A Study of Vancomycin and Daptomycin Minimum Inhibitory Concentration in Clinical Isolates of Staphylococcus Aureus At A Tertiary Care Hospital of Gujarat

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Abstract: Background and objectives: Persistent use of Vancomycin in Staphylococcus aureus infections may lead to increase in minimum inhibitory concentration (MIC) levels and thereby failure of treatment. We determined Vancomycin MIC in these strains to identify the need to switch over to other options of treatment like Daptomycin. Methods: All isolates of Staphylococcus aureus from 1st January 2017 to 31st January 2017 were tested with Vitek 2 automated system and MIC of Vancomycin and Daptomycin was determined using E-strips. Patient related information was collected using a structured proforma. Results: For a total of 85 Staphylococcus aureus isolates, the geometric mean for Vancomycin MIC was 0.68 mg/L, the modal MIC was 1 mg/L, the MIC50 and MIC90 values were 0.5 mg/L and 1 mg/L respectively and 55% of isolates had Vancomycin MIC of ≤ 0.5 mg/L. The geometric mean for Daptomycin MIC was 0.34 mg/L, the modal MIC was 0.25 mg/L, the MIC50 and MIC90 were 0.25 mg/L and 0.5 mg/L respectively and 77% of isolates had Daptomycin MIC of ≤ 0.5 mg/L. Interpretation and conclusion: The MIC of Vancomycin has been at the lower side of susceptible range and therefore could be continued as drug of choice in Staphylococcus aureus infections. [C Modi, Natl J Integr Res Med, 2018; 9(2):44-48]

Key Words: Staphylococcus aureus, Vancomycin, Daptomycin, Minimum Inhibitory Concentration

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Introduction: Staphylococcus aureus, especially methicillin resistant Staphylococcus aureus (MRSA) is an important cause of infections both in hospital and community.[1, 2, 3] Vancomycin, a glycopeptide, has been the choice of treatment for MRSA infections.[1, 3] However, continuous use of Vancomycin over a long period has resulted in reduced susceptibility or increase in resistance to this drug and is a matter of concern.[2, 4] The susceptibility breakpoint of Vancomycin as per Clinical and Laboratory Standards Institute (CLSI) is 2 mg/L.[5] With increasing use of Vancomycin the minimum inhibitory concentrations (MICs) of the isolates may show a shift towards the susceptibility breakpoint and this increase in MIC over a period of time is known as 'MIC creep'.[6] Studies have shown that increasing MIC of Vancomycin, even though in the susceptible range, may pose a risk of treatment failure in MRSA infections.[7]

Daptomycin, a lipopetide has been licensed by FDA for use in MRSA infections especially as an alternative to Vancomycin.[8] Studies have recommended and shown effectiveness of Daptomycin in management of MRSA infections.[9, 10] However there are studies showing that MICs of Daptomycin go hand in hand with Vancomycin.[11]

The purpose of the present study was to determine the level of resistance that has developed in Staphylococcus aureus with persistent use of Vancomycin and thereby decide whether there is need to switch over to other options of treatment like Daptomycin.

Methods: The study was conducted at Microbiology section of Central Diagnostic Laboratory, Shree Krishna Hospital, Karamsad, from 1st January 2017 to 31st December 2017. The study was duly approved by Institutional Ethics Committee.

Source of data: Details about the isolates of Staphylococcus aureus including MIC values of Vancomycin and Daptomycin were collected from Microbiology laboratory.

Method of collection: All Staphylococcus aureus isolates obtained from various clinical specimens received in Microbiology lab were included in the study. Staphylococcus aureus isolated from same clinical specimen from the same patient (isolate from persisting infection following clinical correlation) were excluded from the study.

Clinical specimens received for culture and antimicrobial susceptibility testing at Microbiology lab at Shree Krishna Hospital, Karamsad were processed as per laboratory standard operative procedure for isolation and identification of bacterial isolates. The identification and antimicrobial susceptibility testing of Staphylococcus aureus was done by Vitek 2

automated identification system. All such isolates were further classified as methicillin sensitive and methicillin resistant Staphylococcus aureus based on its susceptibility of Oxacillin as tested by Vitek 2 automated system. All Staphylococcus aureus isolates were further subjected to antimicrobial susceptibility testing for Vancomycin and Daptomycin using Epsilometer strip (E – strip) (Hi Media) having concentration gradient of these antibiotics along its length and the exact minimum inhibitory concentration of both the drugs were noted after an incubation period of 18 – 24 hours.

To further characterize the findings of the study, additional data including type of infection from which the organism had been isolated, type of patient (inpatient/outpatient) and clinical settings (critical/non critical) were collected as per the defined proforma.

