Article published online: 2020-02-19

Original Article

Access this article online
Quick Response Code:

Website: www.jlponline.org
DOI: 10.4103/JLP.JLP_92_17

Vancomycin, linezolid and daptomycin susceptibility pattern among clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) from Sub- Himalyan Center

Afzal Husain, Vinita Rawat, Umesh, Mukesh Kumar, Pankaj Kumar Verma[1]

Abstract:

INTRODUCTION: The efficacy of vancomycin, drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA), has become questionable due to the emergence of MRSA isolates with reduced susceptibility. The present study was conducted to determine the vancomycin, linezolid, and daptomycin susceptibility pattern in clinical isolates of MRSA and to observe minimum inhibitory concentration (MIC) creep over 2 years if any.

MATERIALS AND METHODS: MIC of vancomycin, linezolid, and daptomycin were determined by E-test in 198 MRSA isolates and their MIC 50, MIC 90, and geometric mean MIC were calculated.

RESULTS: While all isolates were sensitive to vancomycin, linezolid, and daptomycin, MIC 90 of vancomycin increased from 1.5 μg/ml in 2015 to 2 μg/ml in 2016. The percentage of isolates with vancomycin MIC >2 μg/ml doubled in 2016 (12.9%) as compared to 2015 (6.1%). MIC 90 for linezolid remained steady as 3 μg/ml, but geometric mean MIC increased from 2.20 μg/ml in 2015 to 2.29 μg/ml in 2016, and more than 40% isolates showed MIC 3 μg/ml. MIC 90 and geometric mean MIC of daptomycin decreased from 0.75 μg/ml to 0.5 μg/ml and 0.50 μg/ml to 0.36 μg/ml in 2015 and 2016, respectively.

CONCLUSION: MIC creep was observed with vancomycin. Although linezolid MIC was within the susceptible zone, more than 40% strains showing MIC 3 μg/ml may herald the future development of either resistant or heteroresistant. Daptomycin showed good sensitivity against MRSA isolates. Therefore, it could be considered as an alternative agent for the treatment of infections caused by MRSA. However, it should be reserved where this class has a clear therapeutic advantage over other anti-MRSA drugs.

Key words:

Daptomycin, linezolid, methicillin-resistant *Staphylococcus aureus*, vancomycin creep

Introduction

Vancomycin has been the cornerstone in the treatment of patients with serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Increased use of vancomycin has resulted in the emergence of MRSA with reduced susceptibility to vancomycin.[1-3] Emergence of vancomycin intermediate or resistant *S. aureus* has created the need for other anti-MRSA antibiotics. Many alternatives for treatment of MRSA infection including linezolid and daptomycin are currently approved by Food and Drug Administration. However, the emergence of resistance to linezolid and daptomycin in MRSA isolates has been recently reported.[4,5] In the present study, we determined vancomycin,

Departments of Microbiology and [1]Surgery, Government Medical College, Haldwani, Uttarakhand, India

Address for correspondence:
Dr. Vinita Rawat, Department of Microbiology, Government Medical College, Haldwani, Uttarakhand, India.
E-mail: drvinitarawat31@rediffmail.com

Submission: 21-05-2017
Accepted: 03-08-2017

How to cite this article: Husain A, Rawat V, Umesh, Kumar M, Verma PK. Vancomycin, linezolid and daptomycin susceptibility pattern among clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) from Sub- Himalyan Center. J Lab Physicians 2018;10:145-8.

linezolid, and daptomycin susceptibility pattern among clinical isolates of MRSA in a tertiary care center, Kumaon Region.

Materials and Methods

MRSA obtained from various clinical samples from July 2014 to June 2016 were prospectively collected. Only one isolate was selected from each patient. In total, 198 isolates were selected. All isolates were identified as *S. aureus* by using standard tests.[6] Methicillin resistance was identified by cefoxitin disc according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[7] Minimum inhibitory concentration (MICs) of MRSA isolates to 3 antibiotics including vancomycin, linezolid, and daptomycin were determined by E-strip (Hi Media Mumbai, India) according to manufacturer's instruction. For disc diffusion, Quality control strains of *S. aureus* ATCC 25923 (Hi Media Mumbai, India) and for MIC, Quality control strains of *S. aureus* ATCC 29213 (Hi Media Mumbai, India) were used with every set of test. MIC 50, MIC 90, and geometric mean MIC for vancomycin, linezolid, and daptomycin were calculated in the fiscal year 2015 and 2016.

