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RESEARCH ARTICLE

Inducible Clindamyc in Resistance among Methicillin-Resistant *Staphylococcus aureus* Isolates in a Tertiary Care Hospital: A Phenotypic Detection

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Abstract

Background: *Staphylococcus aureus* is one of the most commonly isolated pathogens from various clinical specimens, and it is implicated in both community-acquired and healthcare-associated infections. It is an important member of the notorious ESKAPE group of pathogens. They are named so because they are infamous for their abilities to escape antimicrobial action by adopting various resistance mechanisms. Being the 2nd most commonly isolated bacterial species among them, *S. aureus* has its fair share of resistance mechanisms. Methicillin resistance is increasingly being reported worldwide, and *S. aureus* resistant to more than 2 classes of antibiotics is also rising alarmingly. **Objective**: To understand the susceptibility and resistance profile of *S. aureus* isolates with special focus on MRSA isolates and to identify inducible clindamycin resistance among them using CLSI-approved phenotypic detection methods. **Methods:** This was a descriptive cross-sectional study conducted in the Department of Microbiology, Coimbatore Medical College and Hospital, Coimbatore, Tamil Nadu, India, between July 2024 to February 2025. The study included 170 *S. aureus* isolates. **Results:** At the end of this study, the majority of *S. aureus* isolations were from pus samples at 55% followed by blood samples at 30%. Antimicrobial susceptibility testing of 170 isolates showed MRSA in 35.9% isolates. Resistance rates of 89% to ampicillin, 70% to gentamicin, 61% to ciprofloxacin and 53% to erythromycin were recorded, while the susceptibility rates were 100% to linezolid, 91% to doxycycline, 75% to cotrimoxazole, 62% to clindamycin. Inducible clindamycin resistance-ICR was detected by the D-test among 16% of isolates. 100% susceptibility towards vancomycin was established by performing a vancomycin screen agar. **Conclusion**: The results highlighted that MDR *S. aureus* were more common among MRSA isolates, and the need to look out for both constitutive and inducible clindamycin resistance, as clindamycin is favoured by many clinicians to counteract the toxins of *S. aureus*.

Keywords: ICR (Inducible Clindamycin Resistance), MRSA, MSSA, Vancomycin Screen Agar

1. Introduction

Staphylococcus aureus has a prevalence rate of 8.7% nationwide according to the ICMR-AMR- SN annual report 2023 (Indian Council of Medical Research-Antimicrobial Resistance-Surveillance Network), and so it is the most frequently isolated Gram-positive pathogen from various clinical samples[1]. With its nature of exhibiting resistance against many antimicrobials, this pathogen has retained its spot in the WHO's Bacterial Priority Pathogens List 2024. Methicillin-resistant *S. aureus*-MRSA are placed in the high-priority group of pathogens that demands us to carefully monitor the susceptibility and resistance profile of such pathogens[2].

MRSA rates are increasing steadily each year, from 32.8% MRSA in 2017 to 41.6% in 2020, 45.9% in 2022 and finally 48.3% MRSA in 2023[1,3,4]. This upward surge of MRSA prevalence rates brings to focus the urgency of the situation and the need for effective combat

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measures. Also, in *S. aureus* isolates, susceptibility exhibited towards common agents like co-trimoxazole, erythromycin, clindamycin, and ciprofloxacin was more in MSSA in comparison to MRSA[1].

The drug of choice for MRSA, like vancomycin and teicoplanin, showed nearly 100% efficacy against MRSA[1,4]. The frequent use of vancomycin against MRSA may lead to selective antibiotic pressure, leading ultimately to increased vancomycin resistance. This is indeed a huge concern as we do not have many last resort antimicrobials against Vancomycin Intermediate *S. aureus* (VISA) / Vancomycin-Resistant *Staphylococcus aureus* (VRSA)[5].