Statistical analysis: At the end of the study following information was collected for both methicillin sensitive and methicillin resistant Staphylococcus aureus:

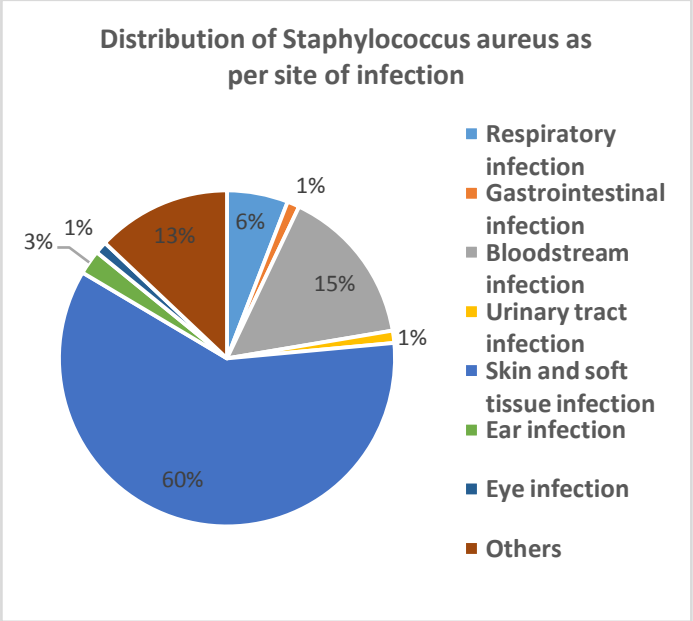
- Percentage susceptibility and percentage resistance to Vancomycin and Daptomycin
- MIC range of Vancomycin and Daptomycin
- Geometric mean MIC for Vancomycin and Daptomycin
- Modal MIC for Vancomycin and Daptomycin
- MIC_{50} and MIC_{90} for Vancomycin and Daptomycin

Vancomycin consumption: According to WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcdd/), the usage of Vancomycin in hospital is described by the defined daily doses per 1000 bed-days. The consumption of Vancomycin was obtained from online module whereas number of in-patient data was collected from medical records.

Ethical issues: As the project involved purely laboratory work and testing of isolates that were isolated from clinical specimens sent to laboratory by the clinician on suspecting infection, a waiver of consent was applied and was approved by Institutional Ethics Committee.

Result: A total of 85 isolates of Staphylococcus aureus were collected during the study period and were included in the analysis. Of these, 77 strains (90.5%) were methicillin susceptible Staphylococcus aureus (MSSA) and eight strains (9.5%) were methicillin resistant Staphylococcus aureus (MRSA). Mean age of patients with infection from Staphylococcus aureus was 40 years. Ninety five percent patients were male whereas nine percent were females. Ninety one percent of the strains were isolated from non-critical area of the hospital whereas nine percent strains were isolated from critical care area. As we had only eight isolates of MRSA, the further analysis was not done separately for MSSA and MRSA.

Figure 1: Distribution of Staphylococcus aureus isolates with respect to site of infection.



Minimum inhibitory concentration: The MIC of Vancomycin and Daptomycin was derived from Vitek 2 automated system as well as through E – strips. There was 100% correlation between MIC reading of Vitek and E – strips for both Vancomycin and Daptomycin.

Minimum Inhibitory Concentrations (MICs) for Vancomycin: The range of MIC for Vancomycin was from 0.125 mg/L to > 256 mg/L. A total of three strains (3.5%) were found to have MIC for Vancomycin of > 256 mg/L and they were not included for further analysis due to high outlier. The geometric mean for MIC for Vancomycin was found to be 9.69 mg/L. However if the three isolates with MIC of > 256 mg/L were excluded, the revised mean was found to be 0.68 mg/L (95% CI 0.61 – 0.75). The modal MIC for Vancomycin was found to be 1 mg/L. The MIC_{50} and MIC_{90} values for Vancomycin was found to be 0.5 mg/L

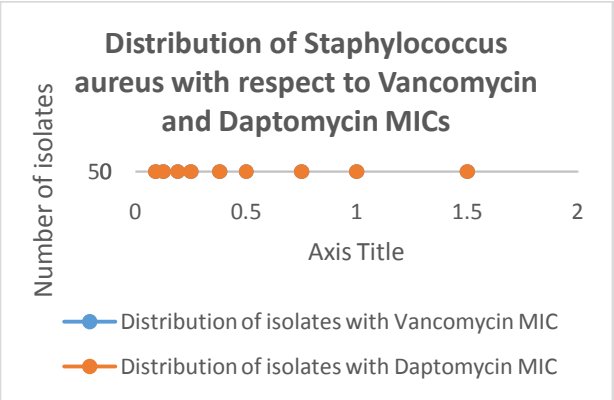
and 1 mg/L respectively. All three isolates whose MIC value for Vancomycin was > 256 mg/L were MRSA strains.

