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# *Staphylococcus aureus* at an Indian tertiary hospital: Antimicrobial susceptibility and minimum inhibitory concentration (MIC) creep of antimicrobial agents

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A B S T R A C T

*Objectives:* *Staphylococcus aureus* causes a variety of symptoms and diseases and has been associated with high morbidity and mortality. A global population drift in clinical *S. aureus* isolates towards reduced antimicrobial susceptibility is being reported. In this study, the antimicrobial susceptibility profile and minimum inhibitory concentration (MIC) creep of vancomycin, linezolid, teicoplanin and rifampicin against clinical *S. aureus* isolates at an Indian tertiary centre from January 2012 to December 2016 were investigated.
*Methods:* All consecutive, non-duplicate *S. aureus* isolates ($n$ = 1466) recovered from hospitalised patients identified by VITEK®2 were included in the study. Clinical isolates were tested against 20 antibiotics and were evaluated according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Statistical significance of the MIC creeps of four antimicrobials (vancomycin, linezolid, teicoplanin and rifampicin) was ascertained.
*Results:* *S. aureus* isolates recovered from all clinical samples demonstrated high resistance to ampicillin, ciprofloxacin and penicillin (75–100%) and low resistance to amikacin, linezolid, netilmicin, nitrofurantoin, teicoplanin and vancomycin (0–13%). The $MIC_{90}$ values (MIC required to inhibit 90% of the isolates) for vancomycin, linezolid and rifampicin decreased, whereas the $MIC_{90}$ for teicoplanin increased. The change in the geometric mean MIC of rifampicin was found to be statistically significant. A statistically significant and progressive MIC creep was observed for teicoplanin and rifampicin.
*Conclusion:* Despite remaining susceptible, *S. aureus* is not inert to antibiotic pressure. Implementation of preventive measures in healthcare settings is required worldwide to combat the increasing number of infections by this pathogen.


## 1. Introduction

*Staphylococcus aureus* causes a variety of symptoms and diseases such as bacteraemia, pneumonia, endocarditis, osteoarticular infections and skin and soft-tissue infections worldwide and has been associated with high morbidity and mortality [1]. Since its discovery in 1880, *S. aureus* has been evolving and developing resistance to different antimicrobials to which it has been exposed. However, emerging methicillin resistance drew much concern and gave rise to serious problems both in hospital and community settings. The progressive increase in minimum inhibitory concentrations (MICs) of vancomycin, linezolid and teicoplanin, described as 'MIC creep', is a graver problem.

Infection with methicillin-resistant *S. aureus* (MRSA) requires a longer duration of antibiotic treatment and results in higher healthcare costs, increased morbidity, prolonged hospital stay and an increased risk of death [2–4]. This risk is more pronounced in patients who have been treated suboptimally, either with an inadequate surgical intervention and/or ineffective antibiotic therapy [5]. In patients with *S. aureus* bacteraemia, higher vancomycin MICs have been associated with prolonged bacteraemia and increased mortality [6]. Since vancomycin has been the cornerstone of treatment of patients with serious MRSA infections, the suggested association between high vancomycin MIC and worse outcomes is alarming [7].

Since antimicrobial surveillance studies are critical, particularly data originating from a region such as India where localised

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patterns of resistance are observed in different geographical regions [8], this retrospective study was conducted over a 5-year period from January 2012 to December 2016 to report the trend of MIC creep for vancomycin, linezolid, teicoplanin and rifampicin in *S. aureus* isolated from clinical samples at a level-1 trauma centre in India.

## 2. Methods

### 2.1. Hospital setting

The Jai Prakash Narayan Apex (JPNA) Trauma Centre of the All India Institute of Medical Sciences is a 186-bed level-1 trauma centre in New Delhi, India. On average, 15 000 samples are processed annually for bacteriological diagnosis. During the study period (January 2012 to December 2016), a total of 66 683 bacterial isolates were recovered from clinical samples, with *S. aureus* constituting 2.2% of the isolates [9]. The entire microbiology data are maintained electronically in the centre's indigenous hospital information system software. All patient names and their clinical samples are coded to maintain confidentiality and to protect patient identity.