Clindamycin is an effective antibiotic in susceptible *S. aureus* isolates, as it can be used alone or in combination with bacteriocidal drugs. The effectiveness of clindamycin lies in its role in inhibiting protein toxin synthesis, which is the key determinant in many staphylococcal infections. It has an excellent oral bioavailability, thereby making it a good choice for treatment[6]. Increasing resistance is reported to clindamycin, too. Erythromycin resistance may sometimes induce clindamycin resistance due to ermA efflux pump mutations, but this ICR detection might be missed if we do not actually look for it. We have to employ the D-test, which is the gold standard phenotypic detection method for ICR. Some automated systems, like Vitek Boast that ICR can be detected in their systems, but the sensitivity and specificity of ICR detection is still a controversy[7].

2. Aim and Objectives

To understand the susceptibility and resistance profile of *S. aureus* isolates with special focus on MRSA isolates, and to identify inducible clindamycin resistance among them using CLSI-approved phenotypic detection methods.

3. Review of Literature

Staphylococcus aureus bacteria are capable of a variety of infectious pathologies ranging from relatively benign skin infections like folliculitis, impetigo, cellulitis, furuncles and carbuncles involving subcutaneous tissues to potentially severe life-threatening systemic illnesses. Community-acquired staphylococcal bronchopneumonia commonly affects the elderly, and it has been associated with viral pneumonia. Post-surgical wound infections may serve as a nidus for the development of systemic infections[8].

Staphylococcal toxins are responsible for food poisoning, Staphylococcal Scalded Skin Syndrome (SSSS) and Toxic Shock Syndrome (TSS). Staphylococcal carriage is high among the general population, with transmission occurring either by direct contact or by airborne routes. The majority of *S. aureus* (>90%) are resistant to penicillin due to production of penicillinases (betalactamases) by these bacteria. Methicillin resistance in *S. aureus* (MRSA) is mediated by the mecA gene and rarely the mecC gene, which are chromosomally mediated, and the expression can be either constitutive or inducible[5].

MRSA carries an extra protein called PBP2 (Penicillin binding protein-2) due to mecA gene. Such an altered PBP2a has a very low affinity towards most of the available beta-lactam drugs. In such conditions, beta-lactams will bind and inhibit the transpeptidase role of native PBP, and therefore, PBP2a is free to carry out the role of cell wall synthesis[5,8]. Thus, MRSA strains can escape beta-lactams except the fifth-generation cephems.

The anti-MRSA antibiotics such as vancomycin and teicoplanin have effective in vitro activity (nearly 100%) against MRSA isolates. As a consequence of the selective pressure of using these antibiotics, it has induced some clinical isolates to become intermediately-susceptible to vancomycin, leading to clinical VISA (a low-grade Vancomycin Intermediate *S. aureus*) and VRSA (a high-grade Vancomycin-resistant *S. aureus*). Transferable gene resistance has led to VRSA, which harbours mecA genes from MRSA and also transferable van A genes from VRE[5].

Van A gene produces low-affinity precursors(d-ala-d-lac or d-ala-d-ser instead of the usual or normal d-ala-d-ala residues) that result in VRSA. A phenomenon called the 'fitness cost' exists that states that those *S. aureus* which acquired the transferable resistant gene van A also acquired compensatory mutations in genes that are essential for its survival. This leads to a failure to thrive well among VRSA isolates[8]. This phenomenon is not common among MRSA. As a result of this, VRSA was observed very rarely(rate is <0.1%), whereas the presence of MRSA is so common (nearly 30%-40%).

Macrolide (Erythromycin) resistance would induce the expression of erm gene, which in turn has the ability to induce clindamycin resistance in *S. aureus*. As an end result, such *S. aureus* strains show resistance to erythromycin, clindamycin and streptogramin B, which together constitute the iMLSB phenotype (inducible Macrolide-Lincosamide-Streptogramin B)[5].

Clindamycin is the sole clinically used drug in its class of antibiotics, the Lincosamides. This agent has gained importance in recent times due to its potent activity in inhibiting protein toxin production; its sensitivity is not hindered by the bacterial load or the stage of the bacterial cells, and its role in modulating the host's immune response[6]. Clindamycin is effective when used alone, but being bacteriostatic, it's always better to augment the action with the use of a beta-lactam antibiotic or vancomycin(cell wall active agent), which is bacteriocidal. Clindamycin can rapidly terminate toxin production, while betalactam agents/ vancomycin can tackle the bacteria[9].

