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# Vancomycin Mic Creep Among Methicillin-Resistant *Staphylococcus aureus*: A Report

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## ABSTRACT

The objective of the study was to analyze the vancomycin MIC distribution against bloodstream MRSA isolates for a period of 1 year in India. This retrospective study analyzed 71 blood stream MRSA strains isolated at a tertiary care hospital in India between January 2008 and December 2008. The vancomycin MIC was determined by broth microdilution method. Only one isolate per patient was analyzed. The range of vanocmycin MIC for the 71 isolates in this study was varied between 0.25-3 μg $mL^{-1}$. Only 29 isolates had MIC less than 1 μg $mL^{-1}$ and 17 isolates MIC were more than 2 μg $mL^{-1}$. In this study the phenomenon of vancomycin MIC creep was noticed in more than 75% of MRSA bloodstream isolates. We suggest further in vivo studies to determine the clinical significance of this MIC creep.

**Keywords:** MRSA, Vanomycin, MIC Creep

## 1. INTRODUCATION

In the developing world the problem of multi-drug resistant gram negative infections dominated over gram-positive infections (Mathai, 2005). But in the recent years due to increased incidence of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) infections (Gopalakrishnan and Sureshkumar, 2010), vancomycin usage has been increased. The widespread use of vancomycin, which has poor tissue penetration and slow bactericidal activity (Gould, 2007a) resulted in emergence of MRSA isolates with reduced susceptibility to vancomycin. This phenomenon is well described in western literature and there is growing evidence the minimum inhibitory concentration of vancomycin against *Staphylococcus aureus* (Saureus) isolates to be increasing incrementally, a process referred to as MIC creep (Steinkraus *et al*., 2007; Gould, 2007b).

The clinical significance of vancomycin MIC creep has been investigated in number of studies conducted in the developed world and demonstrated the relationship between increasing MICs and reduced vancomycin efficacy and greater mortality (Moise and Schentag, 2000; Soriano *et al*., 2008; Howden *et al*., 2004). To the best of our knowledge no studies have examined the creep phenomenon in India. Thus the aim of this study was to analyze the vancomycin MIC distribution in blood MRSA isolates over a period of one year.

## 2. MATERIALS AND METHODS

In this retrospective study we analyzed 71 blood culture isolates of MRSA obtained from patients admitted in 600 bedded tertiary care hospitals in South India between January 2008 and December 2008. Only one isolate per patient was tested. For patients with more than one isolate, only the first isolate was tested. All isolates were identified as *S. aureus* according to conventional laboratory techniques.

According to CLSI standards the *S. aureus* isolates with the MICs of oxacillin mic of 2 microgram $mL^{-1}$ and 4 microgram mL were classified as Methicillin Sensitive

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*Staphylococcus Aureus* (MSSA) and Methicillin Resistant Staph Aureus (MRSA) respectively.

Vancomycin MIC of the 71 MRSA isolates was determined by broth microdilution as described by CLSI (NCCLS, 2003). Vancomycin was tested at a concentration of 0.5 to 32 microgram $mL^{-1}$ and MICs were read manually after 24 h of overnight incubation period. Quality control was performed using CLSI-recommended reference strains. The study was approved by the institution's ethic committee.

## 3. RESULTS

During the study period 71 blood MRSA isolates cultured from 71 patients were analyzed. The 71 isolates were evenly distributed during the entire study period. The MICs of the isolates varied from 0.25-3 microgram $mL^{-1}$.

As shown in **Table 1** the MIC values were divided into the ranges of <1 μg $mL^{-1}$, 1-2 μg $mL^{-1}$ and > 2 μg $mL^{-1}$ and number of MRSA isolates in each range with their percentages were described.

Most of the isolates (54/71-76.05%) MIC were less than 2 microgram $mL^{-1}$ (vancomycin susceptible), but nearly a quarter of isolates (17/71-23.94%) MICs were above 2 microgram $mL^{-1}$. One-third of the isolates (25/71-35.21%) MICs were crept into higher values in this study.