### 2.2. Bacterial isolates

Data on the susceptibility of *S. aureus* isolates were collected from January 2012 to December 2016. All consecutive, non-duplicate *S. aureus* isolates recovered from hospitalised patients were identified by VITEK®2 (bioMérieux, Marcy-l'Étoile, France) according to the manufacturer's instructions [10].

### 2.3. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing of the *S. aureus* isolates was performed by the diffusion testing method using antibiotic disks (HiMedia, Mumbai, India) for amikacin (30 μg), amoxicillin/clavulanic acid (AMC) (20/10 μg), ampicillin (10 μg), ampicillin/sulbactam (SAM) (10/10 μg), cefoxitin (30 μg), ciprofloxacin (5 μg), clindamycin (2 μg), trimethoprim/sulfamethoxazole (SXT) (1.25/23.75 μg), erythromycin (15 μg), gentamicin (10 μg), levofloxacin (5 μg), linezolid (30 μg), netilmicin (30 μg), nitrofurantoin (30 μg), oxacillin (1 μg), penicillin (10 U), rifampicin (30 μg), teicoplanin (30 μg), tetracycline (30 μg) and vancomycin (30 μg) and was evaluated according to Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. Methicillin susceptibility was determined using a cefoxitin disk under CLSI-recommended conditions.

### 2.4. Minimum inhibitory concentration determination and statistical analysis

Antimicrobial susceptibility data of bacterial populations determined by the VITEK®2 system were obtained and were used to calculate $MIC_{50}$ and $MIC_{90}$ values, which represent the MICs at which 50% and 90% of the isolates are inhibited, respectively. The geometric mean MIC was also calculated for each year. Spearman's rank correlation coefficient was calculated for tests of correlation between MICs of various antibiotics over the 5-year period evaluated. Statistical analyses were done using Stata/SE 12.1 (StataCorp LP, College Station, TX). A *P*-value of $\leq$0.05 was considered statistically significant.

## 3. Results

### 3.1. Bacterial isolates

A total of 1466 *S. aureus* isolates were recovered during the 5-year study period, including 834 (56.9%) from pus/wound swabs of post-operative infections, 237 (16.2%) from respiratory samples, 216 (14.7%) from blood, 82 (5.6%) from sterile body fluids, 46 (3.1%) from bone and tissue, 41 (2.8%) from central vascular lines tips and 10 (0.7%) from urine (Table 1). Of the 1466 *S. aureus* isolates, 794 (54.2%) (203, 187, 116, 154 and 134 in 2012–16, respectively) were MRSA and 672 (45.8%) (123, 154, 129, 135 and 131, respectively) were methicillin-susceptible *S. aureus* (MSSA) in 2012 ($n$ = 326), 2013 ($n$ = 341), 2014 ($n$ = 245), 2015 ($n$ = 289) and 2016 ($n$ = 265) respectively.

**Table 1**
Antimicrobial susceptibility determined by the disk diffusion method of *Staphylococcus aureus* clinical isolates ($n$ = 1466) at Jai Prakash Narayan Apex Trauma Centre (New Delhi, India) from January 2012 to December 2016.

