-MDR, -XDR and -PDR	50	62.5
Total	80	100

* MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories, XDR: non-susceptible to ≥1 agent in all but ≤2 categories and PDR: non-susceptible to all antimicrobial agents listed [15].

For phenotypic detection of clindamycin and erythromycin-resistant *S. aureus*, the results of this study are represented in table (3). Among these, 28 (35%) of the isolates were clindamycin resistant and 21 (26%) of these were recorded as constitutive clindamycin resistance as they show resistance towards erythromycin too; while 52 (65%) of the isolates were sensitive to both clindamycin and erythromycin and 7 isolates were reported to be erythromycin sensitive but clindamycin resistant. None of the examined isolates were resistant to ERY and sensitive to CL together, whereas they not considered asinduced macrolide-lincosamide- streptogramin B ($iMLS_B$).

Table (3): The distribution for clindamycin-resistant isolates among the categories of antibiotic resistance.

Susceptibility pattern (phenotype)	Total	
	No.	%
ERY=R; CL=R ($cMLS_B$)	**21**	**26**
ERY=S; CL=S	**52**	**65**
ERY= R; CL=S ($iMLS_B$: D test positive)	**0**	**0**
ERY=S; CL=R	**7**	**8.75**
Total	**80**	**100**

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R=resistant
S=sensitive
ERY=Erythromycin
CL=Clindamycin
iMLSB= induced macrolide-lincosamide- streptogramin B
cMLSB= Constitutive macrolide-lincosamide- streptogramin B

In this study, 53% of *S. aureus* isolates were obtained form 150 clinical samples with a ratio compared with that reported by Shakir *et al.* [16] as they used different sources of the isolate *S. aureus* with a ratio of 25.5% and that obtained by Onanuga *et al.* [17] who isolated only 20.8% of *S. aureus* from various sources, while the results of this study were closely related with both studies reported by Uwaezuoke *et al.* [18] and Yassein *et al.* [19], whereas they obtained 36% and 48% of *S. aureus* isolates from different samples, respectively.

This study reported that 12, 15 and 20% of isolates of *S. aureus* from blood, urine and wound samples, which were different from findings of the study reported by Nsofor *et al.* [20], who obtained 6.7, 25.4 and 29.4% of isolates from blood, urine and wound samples, respectively.

One possible explanation for this patrtern of prevalence. Because of its adaptability to various bacterial environments, *Staphylococcus aureus* is the most common pathogele explanation for this pattern of n found in clinical specimens, and this fact is supported by the high prevalence of the organism.

Among the different clinical specimens studied, the one with the highest prevalence of *Staphylococcus aureus* was found in epidermal swab samples (30%), followed by wound swab samples (20%). This finding is in line with previous reports from Obiazi *et al.* [21] and Nwoire *et al.* [22] which also found that wound swabs contained 48% and 42.53% of *S. aureus* isolates, respectively. While Chigbu *et al.* [23] found the greatest occurrence rate in urine specimens (76.4%), current data show the opposite.

Inadequate personal hygiene and the wounds' exposure may have increased their susceptibility to contamination and infection, leading to the high prevalence of *S. aureus* in wound swabs found in this investigation. Another possible explanation for the high prevalence of *S. aureus* colonisation in this research is that some residents of the region self-medicate their wounds or seek out the services of unlicensed or poorly educated quacks before seeking professional medical help.

The high resistance of *Staph. aureus* to a wide range of routinely used antibiotics results in a subsequent treatment failure and progress of uncomplicated infection to a major problem in the healthcare and community systems. Eight types of antibiotics belong to seven different classes were applied in this study, including CL, CXN, AZM, GEN, VA, TE, CAZ and ERY. According to the results, the tested isolates showed different degrees of resistance to the applied antibiotics such that 12 isolates were recorded as multi-drug resistant (MDR); 11 isolates were extensively drug-resistant (XDR) and 8 were pandrug-resistant (PDR). Among these, 28 (35%) of the isolates were recorded as resistant to CLI and among them 21 (26%) were also resistant to ERY . so, they are considered to have constitutive resistance as they show resistance to both clindamycin and erythromycin. while 52 (65%) of the isolates were sensitive to both clindamycin and erythromycin. furthermore, 7 isolates were reported to be erythromycin sensitive but clindamycin resistant, an indication for expected genetic exchange at the sequence of the gene coding for the erythromycin ribosomal methylase and this result was closely related to that obtained by Moroi and his colleagues in 2019 in Korea [24].

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The same proportion of the examined isolates (26%) was found to be lower than findings of Gurung *et al.*[25], who found that (65%) of these isolates were resistant to AZM.