Minimum Inhibitory Concentrations (MICs) for Daptomycin: The range of MIC for Daptomycin was from 0.09 mg/L to > 256 mg/L. As with Vancomycin, three strains (3.5%) were found to have MIC for Daptomycin of > 256 mg/L and were not included in further analysis. The geometric mean for MIC for Daptomycin was found to be 9.35 mg/L However, if the three isolates with MIC of > 256 mg/L were excluded, the revised mean was found to be 0.34 mg/L (95% CI 0.30 – 0.38). The modal MIC for Daptomycin was found to be 0.25 mg/L. The MIC_{50} and MIC_{90} values for Daptomycin was found 0.25 mg/L and 0.5 mg/L respectively. All three isolates whose MIC value for Daptomycin was > 256 mg/L also had MIC value of > 256 mg/L for Vancomycin and all these three strains were MRSA.

Table: 1 Distribution of strains of Staphylococcus aureus with respect to MIC levels of Vancomycin and Daptomycin

MIC (mg/L)	Staphylococcus aureus strains and Vancomycin MIC distribution (n = 82) (%)	Staphylococcus aureus strains and Daptomycin MIC distribution (n = 82) (%)
≤ 0.5	45 (55%)	63 (77%)
0.5 - ≤ 1	1 (1%)	16 (19%)
1 - ≤ 1.5	32 (39%)	3 (4%)
1.5 - ≤ 2	4 (5%)	0

Figure 2: Distribution of Staphylococcus aureus strains with respect to Vancomycin and Daptomycin MICs.



The consumption of Vancomycin was found to be 0.8 define daily dose/1000 bed-days for the year 2016 and 2017 each.

Discussion: Staphylococcus aureus has been known as an important pathogen in causing infections; both in community as well as in hospital leading to prolonged hospital stays, high healthcare costs as well as considerable morbidity as well as in-hospital mortality.[1] The problem has worsen with emergence of methicillin resistant Staphylococcus aureus (MRSA) whose global prevalence has ranged from 18% to as high as 60%.[2, 4, 6] The severity of infections caused by MRSA cannot only be attributed to several virulence factors exhibited by these strains but also to the fact that resistance is encountered to variety of antimicrobial agents like aminoglycosides, macrolides and fluoroquinolones besides beta lactam group.[1] Vancomycin, a glycopeptide, therefore, remains the mainstay for management of MRSA infections.[3] There has been reports of clinical failure with Vancomycin with emergence of Vancomycin intermediate Staphylococcus aureus (VISA) and Vancomycin resistant Staphylococcus aureus (VRSA) and therefore surveillance studies reporting changes in Vancomycin susceptibility over time in both MSSA and MRSA, also known as MIC creep, have been performed.[3, 4, 6, 7, 11] Vancomycin has been one of the agents used in empirical antimicrobial therapy in suspected gram positive infections at our institute. The prescription of empirical therapy is reviewed following availability of culture reports. To monitor trends in Vancomycin susceptibility, baseline MIC parameters of Vancomycin for both MSSA and MRSA was determined for the year 2017. Daptomycin is not routinely prescribed at our institute, however, Daptomycin has been described as an alternative to Vancomycin in treatment of MRSA infection[9] and therefore baseline MIC parameters for Daptomycin was also determined.

In the present study, geometric mean for MIC for Vancomycin after excluding three isolates having MIC of > 256 mg/L was found to be 0.68 mg/L (95% CI 0.61 – 0.75). This geometric mean was found to be lower compared to other studies where geometric mean for MIC for Vancomycin had increased from ≤ 0.5 mg/L to > 2 mg/L over several years.[4, 11] A study have also reported change in geometric mean for MIC for Vancomycin in MRSA isolates escalating from 0.62 mg/L in 2001 to 0.94 mg/L in 2005.[6] A meta-analysis done to assess the evidence of Vancomycin MIC creep reported a geometric mean of 1.23 mg/L (95% CI 1.13 – 1.33), however this study did not find any evidence of MIC creep phenomenon.[12]