| Antimicrobial agent | Percentage of resistant strains in clinical samples | | | | | | |
|---|---|---|---|---|---|---|---|
| | Pus/wound swabs ($n$ = 834) | Respiratory samples ($n$ = 237) | Blood ($n$ = 216) | Sterile body fluids ($n$ = 82) | Bone and tissue ($n$ = 46) | Central vascular line tips ($n$ = 41) | Urine ($n$ = 10) |
| Amikacin | 24 | 25 | 91 | 0 | 75 | 50 | 0 |
| AMC | 53 | 59 | 73 | 85 | 52 | 84 | 80 |
| Ampicillin | 97 | 98 | 98 | 100 | 91 | 94 | 100 |
| SAM | 20 | 21.3 | 59 | 100 | 37 | 68 | 30 |
| Cefoxitin | 49 | 57.6 | 77 | 83 | 49 | 71 | 70 |
| Ciprofloxacin | 86 | 100 | 94 | 76 | 83 | 80 | 80 |
| Clindamycin | 99 | 31 | 60 | 77 | 22 | 58 | 0 |
| SXT | 52 | 46.7 | 50 | 29 | 59 | 51 | 100 |
| Erythromycin | 52 | 47.9 | 79 | 89 | 46 | 85 | 40 |
| Gentamicin | 28 | 45.5 | 68 | 80 | 36 | 62 | 33.3 |
| Levofloxacin | 56 | 58.5 | 86 | 71 | 47 | 68 | 80 |
| Linezolid | 0 | 1.7 | 1 | 1.2 | 0 | 0 | 0 |
| Netilmicin | 2 | 4.9 | 5 | 0 | 2.4 | 0 | 0 |
| Nitrofurantoin | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Oxacillin | 33 | 41.5 | 68 | 83 | 41 | 54 | 70 |
| Penicillin | 99 | 99.1 | 98 | 100 | 98 | 100 | 100 |
| Rifampicin | 8 | 19.7 | 47 | 52 | 15 | 44 | 0 |
| Teicoplanin | 1 | 1 | 2 | 0 | 4.5 | 0 | 0 |
| Tetracycline | 18 | 13.6 | 46 | 39 | 36 | 43 | 40 |
| Vancomycin | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; SXT, trimethoprim/sulfamethoxazole.

### 3.2. Antimicrobial susceptibility testing

Table 1 shows the antimicrobial susceptibility of the 1466 *S. aureus* isolated from January 2012 to December 2016. Isolates recovered from clinical samples demonstrated high resistance to ampicillin, ciprofloxacin and penicillin (75–100%) and low resistance to amikacin, linezolid, netilmicin, nitrofurantoin, teicoplanin and vancomycin (0–13%). Variable resistance to AMC, SAM, cefoxitin, clindamycin, SXT, erythromycin, gentamicin, levofloxacin, oxacillin, rifampicin and tetracycline was observed (Table 1). The overall frequency of resistance to cefoxitin was higher than that to oxacillin in these isolates. In particular, isolates from sterile body fluid were found to be unique in their SAM susceptibilities. These disease state-specific susceptibilities would be useful to inform decision-making for empirical therapy.

The linezolid $MIC_{90}$ decreased from 4 μg/mL in 2012 to 2 μg/mL in 2013 and remained unchanged until 2016. A drop in the $MIC_{90}$ was observed for vancomycin and rifampicin in 2014. However, the $MIC_{90}$ for teicoplanin increased from 0.5 μg/mL in 2013–2014 to 1 μg/mL in 2015 (Table 2).

### 3.3. Vancomycin, linezolid, teicoplanin and rifampicin MIC creep

MIC creep in *S. aureus* for vancomycin, linezolid, teicoplanin and rifampicin was studied (Fig. 1). All isolates had vancomycin MICs in the susceptible range. A significant and progressive decrease was observed in the percentage of isolates showing a vancomycin MIC of 2 μg/mL ($P = 0.031$ for all *S. aureus* isolates and $P = 0.015$ for MRSA). In 2012, 21% (68/326) of isolates of *S. aureus* isolates had an elevated vancomycin MIC in contrast to 4% (10/265) in 2016 (Table 3). A significant and progressive decrease was observed in the percentage of isolates showing a linezolid MIC of 2 μg/mL ($P = 0.026$). A significant decrease in the percentage of MSSA isolates was observed at a linezolid MIC of ≥4 μg/mL ($P = 0.044$), whilst for MRSA isolates it was significant at an MIC of 2 μg/mL ($P = 0.010$) (Table 3).

