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Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus* Infections in Patients with and Without Diabetes Mellitus: A Hospital-Based Comparative Study

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ABSTRACT

To evaluate MRSA infections with a specific focus on heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) among patients with and without diabetes mellitus, and to assess differences between these two populations.Isolated *S. aureus* strains from diabetic and non-diabetic inpatients across four tertiary hospitals in Coastal Karnataka (South India) were assessed for methicillin resistance and enrolled in the study. Patient-related demographic and clinical information was obtained through a standardized data collection form. Antimicrobial susceptibility testing was conducted using the Kirby–Bauer disk diffusion method. Detection of macrolide–lincosamide–streptogramin B (MLSb) resistance was performed using the D-test. Vancomycin minimum inhibitory concentrations were measured by agar dilution. MRSA isolates were further evaluated for heterogeneous vancomycin-intermediate *S. aureus* (hVISA) using vancomycin screening agar, with confirmation by population analysis profile–area under the curve (PAP-AUC). Statistical evaluation was performed using the chi-square test, and all analyses were conducted in SPSS version 29.0.Among 665 *S. aureus* isolates, 220 (33.1%) were identified as MRSA. Of these, 122 (55.5%) originated from diabetic patients, while 98 (44.5%) were from non-diabetic patients. No significant differences in antimicrobial resistance profiles were observed between MRSA isolates from the two patient groups. However, MRSA-associated foot infections and osteomyelitis were significantly more frequent in diabetic patients. Among the 220 MRSA isolates, 14 (6.4%) were classified as hVISA. The prevalence of hVISA was 9.0% in isolates from diabetic patients and 3.1% in those from non-diabetic patients; however, this difference did not reach statistical significance. Overall, 6.4% of all MRSA isolates were classified as hVISA. The likelihood of hVISA was about three times higher in patients with diabetes than in those without. These results underscore the need to target screening for hVISA among MRSA strains, especially in diabetic individuals.

Keywords: Heterogeneous vancomycin intermediate *S. aureus*, Antimicrobial resistance, Diabetes mellitus, Methicillin-resistant *S. aureus*

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major contributor to healthcare-associated infections (HAIs) [1]. Its multidrug-resistant nature makes treatment particularly difficult [2]. Vancomycin remains the mainstay for managing severe invasive MRSA infections [3]. However, an increasing number of MRSA isolates with diminished vancomycin susceptibility have been reported in recent years [4, 5].

Vancomycin-intermediate *S. aureus* (VISA) and heterogeneous vancomycin-intermediate *S. aureus* (hVISA) were first identified in 1997 [6]. VISA strains exhibit vancomycin MIC values of 4–8 µg/mL, allowing detection

through standard dilution-based techniques [7]. In contrast, hVISA consists of a predominantly susceptible population with a small fraction of cells (approximately 1 in 10^5–10^6) displaying intermediate resistance [5]. Despite this heterogeneity, the overall vancomycin MIC for hVISA remains within the susceptible range (≤ 2 µg/mL) [5, 8].

Routine antimicrobial susceptibility testing in clinical laboratories is often insufficient to identify hVISA [5, 8]. Detection requires specific screening procedures followed by confirmation using population analysis profile–area under the curve (PAP-AUC) [8-10]. Clinical response to vancomycin may be suboptimal in infections caused by hVISA [11]. Therefore, early identification before initiating therapy is important. The first case of vancomycin-resistant *S. aureus* (VRSA) was reported in a diabetic patient in 2002 [12]. While VRSA remains rare, cases of VISA and hVISA continue to be reported globally [4].

Individuals with diabetes are at increased risk of infections due to factors such as hyperglycemia, impaired immune responses, reduced phagocytic function, peripheral neuropathy, and vascular insufficiency [13]. In addition, repeated hospital admissions and prolonged antimicrobial exposure predispose these patients to infections with multidrug-resistant organisms [14]. MRSA is commonly isolated in diabetic foot infections and ulcers [13]. A study from South India also highlighted MRSA as a key pathogen in bone infections, reporting a methicillin resistance rate of 37.0% among *S. aureus* isolates [15].

hVISA is increasingly recognized as an emerging pathogen in healthcare settings [4, 16]. A global meta-analysis reported prevalence rates of 1.5% for VRSA, 1.7% for VISA, and 4.6% for hVISA [4]. In India, the corresponding rates are 1.6%, 4.6%, and 2.5%, respectively [4]. Another study from India found that 12.0% of MRSA isolates with vancomycin MIC ≥ 1 µg/mL were hVISA [17]. Identified risk factors for hVISA include prior MRSA infection, hospitalization, and exposure to vancomycin [5].