Results

A total number of MRSA isolates tested in the fiscal year 2015 and 2016 were 82 and 116, respectively. Source of MRSA isolation was 187 (94.5%) from pus, 7 (3.5%) from blood, and 4 (2%) from body fluids, respectively. MIC 50, MIC 90, and geometric mean MIC for all three antibiotics, namely, vancomycin, linezolid, and daptomycin in fiscal years 2015 and 2016 are depicted in Table 1. MIC distribution in 2015 and 2016 is presented in respectively.

Discussion

MRSA is one of the leading pathogens for hospital- and community-acquired infections. In the present study, resistance to methicillin was seen in 30.7% (198/644) of total *S. aureus* isolates, which is in concordance with other studies conducted in India.[8,9] For decades, vancomycin was the mainstay in the treatment of infections caused by MRSA. However, recently, large number of literature has populated with vancomycin creep,[1-3] where treatment failure has been observed with increased MIC of vancomycin within susceptible zone. CLSI has reduced the vancomycin susceptible breakpoint for *S. aureus* from 4 μg/ml to 2 μg/ml in 2006.

Table 1: Minimum inhibitory concentration 50, minimum inhibitory concentration 90, and geometric mean minimum inhibitory concentration of vancomycin, daptomycin, and linezolid in methicillin-resistant *Staphylococcus aureus* isolates

Antibiotics	2015			2016		
	MIC 50	MIC 90	Geometric mean	MIC 50	MIC 90	Geometric mean
Vancomycin (μg/ml)	1.5	1.5	1.36	1.5	2	1.42
Linezolid (μg/ml)	2	3	2.20	2	3	2.29
Daptomycin (μg/ml)	0.5	0.75	0.50	0.38	0.50	0.36

MIC = Minimum inhibitory concentration

The studies reporting vancomycin MIC creep have shown conflicting results.[1-3,10,11] There are reports of increased MIC over the time, [1-3] but other studies differ with these results.[10,11] Variation in MIC results may perhaps be due to use of different methodologies and guidelines. A large multicenter surveillance studies such as SENTRY have not reported changes in vancomycin susceptibilities over time.[11] The possible explanation for this observation[11] may be that due to pooling of the data from multiple sites could conceal trends that may have existed within an individual institution(s). This highlights the importance of local surveillance of MICs, which would guide clinician in their empiric antibiotic selection in their local area.

In the present study, all MRSA were sensitive to vancomycin like other studies from India.[1,12] The percentage of isolates with vancomycin MIC >2 μg/ml doubled in 2016 (12.9%) as compared to 2015 (6.1%), and 3 isolates showed MIC of 3 μg/ml in the year 2016, suggesting the phenomenon of vancomycin MIC creep [Table 1 and Figures 1, 2]. Due to resource constrain, molecular typing on isolates exhibiting vancomycin creep could not be performed which would have reflected light whether isolates showing vancomycin MIC creep are associated with particular clone.

Daptomycin is cyclic polypeptide semisynthetic antimicrobial agent with activity against broad range of Gram-positive bacteria including MRSA and vancomycin-resistant *S. aureus*.[5] As per CLSI guidelines,[7] susceptibility breakpoint of daptomycin is considered as ≤1 μg/ml for *Staphylococcus*. There is a paucity of literature in daptomycin susceptibility on MRSA from India. Recently, a study from South India[1] documented the MIC range of daptomycin from 0.0064 μg/ml to 1.5 μg/ml among MRSA isolates. Reduced susceptibility to vancomycin has been reported to be associated with reduced susceptibility to daptomycin.[11,13] In the present study, MIC range of daptomycin was 0.19–1 μg/ml. MIC 90 and geometric mean MIC of daptomycin decreased from 0.75–0.5 μg/ml to 0.50–0.36 μg/ml in 2015 and 2016, respectively, despite vancomycin MIC creep. Few other studies [1,14] have also observed similar trend of decreased MIC of daptomycin with an increase in vancomycin MIC.