Thus, whilst vancomycin and linezolid MICs decreased, teicoplanin MICs for MSSA increased to 1.0 μg/mL ($P = 0.003$) (Table 3). A total of 17 isolates (1.2%) were found to be resistant to teicoplanin. The findings may be involved in the deliberation of choosing alternative medications for patients with teicoplanin treatment failure. The percentage of MRSA isolates with a rifampicin MIC of 0.25 μg/mL increased significantly from 3.0% (6/203) in 2012 to 64% (86/134) in 2016. Meanwhile, the percentage of MRSA isolates with an MIC of 0.50 μg/mL decreased significantly from 59% (120/203) to 0%.

Moreover, 19% of strains were resistant to rifampicin. A significant increase in the percentage of MRSA isolates at an MIC of 0.5 μg/mL was observed ($P = 0.041$).

The impact of these changes on clinical treatment response requires further investigation. The question of whether cross-resistance exists between teicoplanin and rifampicin in MRSA isolates can only be answered after further studies.

**Table 2**
Minimum inhibitory concentrations (MICs) of vancomycin, linezolid, teicoplanin and rifampicin against *Staphylococcus aureus* isolated at Jai Prakash Narayan Apex Trauma Centre (New Delhi, India) from January 2012 to December 2016.

| Antimicrobial agent | Year | MIC (μg/mL) | | | | %S/R |
|---|---|---|---|---|---|---|
| | | GM | Range | $MIC_{50}$ | $MIC_{90}$ | |
| Vancomycin | 2012 | 0.76 | 0.25–2 | 0.5 | 2 | 100/0 |
| | 2013 | 0.77 | 0.25–2 | 0.5 | 2 | 100/0 |
| | 2014 | 0.84 | 0.25–2 | 0.5 | 1 | 100/0 |
| | 2015 | 0.65 | 0.25–2 | 0.5 | 1 | 100/0 |
| | 2016 | 0.72 | 0.5–2 | 0.5 | 1 | 100/0 |
| Linezolid | 2012 | 1.87 | 1–8 | 2 | 4 | 98/2 |
| | 2013 | 1.86 | 1–8 | 2 | 2 | 99/1 |
| | 2014 | 1.95 | 1–8 | 2 | 2 | 100/0 |
| | 2015 | 1.64 | 1–4 | 2 | 2 | 100/0 |
| | 2016 | 1.71 | 1–4 | 2 | 2 | 100/0 |
| Teicoplanin | 2013 | 0.51 | 0.25–4 | 0.5 | 0.5 | 100/0 |
| | 2014 | 0.56 | 0.25–8 | 0.5 | 0.5 | 100/0 |
| | 2015 | 0.55 | 0.25–8 | 0.5 | 1 | 100/0 |
| | 2016 | 0.56 | 0.25–8 | 0.5 | 1 | 100/0 |
| Rifampicin | 2012 | 0.76 | 0.03–32 | 0.5 | 32 | 80/20 |
| | 2013 | 0.57 | 0.03–32 | 0.5 | 32 | 80/20 |
| | 2014 | 0.07 | 0.03–4 | 0.03 | 4 | 80/20 |
| | 2015 | 0.12 | 0.03–4 | 0.03 | 4 | 70/30 |
| | 2016 | 0.10 | 0.03–4 | 0.03 | 1 | 90/10 |

GM, geometric mean; $MIC_{50/90}$, MIC at which 50% and 90% of the isolates are inhibited, respectively; S, susceptible; R, resistant.

## 4. Discussion

Emerging antimicrobial resistance is a matter of concern and a great challenge to clinicians and microbiologists alike. One of the prime threats is the emergence and spread of multidrug-resistant staphylococci, e.g. MRSA. Within the susceptible population of *S. aureus*, a changing pattern of vancomycin, linezolid and rifampicin MICs has been observed in our centre, demonstrating an overall population drift in clinical *S. aureus* isolates towards reduced antimicrobial susceptibility. However, no significant changes in the geometric mean MICs or $MIC_{50}$ values of vancomycin, linezolid or teicoplanin were observed during the study period. A statistically significant change in the geometric mean MIC of rifampicin was observed ($P = 0.049$) (Table 3). Other studies conducted across the globe have recently reported this phenomenon of MIC creep, which varies considerably owing to differences in epidemiological and clinical factors. Variation in antimicrobial susceptibility testing methods, selective pressure generated by high-dose antimicrobial therapy, differences in medical and surgical therapy of invasive *S. aureus* infections, and differing severity of illness of the patient populations with different co-morbid conditions could be some of the possible reasons of the varied MIC creep reported.