This study found that 26% of isolates were resistant to ERY, which was lower than the findings of Mokta *et al.* [26] who showed that 39% of isolates in their specimens were resistant to ERY. In studies by Jarajreh et al., [27], Thapa *et al.* [28] and Gurung *et al.* [25], 78, 47 and 46.2% of isolates were resistant to ERY, respectively. Another study reported that resistance rates to ERY were (58%) [29], which was higher than the findings of this study. Also, Kishk *et al.* [13], indicated that (54%) of their isolates showed resistance to ERY.

In study conducted by Gurung *et al.* [25], 75% of isolates were resistant to FOX, which is higher than that we recorded. According to this study, 35% of isolates were resistant to CLI, which was higher than finding of study reported by Gurung *et al*. [25], who found that 25% of isolates were resistant to this antibiotic. This variability against antibiotics among different years may due to the variability in the number of isolates and mechanisms of antimicrobial resistance in bacteria are due to several mechanisms included degradations of antibacterial drugs by enzyme, alterations of bacterial proteins that are antimicrobials targets, and alteration in permeability of membranes to antibiotics. Antibiotic resistance can be by plasmids mediated and transposons [30]. So, the resistance to antibiotic is considered an international problem that is associated with serious infections that are difficult or cannot be treated. Bacteria that important in people infection have increasing resistance that's include *S. aureus* and *Escherichia coli* that considered very common in this field [1]. Suffering, increased complications and higher death rates are seen with people that infected in resistant bacteria. Wherever antibiotics are used, antibiotic resistance is developed in both medicine and community.

Poor hygiene, poor water sanitation and poor infection control supply good environments for spreading the resistant bacteria. Most the antibiotic utilization in the world involves in food animals. This utilization result in the growing of resistant bacteria that transmit to people by water and food chain [31].
One of the most popular drugs treating Staphylococcal infections, especially those of the skin and soft tissues, is clindamycin [32]. Isolates with an inducible MLSB (iMLSB) phenotype must be distinguished from those with an MS phenotype to avoid treatment failures caused by clindamycin. According to the results of this study, majority of isolates were $cMLS_B$, which disagreed with Tiwari *et al.* [33], who indicated that 64% of isolates were $cMLS_B$ and 38 of isolates were $iMLS_B$. Erythromycin resistance was detected in 61.4% of the isolates in investigation of Gupta *et al.* [34], which is higher than that found in the results of this study (26%). They reported that a total of 47.20 percent of the erythromycin-resistant *Staphylococcus aureus* isolates had the MS phenotype, 31.67% had cMLSB resistance, and 21.1% had iMLSB resistance.

The highest frequency of the iMLSB phenotype was recorded by Steward et al. [35] at 16.4%, with cMLSB at 12.5% and MS at 7.8%. The results of this study disagree with both Regha *et al*. [36] and Deotale *et al*. [37] who found that iMLSB was the most common phenotype, with cMLSB coming in second and MS phenotypic third. In contrast, Dubey et al. [38] found that iMLSB was the highest, followed by MS phenotypic and cMLSB, demonstrating that researchers found varying rates in their investigations. In addition, Prabhu *et al.* [39] 9.47 and 10.52% of isolates were $cMSL_B$ and $iMSL_B$, respectively, which was lower than that found in this study.

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Generally, reasons for the discrepancy in results of different studies, in addition to results of this study, include differences in antibiotic exposure between populations or regions, which in turn cause different patterns of resistance. However, resistance rates may be influenced by the kinds and frequency of antibiotics administered in a certain community or healthcare system. The development of resistance to antibiotics might be accelerated by their misuse or excessive usage [40,41]. The reliability of resistance rate estimations is affected by the sample population's size and representativeness. Adaptation by microbes, changes in antibiotic prescription practices, and new infection control methods may all cause resistance patterns to develop over time [42,43].

Conclusions

Vancomycin (VA.) not recommended as effective antibiotic against *S. aureus.* There is a correlation between regional differences in infection patterns and medication use and the prevalence of MLS_B resistance. Thus, in order to prevent treatment failures, it is imperative that all healthcare facilities continuously monitor *S. aureus* for MLS_B resistance by testing erythromycin and clindamycin-resistant isolates with the D-test Inducible clindamycin resistance *in vitro* is another important concept for physicians to be aware of. According to the results obtained, possible medication to explore for treatment in such circumstances include vancomycin and Cefoxitin.

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Author's Declaration

- We hereby confirm that all the Figures and Tables in the manuscript are original and have been created by us.
- We have obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University/College of Biotechnology]. This approval underscores our commitment to ethical research practices and the well-being of our participants.
- Ethical Clearance: The project was approved by the local ethical committee at [Al-Nahrain University/College of Biotechnology], ensuring adherence to ethical standards and the protection of participants' rights and welfare.

Author's Contribution Statement

[Samah Anwer Thamer]: Played a critical role in the statistical analysis of the data and interpretation of the results.

[Dhafar N. Al-Ugaili2]: Played a critical role in supervising the research, providing guidance, and designing the study .

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