There is limited information regarding hVISA infections among diabetic patients in South India. Therefore, the present study aimed to investigate MRSA infections, with particular emphasis on hVISA, in diabetic and non-diabetic patients and to compare the findings between these groups.

Materials and Methods

Study setting and design

A cross-sectional investigation was carried out in a hospital setting, involving MRSA isolates obtained from both diabetic and non-diabetic patients admitted to four tertiary care centers (two government and two private) affiliated with a private medical college in Coastal Karnataka, India. The government hospitals had capacities of 1000 and 260 beds, whereas the private hospitals had 350 and 600 beds. The study was conducted in the Department of Microbiology from February 2019 to March 2020. Identification of healthcare-associated infections (HAIs) was based on the criteria established by the Centers for Disease Control and Prevention (CDC) [18].

The study protocol was reviewed and approved by the Institutional Ethics Committee of Kasturba Medical College, Mangalore. The bacterial isolates were obtained from routine diagnostic clinical specimens processed in the laboratory, and all data were anonymized before analysis. Consequently, informed consent from patients was not required.

Isolation and identification of bacteria

Identification of *S. aureus* isolates was performed using conventional microbiological techniques, including Gram staining, assessment of colony characteristics, detection of beta-hemolysis, pigment production, and standard biochemical tests such as catalase, coagulase, DNase activity, and mannitol fermentation [19].

Methicillin resistance was assessed using the cefoxitin (30 µg) disk diffusion method in accordance with CLSI guidelines [7]. Isolates showing a zone of inhibition ≤ 21 mm were categorized as methicillin-resistant. Quality control was ensured using *S. aureus* ATCC 43300 and *S. aureus* ATCC 25923 as positive and negative controls, respectively. Methicillin resistance was further confirmed by PCR detection of the mecA gene [20].

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing using kirby-bauer disk diffusion method

Antibiotic susceptibility profiles were assessed using the Kirby-Bauer disc diffusion method [7]. The tested antimicrobial agents (BD BBL™ Sensi-Disc™) included ciprofloxacin (5 µg), clindamycin (2 µg), erythromycin (15 µg), gentamicin (10 µg), linezolid (30 µg), rifampicin (5 µg), teicoplanin (30 µg), tetracycline (30 µg), and

trimethoprim–sulphamethoxazole (1.25/23.75 µg). Zone diameters were evaluated according to CLSI interpretive standards [7]. Quality control was ensured using *S. aureus* ATCC 25923.

Detection of macrolide, lincosamide, and streptogramin B (MLS_B) phenotypes

Detection of macrolide–lincosamide–streptogramin B (MLSB) resistance among MRSA isolates was performed using the D-test [7]. A standardized bacterial suspension equivalent to 0.5 McFarland (≈1.5×10^8 CFU/mL) was used to inoculate Mueller–Hinton agar plates. Discs of clindamycin (2 µg) and erythromycin (15 µg) (BD BBL™ Sensi-Disc™) were placed 15 mm apart (edge to edge). Following incubation at 35°C for 16–18 hours, results were interpreted based on CLSI recommendations [7].

a: Inducible resistance (iMLSB) was indicated by a blunted, D-shaped inhibition zone around clindamycin adjacent to the erythromycin disc. b: Lack of inhibition zones around both discs denoted constitutive resistance (cMLSB phenotype). c: Resistance to erythromycin with a well-defined, circular inhibition zone around clindamycin, without any distortion, was categorized as the MSB phenotype.

Determination of minimum inhibitory concentration (MIC) of vancomycin

Vancomycin minimum inhibitory concentrations (MICs) for the test isolates were determined by agar dilution [7]. Mueller–Hinton agar plates were prepared with serial concentrations of vancomycin (32, 16, 8, 4, 2, 1, 0.5, 0.25, and 0.125 µg/mL) (Sigma Chemical).

A few colonies from overnight growth on blood agar were inoculated into Mueller–Hinton broth and incubated at 37°C for 4–6 hours until turbidity corresponded to a 0.5 McFarland standard (approximately 1.5×10^8 CFU/mL). This suspension was then diluted tenfold to obtain a working inoculum of 1.5×10^7 CFU/mL. A volume of 2 µL of this inoculum was spot-inoculated onto the prepared agar plates, which were subsequently incubated at 35°C for 24 hours.