Being the choice of MRSA therapy for the past decades, vancomycin has exerted considerable selection pressure on *S. aureus* strains in healthcare settings. However, in this study no vancomycin or linezolid MIC creep was observed either in MRSA or in all *S. aureus* isolates taken together. This is most likely because of adherence to recent guidelines such as considering alternative antibiotics in complicated MRSA infections when the vancomycin MIC is ≥2 μg/mL [12]. This is also in concordance with similar reports from other parts of the world [1].

A higher teicoplanin MIC (> 1.5 μg/mL) has been reported to be a predictor of an unfavourable outcome and higher mortality rate among teicoplanin-treated MRSA bacteraemia patients [3]. At our centre, rifampicin and teicoplanin MIC creep was observed only in the case of MRSA and MSSA strains, respectively. These MIC creeps are highly suggestive of *S. aureus* not being inert to antibiotic pressure despite remaining susceptible to these antimicrobials. It may, however, be an oversimplification to say that *S. aureus* strains demonstrating MIC creep are becoming more virulent, as the virulence mechanisms of this pathogen are extremely elegant and multifarious. None the less, emerging evidence suggests that this phenomenon of MIC creep could be just the tip of the iceberg.

Although this is a single-centre study, the study hospital is a referral and teaching hospital providing healthcare services to patients from adjacent regions. Thus, geographical limitation may have a narrow impact on the applicability of the results to isolates from other areas in India. Additional studies are required to investigate whether the different clonal dissemination in MRSA strains correlates with the emergence of MIC creep. Since there was no outbreak of *S. aureus* in our hospital, we did not explore the