The spectrum of clinical activity of Clindamycin ranges from infections caused by anaerobes (*e.g.*, Bacteroides fragilis, Clostridium perfringens, Fusobacterium species, Prevotella melaninogenicus, and Peptostreptococcus species) to susceptible Staphylococci and Streptococci, so that it is used in the treatment of dental infections, anaerobic lung abscesses and SSTIs (Skin and soft tissue infections)[6]. The drug is bacteriostatic against some organisms while being bactericidal against others.

Linezolid (Oxazolidinone) resistance was encountered very rarely; however, since this drug is considered an important anti-TB agent, its use is not encouraged for *S. aureus* infections.

The CLSI M100 document allows the use of cefoxitin as a surrogate for oxacillin for *S. aureus* by the disk diffusion method or by calculating MIC. Those isolates that are cefoxitin resistant are reported as methicillin(oxacillin) resistant *S. aureus*. Vancomycin resistance can be screened using vancomycin screen agar and can be confirmed by vancomycin MIC of ≤2 µg/ml as vancomycin susceptible, MIC of 4-8 µg/ml as VISA and MIC of ≥16 µg/ml as VRSA[10].

Inducible clindamycin resistance can be detected by D-zone disc diffusion test using erythromycin 15 µg and clindamycin 2 µg discs or by using the broth microdilution method, where a combination of erythromycin 4 µg/ml and clindamycin 0.5 µg/ml is taken in the same well[10].

4. Materials and Methods

This was a descriptive cross-sectional study conducted in the Department of Microbiology, Coimbatore Medical College and Hospital, Coimbatore, Tamil Nadu, India, between July 2024 and February 2025. The study included 170 *S. aureus* isolates. These bacteria were isolated and identified by using standard culture and biochemical characterisation methods. Colony morphology was noted on a nutrient agar plate that showed small 1-2 mm golden yellow colonies with non-diffusible pigmentation. 5% sheep blood agar showed beta-hemolytic golden yellow colonies. Colony Gram's staining revealed Gram-positive cocci arranged in clusters. Further biochemical tests revealed catalase test positive, coagulase test (both slide and tube coagulase tests) positive, and urea hydrolysis test positive. Hugh-Leifson's oxidative-fermentative test demonstrated a fermentative pattern, and 1% mannitol was fermented with gas production.

Antimicrobial Susceptibility Testing (AST) was performed on all 170 isolates by using the Kirby-Bauer Disc Diffusion method, and the zones were interpreted according to CLSI M100 documents, 35th edition. Methicillin-Resistant *Staphylococcus aureus* was identified using a cefoxitin disc, and those isolates with a zone of inhibition of ≤21 mm were taken as MRSA. Isolates with cefoxitin ≥22 mm zone were taken as MSSA.

Vancomycin Screen Agar (VSA): The Vancomycin Screen agar is prepared by using Brain Heart Infusion (BHI) agar supplemented with 6 µg/ml vancomycin, used as the screening medium. To prepare 100 ml of BHI agar with this concentration, a 1 mg/ml vancomycin stock solution was stored in the freezer. An aliquot of 600 µl was taken from the stock and added to 100 ml of autoclaved BHI agar medium to create the screening plates. Fresh subcultures from glycerol stocks were prepared on non-selective media the day before the VSA test. The cultures were incubated at 35–37°C for 18 to 24 h in a BOD incubator. A fresh culture of the ATCC control strain(Enterococcus faecalis), along with

the test strain, was prepared. A standardised inoculum of 0.5 McFarland (approximately 1.5 × 10^8 CFU/ml) was prepared using the direct colony suspension method. For plate inoculation, a square grid template was created on VSA. Using a micropipette, a 10 µl drop of the inoculum suspension (final concentration of 10^6 CFU/ml) was spot inoculated onto the BHI agar plate containing 6 µg/ml vancomycin. The plates were incubated at 35 ± 2°C for 24 h in ambient air.