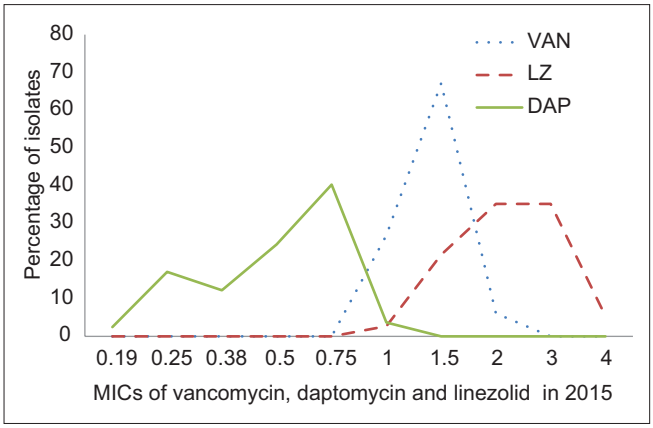

Figure 1: Minimum inhibitory concentrations of vancomycin, daptomycin, and linezolid in 2015

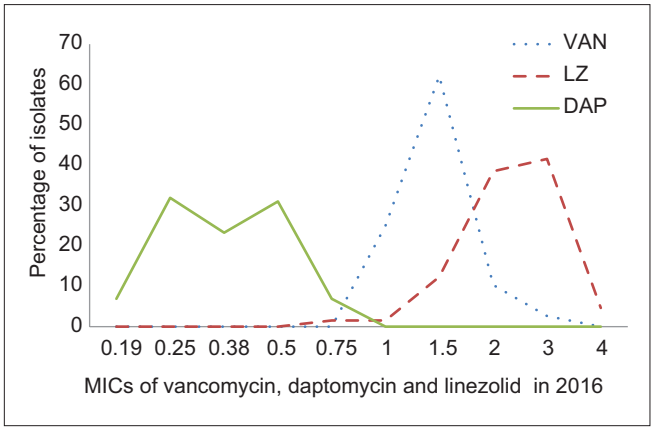

Figure 2: Minimum inhibitory concentrations of vancomycin, daptomycin, and linezolid in 2016

Linezolid is usually bacteriostatic against staphylococci and enterococci. Due to ease of oral administration, it is frequently used in community and hospital setting. Being a synthetic drug, the probability of naturally occurring resistant mechanism is very low.[15]

In the present study, all the MRSA isolates were sensitive to linezolid. Similar findings with no resistance against linezolid have been documented in many others studies.[12,16] However, recently, cfr gene carrying MRSA and resistance due to mutation in 23S rRNA has been reported from India.[4,15] Cfr gene has great potential of dissemination due to its association with mobile segment.[4] In the present study, MIC 90 for linezolid remained steady as 3 μg/ml, but geometric mean MIC increased from 2.20 μg/ml in 2015 to 2.29 μg/ml in 2016. Hence, for close scrutiny, MICs should not only be measured by percentile susceptible markers but also by geometric mean statistics.

Conclusion

MIC creep was notably observed with vancomycin. Although linezolid MIC was within the susceptible zone, more than 40% strains showing MIC >3 μg/ml may herald the future development of either resistant or heteroresistant. Daptomycin showed good sensitivity against MRSA isolates and can be used as alternative agents for the treatment of infections caused by MRSA in our setup. However, it should be reserved where this class has clear therapeutic advantage over other anti-MRSA drugs.

Limitations

We did not have data on antibiotic use in our hospital that would have clarified the relationship between antibiotic use and changes in MIC pattern. We could not explore the impact of vancomycin MIC creep on clinical outcome. Molecular typing on isolates exhibiting vancomycin creep could not be performed which would have reflected light on spread of particular clone with higher vancomycin creep.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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