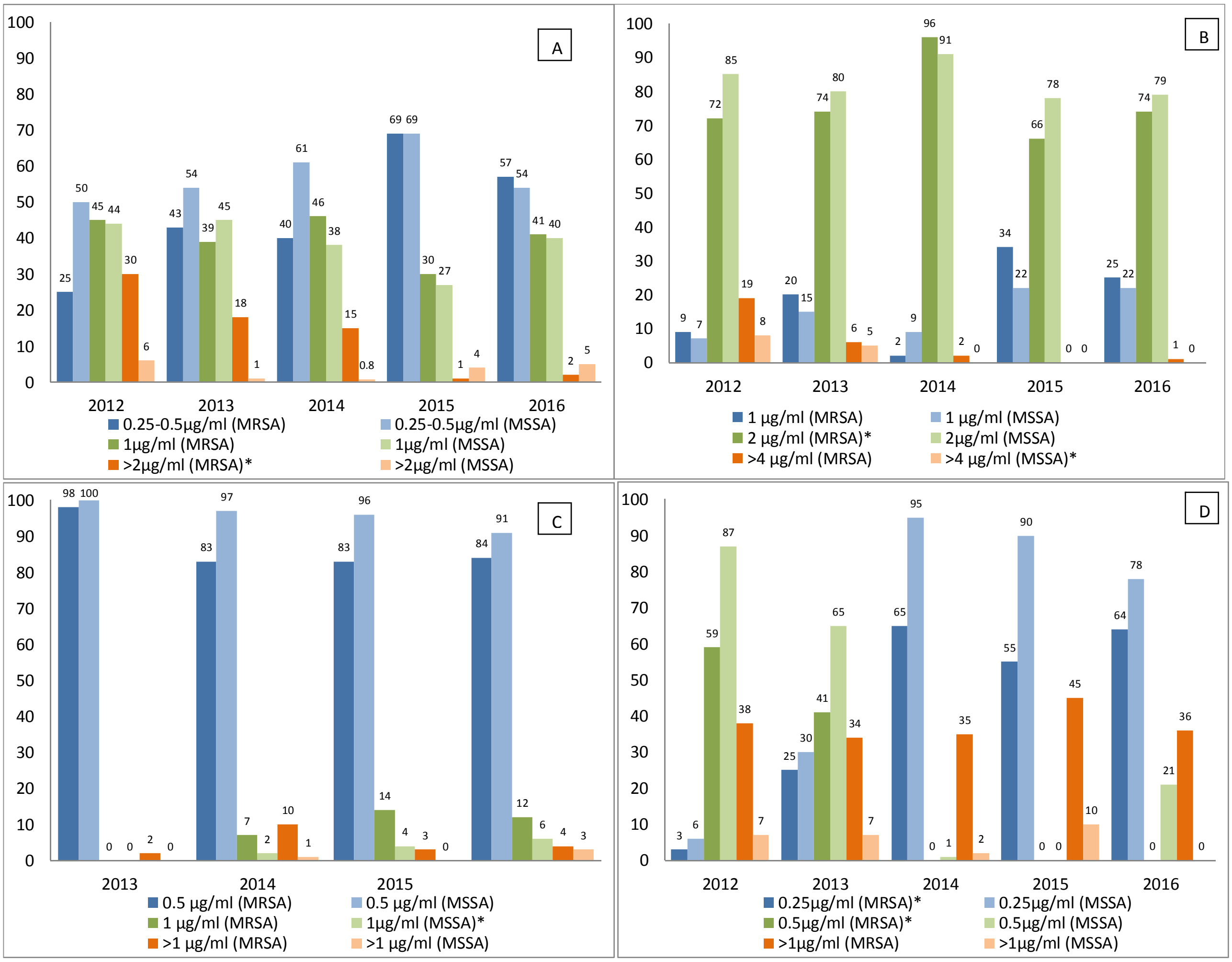


**Fig. 1.** Distribution of *Staphylococcus aureus* minimum inhibitory concentrations (MICs) for (A) vancomycin, (B) linezolid, (C) teicoplanin (2013–2016) and (D) rifampicin during 2012–2016. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*. *x*-axis, percentage of strains; *y*-axis, year of data collection. * $P \leq 0.05$.

**Table 3**

Trend analysis of vancomycin, linezolid, teicoplanin and rifampicin minimum inhibitory concentrations (MICs) determined by VITEK® 2 of *Staphylococcus aureus* isolated at Jai Prakash Narayan Apex Trauma Centre (New Delhi, India) from January 2012 to December 2016.