The results were interpreted using transmitted light to identify colonies or light growth films. The presence of more than one colony or a light film of growth indicated reduced susceptibility to vancomycin, suggesting presumptive resistance. When no growth appeared on the screen agar plate, the *S. aureus* isolate was considered vancomycin sensitive. If growth occurred at 6 µg/ml on the VSA plate, the presence of VRSA was suspected, and Broth Microdilution (BMD) was recommended to determine the vancomycin MIC.

Quality control strains were used to validate the test results. Enterococcus faecalis ATCC 29212 served as the negative control strain, exhibiting susceptibility or no growth.

Inducible clindamycin resistance: Standard inoculum of the test isolate was prepared and matched to 0.5 McF standard; lawn culture was made on MHA. Erythromycin disc 15 µg and Clindamycin disc 2 µg were placed after the plate dried. (discs are spaced 15-26 mm apart-edge to edge). Plates are incubated at 35±2°C for 16-18 hrs. The presence of a clindamycin zone getting flattened adjacent to the erythromycin disc to form a 'D' (called as D-zone) indicated ICR. No D zone formation, but hazy growth is seen in the zone of clindamycin are reported as clindamycin-resistant isolates. The interpretation of this test is as follows,

MS Phenotype is detected when Staphylococcal isolates exhibit resistance to erythromycin (zone size ≤ 23 mm) and susceptibility to clindamycin (a circular zone size ≥ 21 mm). Inducible MLSB Phenotype (iMLSB) is detected when Staphylococcal isolates show resistance to erythromycin (zone size ≤23 mm) and susceptibility to clindamycin (zone size ≥21 mm) by forming a D-shaped zone of inhibition around clindamycin with flattening towards the erythromycin disc.

Constitutive MLSB Phenotype (cMLSB) was detected in those Staphylococcal isolates with resistance to both erythromycin (zone size ≤23 mm) and clindamycin (zone size ≤21 mm).

Statistical analysis: The data obtained were manually entered into Microsoft Excel and analysed.

5. Results (Including Observations)

Out of the 2149 culture-positive growths, 170 of them were isolated and identified as *Staphylococcus aureus*. This gave a prevalence rate of 7.91% in this tertiary care hospital. The clinical samples from which isolation was made were majority from pus samples at 55% (n=93), from blood samples at 30% (n=51), from urine and central venous catheter tips both at 5% (n=9), while sputum and body fluids samples were at 3% and 2%, respectively (n=5 and n=3, respectively).

Antimicrobial susceptibility testing of all the 170 isolates showed cefoxitin susceptibility in 64% (n=109) and cefoxitin resistance, which implies MRSA was noted among 36% (n=61) isolates (Table 1). Figure 1 showed that ampicillin was resistant in 89% (n=152) while susceptibility was seen only in 11% (n=18) of isolates. Gentamicin recorded resistance rates of 59% (n=99), while susceptible to the remaining 41% (n=71). Fluroquinolone ciprofloxacin also recorded a >50 % resistance rate of 61% (n=104) with a susceptibility rate at 39% (n=66). Cotrimazole was found to be 75% (n=127) susceptible and 25% (n=43) resistant. Erythromycin showed nearly 50% susceptibility and resistance rates (resistant in n=84 and susceptible

Table 1. AST done by Kirby-Bauer disk diffusion method and Vancomycin screen agar for all Staphylococcus aureus isolates (n=170)

Antibiotics	Susceptible		Resistant	
	No. of isolates	Percentage %	No. of isolates	Percentage %
Ampicillin	18	10.6	152	89.4
Cotrimoxazole	127	74.7	43	25.3
Ciprofloxacin	66	38.8	104	61.2
Erythromycin	86	50.6	84	49.4
Clindamycin	98	57.6	72	42.4
Doxycycline	155	91.2	15	8.8
Gentamicin	71	41.2	99	58.8
Vancomycin	170	100	0	-
Linezolid	170	100	0	-