The MIC was defined as the lowest vancomycin concentration that completely inhibited visible bacterial growth, and results were interpreted according to CLSI criteria [7]. Isolates were categorized as vancomycin-susceptible *S. aureus* (VSSA) when MIC ≤ 2 µg/mL, VISA at 4–8 µg/mL, and VRSA at ≥ 16 µg/mL [7]. Quality control included *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213 as susceptible strains, and *E. faecalis* ATCC 51299 as the resistant control.

Identification of hVISA

Screening for hVISA

For the detection of hVISA, brain heart infusion (BHI) agar (HiMedia, Mumbai) supplemented with 16 g/L pancreatic digest of casein (Sigma Chemical) and 4 µg/mL vancomycin (Sigma Chemical) was employed as screening medium [8].

Standardized bacterial suspensions corresponding to McFarland 0.5 and 2.0 were prepared. From each suspension, four 10 µL aliquots were spotted onto the surface of the selective medium and allowed to dry for 10 minutes before incubation. Plates were incubated at 35°C for 48 hours, after which they were inspected for visible growth. The presence of ≥ 2 colonies in any inoculated spot was interpreted as indicative of hVISA [8].

Quality control organisms included *S. aureus* ATCC 25923 (negative control) and *S. aureus* ATCC 700698 (Mu3 strain, positive control).

Confirmation of hVISA

The VISA confirmation was performed using the modified population analysis profile–area under the curve (PAP-AUC) technique, as described by Wootton *et al*. [9].

In brief, isolates were cultured in brain heart infusion (BHI) broth at 35 °C for 6 hours, after which the bacterial suspension was standardized to a 0.5 McFarland turbidity (≈1.5×10^8 CFU/mL). This suspension was further diluted in serial steps (10^{-2} to 10^{-5}), and the dilution corresponding to ~10^4 CFU/mL was selected for testing [10]. A 10 µL volume of this inoculum was inoculated onto BHI agar plates supplemented with increasing vancomycin concentrations (16, 8, 4, 2, 1, 0.5, 0.25, and 0.125 µg/mL).

Staphylococcus aureus ATCC 700698 (Mu3 strain) was used as the hVISA reference control. After incubation at 35°C for 48 hours, growth at each antibiotic concentration was recorded. PAP curves were generated and analyzed using GraphPad Prism version 9.0 (GraphPad Software, USA), and the AUC ratio was calculated relative to the

Mu3 strain. Isolates with ratios of 0.9–1.3 were interpreted as hVISA, while values >1.3 were considered VISA [10].

Statistical analysis

The proportion of MRSA among all *S. aureus* isolates and the frequency of hVISA among MRSA strains were calculated as percentages. Associations between categorical variables were evaluated using the chi-square test. A P-value ≤ 0.05 was considered indicative of statistical significance. All analyses were performed using IBM SPSS Statistics, Version 29.0 (IBM Corp., Chicago, IL, USA).

Results and Discussion

Among hospitalized patients, a total of 665 non-duplicate *S. aureus* isolates were recovered, of which 357 (53.7%) came from individuals with diabetes and 308 (46.3%) from those without diabetes. MRSA accounted for 220 isolates (33.1%) overall. Within this subset, 122 isolates (55.5%) were derived from diabetic patients and 98 (44.5%) from non-diabetic patients.

The diabetic cohort had a mean age of 58 years (median 57), whereas the non-diabetic group had a markedly younger distribution with a mean age of 27 years (median 28). MRSA isolates were obtained from various clinical sources, including pus, tissue specimens, bloodstream infections, and intravenous catheter tips.

When stratified by hospital type, MRSA prevalence among *S. aureus* isolates was comparable across the two public and two private tertiary centers, recorded as 33.1% (93/281), 31.0% (9/29), 32.7% (54/165), and 33.7% (64/190), respectively.

Overall, 143 MRSA isolates (65.0%) were recovered from male patients, while 75 (35.0%) were recovered from female patients. Statistical comparison showed a higher burden of MRSA infection in diabetic males compared with non-diabetic males. Additionally, MRSA-related foot infections and osteomyelitis were more frequently observed in the diabetic population **(Table 1).**

Table 1. Detailed gender distribution and clinical characteristics of MRSA cases in both study groups.