## 4. DISCUSSION

In January 2006, CLSI revised the vancomycin MIC interpretive criteria for *S. aureus*. The isolates with vancomycin MICs of<2 g $mL^{-1}$ and >16 g $mL^{-1}$ are currently defined as vancomycin susceptible Staph aureus and Vancomycin Resistant Staph Aureus (VRSA), respectively and isolates for which vancomycin MICs are 4 to 8 g $mL^{-1}$ are classified as vancomycin intermediate (Tenover and Moellering, 2007).

In our study nearly one-quarter of MRSA isolates MICs were above 2 microgram $mL^{-1}$ and 35% of the isolates MICs were in the range of 1-2 μg $mL^{-1}$. Similar finding was noticed in several single centre studies conducted in the western; world in the past decade (Steinkraus *et al*., 2007; Wang *et al*., 2006; Rybak *et al*., 2008).

**Table 1.** MICs of MRSA isolates

| MIC range | Number of isolates (%) |
|---|---|
| <1 microgram $mL^{-1}$ | 29 (40.84%) |
| 1-2 microgram $mL^{-1}$ | 25 (35.21%) |
| >2 microgram $mL^{-1}$ | 17 (23.94%) |

But large multicentre surveillance studies such as SENTRY have not reported changes in vancomycin susceptibilities over time (Jones, 2006). The possible explanation for this difference was due to pooling of the data from multiple sites can obscure trends that may exist within a individual institution (s) or country as a result of differences in patient populations and vancomycin usage patterns (including magnitude of usage, dosing and appropriateness of use). This highlights the importance of site-specific surveillance of MICs for guiding clinicians on the probable susceptibility of *S. aureus* infections to vancomycin in their patients and helping in their empiric antibiotic selection against them.

Analyzing the components of vancomycin MICs range showed that there has been a large increase in the proportions of strains with MIC >1 μg $mL^{-1}$ (54/71-76.05%) and only 29 isolates had MIC <1 μg $mL^{-1}$. This phenomenon was similar to Steinkraus *et al*. (2007) study which showed 3 fold increases in vancomycin MIC greater than 1 μg mL. Outside the susceptible range was observed in 17 isolates (23.94%). MIC greater than 2 μg $mL^{-1}$ was previously reported by Wang *et al*. (2006), but the proportion was very less in their study (0.2 to 0.8%). However, study of hospitals in Las Cruces, NM USA showed very high prevalence (35/43 isolates-81.39%) (Robinson *et al*., 2007). The key reason postulated for vancomycin MIC creep was exposing strains to subinhibitory concentrations of vancomycin (Helmecke *et al*., 2007).

The clinical significance of MIC creep noticed in this study was not clear. However the importance of MIC creep was highlighted in several previous reports of treatment failure against vancomycin susceptible isolates with high MIC values (Charles *et al*., 2004). Further patients with a MRSA bloodstream infection with a vancomycin MIC (≥1.5 mg $L^{-1}$) were reported to have a longer duration of bacteraemia, a higher probability of recurrence within 60 days after vancomycin discontinuation and prolonged hospital stay (Lodise *et al*., 2008). The treatment success was significantly lower for patients with MRSA isolates with a vancomycin MIC of 1 to 2 μg $L^{-1}$ compared to patients with a vancomycin MIC≤0.5 mg $L^{-1}$ (Sakoulas *et al*., 2004).

The main limitation of this study was retrospective in nature and the clinical parameters and outcome measures were not analyzed.

## 5. CONCLUSION

An extremely high prevalence of MRSA isolates with higher MIC was confirmed among *S. aureus* clinical isolates in this study. This may raise more concerns about the potential chance of failure of treatment of *S. aureus* infections with vancomycin. Accurate MIC measurement and periodic surveillance are important in order to assess and monitor the susceptibility of strains detected in individual hospitals, which provides a guideline for the probable MIC of an individual isolate and thus helps in choosing the correct empiric antibiotic therapy.

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