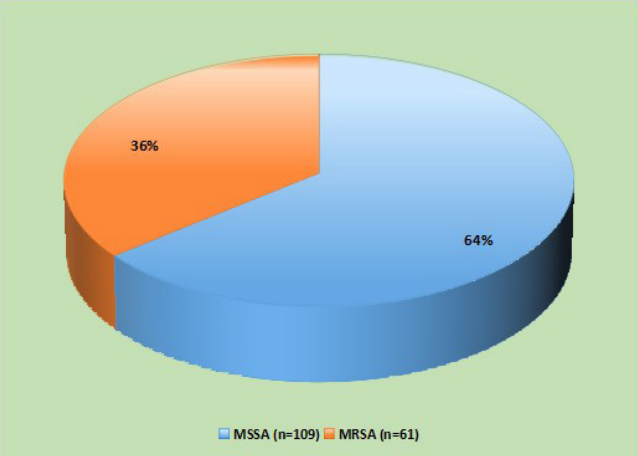

Figure 1. Distribution of MSSA and MRSA among 170 Staphylococcus aureus isolates.

Table 2. Antimicrobial susceptibility testing results of n=61, MRSA isolates

Antibiotics	Susceptible		Resistant	
	No of isolates	Percentage %	No of isolates	Percentage %
Ampicillin	0	-	61	100
Cotrimoxazole	43	70.5	18	29.5
Ciprofloxacin	13	21.3	48	78.7
Erythromycin	21	34.4	40	65.6
Clindamycin	30	49.2	31	50.8
Doxycycline	52	85.2	9	14.8
Gentamicin	22	36	39	64
Vancomycin	61	100	0	-
Linezolid	61	100	0	-

in n=86 isolates). 91% (n=155) isolates exhibited susceptibility to doxycycline. A similar pattern was seen with clindamycin, with 57% (n=98) susceptibility and 43% (n=72) resistance.

Vancomycin screen agar revealed no growth when tested, and hence 100% susceptibility towards vancomycin was established. So all 170 *S. aureus* isolates were vancomycin susceptible. Similar 100% susceptibility was noted towards linezolid (Table 2, Figure 2).

The antimicrobial susceptibility testing among MSSA and MRSA isolates is compared, and it was found that MRSA isolates exhibit at least>10-15 % increased resistance to cotrimoxazole, ciprofloxacin, erythromycin and clindamycin when compared with

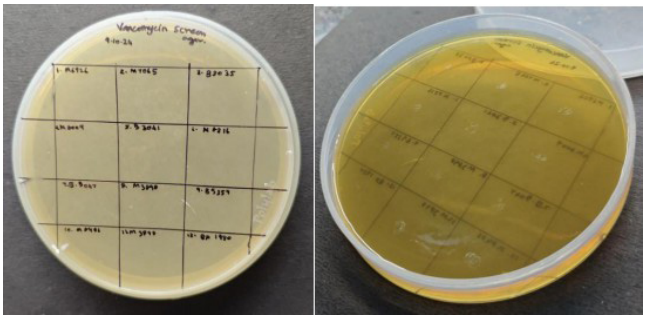

Figure 2. Vancomycin screen agar showing no growth for the tested isolates.

Table 3. Susceptibility to erythromycin and clindamycin among all *S. aureus* isolates

Erythromycin (ERY) and Clindamycin (CD)			
Susceptibility pattern	**Phenotype**	**Number of isolates**	**Percentage %**
ERY- S, CD -S		76	45 %
ERY-R, CD -R	Constitutive MLSB	35	20 %
E-R, CD-S (D test positive)	Inducible iMLSB	27	16 %
E-R, CD-S (no D zone)	MS	32	19 %
Total		170	100 %

Table 4. Comparison of erythromycin and clindamycin resistance with Methicillin resistance