Clinical characteristics of MRSA cases	P-value	Total (n = 220)	Non-diabetic group (n = 98), n (%)	Diabetic group (n = 122), n (%)
Sex distribution				
Male	0.010*	143	55 (56.1)	88 (72.1)
Female	0.010*	77	43 (43.9)	34 (27.9)
Skin and soft tissue infections (n = 186)				
Post-surgical site infection	0.946	87	39 (39.8)	48 (39.3)
Wound-related infection	< 0.001*	27	25 (25.5)	2 (1.6)
Foot infection/ulceration	< 0.001*	34	3 (3.1)	31 (25.4)
Abscess formation	0.327	18	10 (10.2)	8 (6.5)
Cellulitis	0.575	6	2 (2.0)	4 (3.3)
Carbuncle	0.264	5	1 (1.0)	4 (3.3)
Gangrene	0.694	3	1 (1.0)	2 (1.6)
Necrotizing fasciitis	0.203	2	0 (0.0)	2 (1.6)
Infection at the umbilical site	0.113	2	2 (2.0)	0 (0.0)
Burn-associated wound infection	0.113	2	2 (2.0)	0 (0.0)
Deep-seated infections (n = 34)				
Bacteremia	0.954	25	11 (4.1)	14 (7.4)
Osteomyelitis	0.026*	6	0 (0.0)	6 (4.9)
Septic arthritis	0.876	2	1 (1.0)	1 (0.8)
Sepsis	0.263	1	1 (1.0)	0 (0.0)

Note: P-value ≤ 0.05 was considered statistically significant. Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

The antimicrobial susceptibility patterns of MRSA isolates are summarized in **Table 2.** No statistically significant differences in resistance profiles were observed between isolates from diabetic and non-diabetic patients.

High resistance rates (>80%) were observed for both ciprofloxacin and erythromycin. Overall, 72.3% of MRSA isolates exhibited multidrug resistance. In contrast, all isolates remained fully susceptible to linezolid and teicoplanin.

All 220 MRSA isolates were vancomycin-susceptible by agar dilution testing (MIC ≤ 2 µg/mL). The MIC50 and MIC90 values for vancomycin were 1 µg/mL and 2 µg/mL, respectively.

Table 2. The detailed antimicrobial resistance profiles of MRSA isolates from both study groups.

Antimicrobial agents (potency)	P-value	Total n = 220	Non-diabetic patients (n = 98) number (%)	Diabetic patients (n = 122) number (%)
Ciprofloxacin (5 µg)	0.219	193	83 (84.7)	110 (90.2)
Clindamycin (2 µg)	0.337	35	13 (13.5)	22 (18.3)
Erythromycin (15 µg),	0.284	186	80 (81.6)	106 (86.8)
Gentamicin (10 µg)	0.786	110	48 (48.9)	62 (50.8)
Linezolid (30 µg)	-	0	0 (0.0)	0 (0.0)
Rifampicin (5 µg)	0.828	17	8 (8.2)	9 (7.4)
Teicoplanin (30 µg)	-	0	0 (0.0)	0 (0.0)
Tetracycline (30 µg)	0.835	68	31 (31.6)	37 (30.3)
Trimethoprim- sulphamethoxazole (1.25 µg/23.75 µg)	0.306	105	43 (43.8)	62 (50.8)
MLS_B phenotype				
$iMLS_B$	0.536	63	26 (26.5)	37 (30.3)
MS_B	0.618	88	41 (41.8)	47 (38.5)
$cMLS_B$	0.337	35	13 (13.3)	22 (18.0)
hVISA	0.072	14	3 (3.1)	11 (9.0)

Note: P-value ≤ 0.05 was considered statistically significant. Abbreviations: cMLSB = constitutive clindamycin resistance; hVISA = heterogeneous vancomycin-intermediate *Staphylococcus aureus*; iMLSB = inducible clindamycin resistance; MLSB = macrolide–lincosamide–streptogramin B; MRSA = methicillin-resistant *Staphylococcus aureus*.

hVISA was detected in 14 of the 220 MRSA isolates (6.4%) using the modified PAP-AUC assay. No isolates fulfilled the criteria for VISA. When stratified by patient group, the difference in hVISA occurrence between diabetic and non-diabetic patients was not statistically significant (P = 0.072) **(Table 2).**

Clinically, hVISA infections in diabetic patients most commonly presented as skin and soft tissue infections, although two episodes of bacteremia were also documented. Notably, the majority of hVISA isolates from diabetic patients (10 of 11) showed vancomycin MIC values in the range of 1–2 µg/mL **(Table 3).**

Table 3. Demographic and clinical features of diabetic patients with hVISA infection.