| Vancomycin MIC | | | | | | | | Linezolid MIC | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | | 2012 | 2013 | 2014 | 2015 | 2016 | *P*-value* | Year | | 2012 | 2013 | 2014 | 2015 | 2016 | *P*-value* |
| 0.25–0.50 μg/mL | MRSA | 51 | 80 | 46 | 106 | 76 | 0.396 | 1 μg/mL | MRSA | 18 | 37 | 2 | 53 | 33 | 0.534 |
| | MSSA | 62 | 83 | 79 | 93 | 71 | 0.533 | | MSSA | 8 | 22 | 11 | 30 | 28 | 0.119 |
| | Total | 113 | 163 | 125 | 199 | 147 | 0.406 | | Total | 26 | 59 | 13 | 83 | 61 | 0.356 |
| 1.0 μg/mL | MRSA | 91 | 73 | 53 | 46 | 55 | 0.064 | 2 μg/mL | MRSA | 147 | 139 | 112 | 101 | 99 | 0.010# |
| | MSSA | 54 | 69 | 49 | 37 | 53 | 0.427 | | MSSA | 105 | 123 | 118 | 105 | 103 | 0.525 |
| | Total | 145 | 142 | 102 | 83 | 108 | 0.116 | | Total | 252 | 262 | 230 | 206 | 202 | 0.026# |
| ≥2.0 μg/mL | MRSA | 61 | 34 | 17 | 2 | 3 | 0.015# | ≥4 μg/mL | MRSA | 38 | 11 | 2 | 0 | 2 | 0.086 |
| | MSSA | 7 | 2 | 1 | 5 | 7 | 0.785 | | MSSA | 10 | 9 | 0 | 0 | 0 | 0.044# |
| | Total | 68 | 36 | 18 | 7 | 10 | 0.031# | | Total | 48 | 20 | 2 | 0 | 2 | 0.062 |
| GM MIC | | 0.76 | 0.77 | 0.84 | 0.65 | 0.72 | 0.444 | GM MIC | | 1.87 | 1.86 | 1.95 | 1.64 | 1.71 | 0.214 |
| Teicoplanin MIC | | | | | | | | Rifampicin MIC | | | | | | | |
| 0.50 μg/mL | MRSA | NA | 183 | 96 | 128 | 113 | 0.391 | 0.25 μg/mL | MRSA | 6 | 46 | 75 | 85 | 86 | 0.025# |
| | MSSA | NA | 154 | 125 | 130 | 119 | 0.159 | | MSSA | 7 | 46 | 125 | 122 | 102 | 0.091 |
| | Total | NA | 337 | 221 | 258 | 232 | 0.315 | | Total | 13 | 92 | 200 | 207 | 188 | 0.055 |
| 1.0 μg/mL | MRSA | NA | 0 | 8 | 22 | 16 | 0.164 | 0.50 μg/mL | MRSA | 120 | 77 | 0 | 0 | 0 | 0.041# |
| | MSSA | NA | 0 | 3 | 5 | 8 | 0.003# | | MSSA | 107 | 97 | 1 | 0 | 29 | 0.125 |
| | Total | NA | 0 | 11 | 27 | 24 | 0.088 | | Total | 227 | 174 | 1 | 0 | 29 | 0.071 |
| >1.0 μg/mL | MRSA | NA | 4 | 12 | 4 | 5 | 0.833 | ≥1 μg/mL | MRSA | 77 | 64 | 41 | 69 | 48 | 0.325 |
| | MSSA | NA | 0 | 1 | 0 | 4 | 0.250 | | MSSA | 9 | 11 | 3 | 13 | 0 | 0.436 |
| | Total | NA | 4 | 13 | 4 | 9 | 0.822 | | Total | 86 | 75 | 44 | 82 | 48 | 0.330 |
| GM MIC | | NA | 0.51 | 0.56 | 0.55 | 0.56 | 0.241 | GM MIC | | 0.76 | 0.55 | 0.07 | 0.1 | 0.1 | 0.049# |

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; GM, geometric mean; NA, not available.

* *P*-value for linear trend by Pearson's correlation test.

\# Statistically significant association ($P \leq 0.05$).

genetic relatedness of the *S. aureus* strains and speculated the impact of clonal dissemination of strains to be limited.

These data would ultimately guide the rational use of antibiotics in trauma patients and the formation of antibiotic policies to curb antibiotic abuse and misuse.

## 5. Conclusion

Infection with multidrug-resistant bacteria leads to post-trauma complications causing high morbidity and mortality among trauma patients. To achieve the best possible outcomes while decreasing the risk of post-trauma complications, treatment of such infections in trauma patients requires an extremely systematic approach. Multidisciplinary measures from scientists, pharmacists, microbiologists and clinicians need to be taken to meet the challenges of MIC creep.

Implementation of preventive measures in healthcare settings should be undertaken, such as the adoption of rapid point-of-care molecular tests to quickly differentiate MRSA from β-lactam-susceptible strains and thus to switch patients with the latter to superior β-lactam therapy; optimisation of doses of these antibiotics; and switching to alternative and/or combination antibiotic therapy when a higher antibiotic MIC is observed even within the susceptible range.

These trends of antimicrobial susceptibility are significant because local isolates from patients at JPNA Trauma Centre could also spread to other geographical regions. However, the global generalisability of these results requires further study. Many questions remain unanswered, leaving a pertinent gap between laboratory science and clinical medicine. *S. aureus* infections are emerging to be more challenging for physicians, microbiologists, pharmacists, scientists and, most importantly, patients.

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## Competing interests

None declared.

## Ethical approval

Not required; all tests were routinely performed and data were obtained from the hospital records without disclosure of any patient details.

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