Erythromycin (ERY) and Clindamycin (CD)			
Susceptibility pattern	**Phenotype**	**MSSA (n=109)**	**MRSA (n=61)**
ERY- S, CD -S		65 (60 %)	21 (34 %)
ERY-R, CD -R	Constitutive MLSB	31 (28 %)	14 (23 %)
ERY-R, CD-S (D test positive)	Inducible iMLSB	10 (9 %)	17 (28 %)
E-R, CD-S (no D zone)	MS	3 (3 %)	9 (15 %)
Total		**109 (100 %)**	**61 (100 %)**

the resistance rates among MSSA isolates (Table 3). The D-zone test, which indicates inducible clindamycin resistance due to erythromycin resistance, was positive in 16% (n=27) of total isolates. ICR among MRSA isolates was 63% (n=17) when compared with MSSA isolates 36% (n=10) (Table 4, Figures 3, 4)

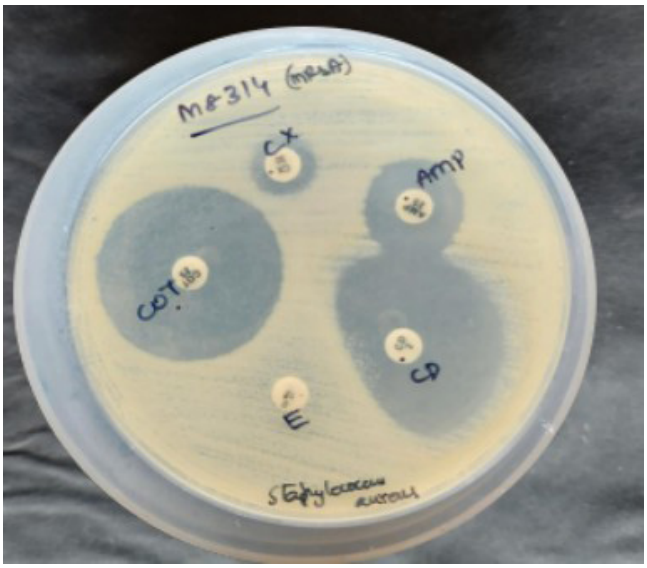

Figure 3. AST testing of the Staphylococcal isolate showed D zone formation around clindamycin, with flattening noted in the zone of inhibition towards the side of erythromycin (inducible clindamycin resistance with D-test positive). Cefoxitin resistance denotes MRSA.

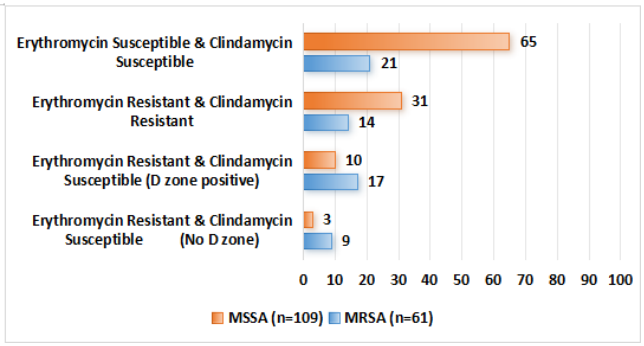

Figure 4. Distribution of Erythromycin and Clindamycin phenotypes among MSSA and MRSA isolates.

6. Discussion

2023 annual Indian data of AMRSN-ICMR(10) has reported a prevalence rate of 8.95% *S. aureus*(n=8900) among all culture positive isolates (n=99492) from all clinical samples. This is in concordance with this study of a total of 2849 culture-positive samples, *S. aureus* n=170, the prevalence rate being 5.97% (n=170).

The 2023 annual data states nearly 50%(48.44%) of MRSA isolates are all over India. Nandhana *et al.*[11] have reported 40.35% MRSA isolates. Joshi S *et al.*[12] have reported 41% MRSA. Similarly, studies like Wattal *et al.*[13], Jindal *et al.*[14] and Eshwara *et al.*[15] have shown the prevalence of MRSA to be between 13-47% which corresponds with this study result of 35.8% (n=61) MRSA isolates.