hVISA strains	Age of the patients	Gender	Hospital	Clinical condition	AUC_{test}/AUC_{Mu3} ratio	Vancomycin MIC (µg/mL)
1	69	Female	Private hospital 1	Bacteremia	0.93	1.0
2	61	Male	Private hospital 1	Diabetic foot ulcer	1.0	1.0
3	57	Male	Public hospital 1	Surgical site infection	0.93	1.0
4	85	Male	Public hospital 1	Surgical site infection	0.93	0.5
5	62	Male	Private hospital 1	Surgical site infection	1.0	1.0
6	64	Male	Private hospital 1	Wound gaping at the site of the chemoport	1.0	2.0
7	54	Male	Public hospital 1	Bacteremia	1.0	1.0
8	65	Female	Public hospital 1	Surgical Site Infection	1.0	1.0
9	45	Male	Private hospital 1	Gluteal abscess	1.0	2.0

10	75	Female	Private hospital 1	Right T3 gangrene	1.0	2.0
11	70	Male	Private hospital 1	Cellulitis	0.93	1.0

Note: Identification of hVISA was performed using the PAP-AUC method, with isolates categorized as hVISA when the ratio of the test strain AUC to the Mu3 reference strain AUC ranged from 0.9 to 1.3.

Abbreviations: AUC, area under the curve; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*; MIC, minimum inhibitory concentration.

In the present study, MRSA accounted for 33.1% of all *S. aureus* isolates obtained from healthcare-associated infections (HAIs). The reported prevalence of MRSA varies considerably across different regions of the country [17, 21, 22]. A prior investigation conducted at the same institution in 2016 documented a rate of 30.2%, suggesting a gradual increase in the local burden of MRSA over time [23]. Similarly, higher HA-MRSA rates (38.6%) have been reported from Mangalore [21]. Another regional study also demonstrated an upward trend, with prevalence rising from 28.0% in 2017 to 35.1% in 2019 [24].

MRSA infection is generally reported more frequently among patients with diabetes compared to non-diabetic individuals [14, 25]. The findings of the present study align with this observation. Differences in patient demographics, geographic variation, prior antimicrobial exposure, sample size, and methodological approaches may all contribute to variability in reported MRSA rates [26].

Regarding infection type, superficial infections, such as skin and soft-tissue involvement, were more common than deep-seated disease. However, diabetic patients showed a significantly higher proportion of foot infections and osteomyelitis compared with non-diabetic patients. These findings are consistent with the report by Shah and Hux [27], who described a fourfold increased risk of osteomyelitis in diabetic individuals. A study from South India has also identified MRSA as an important pathogen in bone-related infections [15]. Furthermore, *S. aureus* remains the leading cause of diabetic foot infections in several Western studies [28, 29].

Antimicrobial susceptibility testing showed that all MRSA isolates were susceptible to linezolid and teicoplanin, consistent with previous reports [23, 30]. High resistance rates were observed for ciprofloxacin and erythromycin (>80%), in agreement with earlier findings [25]. No meaningful differences in resistance patterns were identified between isolates from diabetic and non-diabetic patients. Overall, 72.3% of MRSA strains exhibited multidrug resistance, indicating limited therapeutic options.

The MLSB resistance group (macrolides, lincosamides, and streptogramin B) includes clindamycin, an important option for treating MRSA-associated skin and soft tissue infections [31, 32]. However, inducible clindamycin resistance (iMLSB) limits its clinical utility [31, 33]. Such isolates may appear erythromycin-resistant but clindamycin-susceptible in routine testing, and therefore require D-test confirmation [31, 33]. In this study, inducible resistance was observed in 30.0% of MRSA isolates from diabetic patients and 26.5% from non-diabetic patients.

hVISA was detected in 6.4% of MRSA isolates, with a markedly higher frequency in diabetic patients (approximately 3-fold). Most hVISA-related infections in diabetics were associated with skin and soft tissue involvement, although two cases of bloodstream infection were also identified. Previous reports have documented reduced vancomycin efficacy in hVISA infections [4, 5, 11, 34].

Although VISA and VRSA were not detected in this study, the presence of hVISA remains clinically significant, as it may represent a potential precursor to VISA development [5, 6]. Therefore, continued surveillance is warranted. Strengthening antimicrobial stewardship and reinforcing infection control practices may help limit further emergence and spread of hVISA within healthcare settings.

Conclusion

hVISA was identified in 6.4% of MRSA isolates recovered from healthcare-associated infections. Its occurrence was approximately three times higher among patients with diabetes compared to those without. These findings highlight the clinical relevance of routinely screening MRSA isolates for hVISA, particularly in diabetic populations where the risk appears elevated.

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Conflict of Interest: None

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Ethics Statement: The study protocol was reviewed and approved by the Institutional Ethics Committee of Kasturba Medical College, Mangalore, India (Reference No. IEC KMC MLR 03-19/75; dated 20 March 2019).

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