The modal MIC for Vancomycin in the present study was found to be 1 mg/L. In a previous study conducted on Vancomycin MIC creep, the modal MIC for Vancomycin in MRSA had increased from 0.75 mg/L to 1 mg/L from 2001 to 2005.[6] The MIC_{50} and MIC_{90} values for Vancomycin in Staphylococcus aureus in the present study was found to be 0.5 mg/L and 1 mg/L respectively suggesting that 50 percent isolates would have been inhibited at a concentration of ≤ 0.5 mg/L and 90 percent of isolates would have been inhibited at a concentration of 1 mg/L. A previous study reported no change in the MIC_{50} and MIC_{90} values for Vancomycin in both MSSA and MRSA strains from 2002 to 2006[2] whereas another study reported a rise of MIC_{50} value from 0.75 mg/L to 1 mg/L in MRSA strains from 2001 to 2005.[6] At present, the MIC_{50} and MIC_{90} values for Vancomycin in our institute are lower or equivalent to published reports.

In the present study, as shown in Table 1, 55% isolates of Staphylococcus aureus had Vancomycin MIC values of ≤ 0.5 mg/L whereas none of the isolates (excluding the three outliers) had MIC value of ≥ 2 mg/L. In a study conducted by Wang et al. 79% isolates of Staphylococcus aureus had Vancomycin MIC value of ≤ 0.5 mg/L in 2000 which had declined to 60% in the year 2004 whereas percentage of isolates with MIC > 1 mg/L had increased from 19% in 2000 to 70% in 2004 suggesting an increase in MIC creep over a period of five years.[4] In a study conducted by Chang et al. to assess Vancomycin MIC creep in MRSA, percentage of isolates with an MIC of 1 mg/L had significantly increased from 37% in 2006 to 75% in 2010 whereas percentage of isolates with MIC of ≤ 0.5 mg/L had decreased from 60% in 2006 to 15% in 2010.[3] Several other studies demonstrated a rise in MIC values of Vancomycin with a similar trend within susceptible range for Staphylococcus aureus.[6, 11] Although Vancomycin MIC creep has been observed at isolated places around the globe, when large samples of Staphylococcus aureus were pooled together from multiple centres showing both presence and absence of Vancomycin MIC creep, a net neutralization effect was observed with no overall changes in Vancomycin susceptibility.[11]

In a study conducted by Chang et al. there was a significant association between changes in Vancomycin consumption and sensitivity to Vancomycin. Vancomycin consumption had increased from 1.2 defined daily dose/1000 bed-days in 2006 to 5.3 defined daily dose/1000 bed-days in 2010. The percentage of MRSA isolates with Vancomyin MIC of 1 mg/L had increased from 37% to 75% during the same period.[3] The consumption of Vancomycin at our institute had remained static (0.8 defined daily dose/1000 bed-days) for the year 2016 and 2017. The lower geometric mean of Vancomycin at our institute may be attributed to a lower consumption of Vancomycin.

The significance in monitoring Vancomycin MIC creep in Staphylococcus aureus is evidenced by the fact that infections caused by strains with higher MICs in susceptible breakpoint range have been associated with failure of treatment with Vancomycin.[3, 11] Moreover, with increase in Vancomycin MIC creep, switching over to an alternative agents like Daptomycin have also been evaluated. Although Daptomycin has demonstrated good activity against gram positive organisms including MRSA and Vancomycin resistant Enterococci,[8] a study has shown no difference in failure rates of treatment between Vancomycin and Daptomycin in treating MRSA bacteremia.[10] Published literature has also described presence of Vancomycin cross resistance creeps where Staphylococcus aureus with higher Vancomycin MICs also tend to have higher Daptomcyin MICs.[11] Daptomycin, in MRSA infections with high Vancomycin MICs, is still preferred over Vancomycin due to lower rates of acute kidney injury with Daptomycin compared to Vancomycin as well as its ease of administration with once daily dose.[9, 10]

When susceptible MIC parameters for Daptomycin against Staphylococcus aureus were studied, the geometric mean for Daptomycin was found to be 0.34 mg/L (95% CI 0.30 – 0.38) which was much lower than that of Vancomycin. In contrast to Vancomycin, 77% of isolates were having Daptomycin MIC of ≤ 0.5 mg/L as shown in Figure 4. In the present study as we have described MIC data for a single year, it would be interesting to see whether Vancomycin creep is observed at our institute in future and whether cross resistance creep in Daptomycin is observed concurrently.

Conclusion: The level of MIC of Vancomycin in Staphylococcus aureus has been towards the lower side of the susceptible range and therefore could still be effectively used to treat infections caused by Staphylococcus aureus. The MIC of Vancomycin should be closely monitored over next few years to

identify development of MIC creep in Staphylococcus aureus.

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