Sample-wise distribution revealed the majority of *S. aureus* isolations are from pus at 55% (n=93), followed by blood at 30% (n=51). Urine and catheter tips each recorded 5.2% (n=9) with sputum at 3% (n=5) and body fluids, including CSF at 1.6% (n=3). All India 2023 data has recorded similar findings with pus being the predominant sample for *S. aureus* at 59.3% and blood at 16.5%[10]. Pai *et al.*[16], a Mangalore study reported near equal isolation of *S. aureus* from both pus and blood (27.07% and 22.22%, respectively). Khan *et al.*'s[17] study (Lucknow), Kaur *et al.*'s[18] study (Pune), and Punjab Arora *et al.*[19] reported pus as the most frequent sample of *S. aureus* isolation, followed by blood. Tsering *et al.*'s[20] study from Sikkim had reported discordantly that the maximum samples of *S. aureus* isolation were from pus (45%) followed by urine samples (20.5%).

AST done on *S. aureus* in this study has recorded a 89.4% resistance towards ampicillin (n=152), 61.2% towards ciprofloxacin (n=104), 52.8% resistance towards erythromycin (n=85) and 58.8% resistance towards aminoglycoside gentamicin (n=99). Nirwan *et al.*[21], a Jaipur study comparing hospital and community-acquired *S. aureus* infections, has reported resistance of 72.2% to Gentamicin, 67.8% to ciprofloxacin and 61.7% to erythromycin, which showed a higher gentamicin and erythromycin resistance when compared with this study.

This study has shown 25.3% (n=43) resistance to cotrimoxazole. This resistance rate is minimal when analysing Kaur *et al.*[18,] which has reported a 100% resistance and Kali *et al.*[22,] A Pondicherry study which has reported 85.4% resistance to cotrimoxazole. Nirwan Abbas Ameer *et al.*[21], Jaipur has 32.16% resistance to cotrimoxazole, which is still a little higher when compared with this study. Overall clindamycin resistance in this study is 38.5% (n=62). This is similar to Nirwan Abbas Ameer *et al.*[21] who reported 46.15% clindamycin resistance. This result is discordant with Kaur *et al.*[18], who had 100% resistance to both erythromycin and clindamycin.

As erythromycin resistance can induce clindamycin resistance too, this study found inducible clindamycin

resistance to be 15.9% (n=27). Prabhu *et al.*[23], a Karnataka study, have reported 10.52% iMLSB phenotype, implying that 10.52% were inducible clindamycin resistant(ICR) isolates among a total of 190 tested *S. aureus* isolates. Nikkam *et al.*[24]. A Maharashtra-based study has recorded ICR at 25.74 % among 101 *S. aureus* isolates. Gandhi *et al.*[25], a Gujarat study has reported a high ICR rate of 37.5% among its 232 *S. aureus* isolates.

While associating ICR resistance with methicillin resistance, this study has given its results as 28% (n=17) ICR was encountered with MRSA, while 9% (n=10) was with MSSA. This is similar to Prabhu *et al.*[23], Karnataka, which has reported 20% ICR was noted among MRSA isolates and 6.15% ICR with MSSA isolates. Nikkam *et al.*[24], Maharashtra, have given in their report that ICR among MRSA was 29.7% while that of ICR with MSSA was 3%. Gandhi *et al.*[25], Gujarat recorded 59.34% ICR among its MRSA isolates and 12.84% ICR among its MSSA isolates. All these studies have reported a higher incidence of ICR in MRSA isolates, which is concordant with this study.

7. Summary and Conclusion

As *S. aureus* is most frequently isolated from skin and soft tissue infections, treating clinicians almost always start an empirical treatment with vancomycin or linezolid along with clindamycin. With S. aureus exhibiting nearly 100% susceptibility towards vancomycin and linezolid, the antibiotics can be continued or de-escalated depending on the antimicrobial susceptibility results from the Microbiology lab. The same cannot be said for clindamycin, as some S. aureus strains are constitutively resistant to it, while the resistance of erythromycin also induces clindamycin resistance. This added resistance can be easily identified by performing a simple D-test. As >50% resistance is noted against erythromycin, the chances of inducing clindamycin resistance also increase manyfold. Clindamycin is usually kept as a reserve drug, and it is used only in severe infections. Knowing the correct susceptibility pattern of clindamycin, it is a good alternative to vancomycin even in MRSA. So D-test is a feasible and reliable method to recognise constitutive and inducible clindamycin resistance in clinical practice.

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