

## Original Research Article

# Current clinical trends in the management of gram positive infections in Indian critical care settings: a survey

Ritika Rampal, Jaishid Ahdal\*, Kriti Kaushik, Rishi Jain

Department of Medical Affairs, Wockhardt Ltd., Mumbai, Maharashtra, India

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### \*Correspondence:

Dr. Jaishid Ahdal,

E-mail: jahdal@wockhardt.com

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## ABSTRACT

**Background:** In India, gram-positive infections (GPIs) particularly, methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence is reported to increase exponentially. The overall mortality rate among patients with multi drug resistant GPIs in ICU setting are as high as 16%, despite the availability of various therapeutic options. Aim of the study is to determine the burden of GPIs in critical care settings and to understand the practising behaviour among the specialists in the management of MRSA infections.

**Methods:** The survey was conducted among 264 critical care specialists who attended the Annual National Conference of Indian Society of Critical Medicine held in February 2019 at Mumbai. The delegates were administered a validated 10 question survey.

**Results:** In the survey, 72% of the respondents agreed to the rising prevalence of MRSA and associated increased mortality rate of >16%. Empirical gram positive cover is being given to 30-40% of ICU patients, with ABSSSI being listed as a major indication followed by CAP, VAP, CLABSI and DFI. 46% of the doctors listed vancomycin as their preferred anti-MRSA agents followed by teicoplanin and linezolid. However, more than 80% of the doctors feel that nephrotoxicity in vancomycin, thrombocytopenia in linezolid and poor biofilm penetration are major limitations of these anti-MRSA agents.

**Conclusions:** The survey highlighted the increasing trend in the prevalence and associated mortality in GPIs in critical care settings in India. Further, the limitations of existing anti-MRSA agents have invoked the need for a newer agent with a broad spectrum anti-bacterial activity along with improved safety profile and effective biofilm penetration, which can be used as a suitable alternative empiric therapy to manage GPIs.

**Keywords:** Biofilm, Gram positive infections, ICU infections, Linezolid, MRSA prevalence, Mortality, Vancomycin

## INTRODUCTION

Infectious diseases are a national health threat leading to an increased morbidity and mortality among hospitalised patients in India.<sup>1</sup> The crude mortality rate of infectious disease in India is 416.75 per 100,000 persons.<sup>2</sup> Recent reports have shown the ICU mortality rate to range from 34 to 56% in patients with sepsis during the ICU stay, making the intensive care units (ICU) one of the major

sources of acquiring the nosocomial infections.<sup>3,4</sup> Immunocompromised patient group, use of invasive devices such as catheters, central venous cannulations, intravenous fluid therapy along with unregulated use of broad spectrum antibiotics, gives the multi drug resistant (MDR) bacteria perfect opportunity to amplify and thrive.

While both multi drug resistant (MDR) gram negative and gram positive infections (GPI) contribute in ICU

mortality, however GPIs especially methicillin resistant *Staphylococcus aureus* (MRSA) is associated with worse clinical outcomes, than methicillin sensitive *Staphylococcus aureus* (MSSA), in ICU patients.<sup>5</sup> MRSA is a life threatening pathogen which is now endemic with the overall prevalence escalating from 29% in 2009 to 47% in 2014.<sup>6</sup> According to the national guidelines on antimicrobial use, patients infected with MRSA had a higher mortality rate.<sup>7</sup> Moreover, the MRSA infection is more dominant in the ICU settings which is supported by a recent ICMR-AMRSN study which associated highly elevated MRSA prevalence with an increased resistance to antimicrobials in the ICU as compared to ward/OPD.<sup>8</sup>

Vancomycin has been the traditional therapy for use against MRSA infections.<sup>9,10,11</sup> However, its role in nephrotoxicity, variable bactericidal activity and tissue penetration along with rising hetero-resistant intermediate strains have led to the considerations of alternatives to vancomycin therapy.<sup>12-14</sup> Linezolid, on the other hand, is effective for the treatment of complicated SSTIs and pneumonia however, its bacteriostatic nature limits its use in severe MRSA infections like bacteraemia and endocarditis. Other notable side effects of linezolid are thrombocytopenia, peripheral and optic neuropathy and serotonin syndrome.<sup>15-18</sup>

The article reports the survey results indicating the MRSA prevalence across India and showcases different clinical opinions of critical care specialists pertaining to the choice of treatment and the management of the MRSA infections such as line related infections, bacteraemia, pneumonia and skin and soft tissue infections.

## METHODS

The survey was conducted among 264 critical care specialists attending 25<sup>th</sup> Annual National Conference of India Society of Critical Medicine organised from 1<sup>st</sup>-3<sup>rd</sup> February, 2019 in Mumbai. A ten question validated survey was prepared wherein; the delegates were randomly recruited and were asked to fill the survey on the basis of their clinical opinions and practice. The questions focussed on the prevalence of MRSA, associated mortality rate, choice of anti-MRSA agents and their limitations in their respective ICU set up.

The questionnaire was administered using online software developed by SurveyMonkey. All the responses were kept anonymous. The analysis of the survey was done based on the number of delegates answering each question. It was mandatory for the delegates to answer all questions in the survey. Bar graphs and pie charts were made using simple counts and proportion for each survey question.

## RESULTS

The questions of the survey are summarised in Table 1.

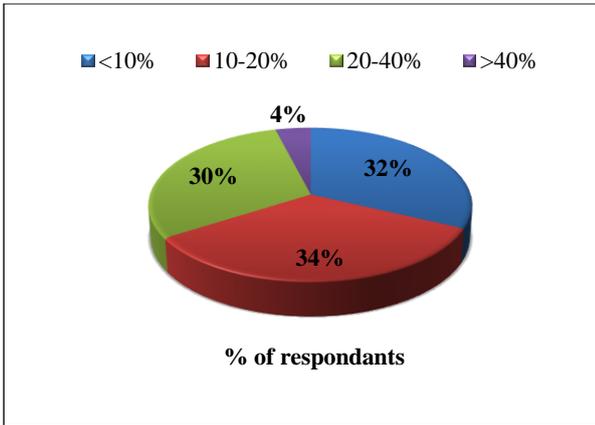
**Table 1: Questions of the survey administered to the delegates on the management of GPIs.**

Sr. no.	Survey Questions
1.	What is the prevalence of MRSA in your ICU setup?
2.	Centre for Disease Dynamics, Economics and policy data shows that there is an increasing trend in the prevalence of MRSA in India. Do you see a similar trend in your hospital?
3.	A recently published multi-institutional observational study across India concluded that the mortality rate among patients with multi-drug resistant gram positive infections in ICU settings are as high as 16%. Do you find a similar trend in your ICUs?
4.	In what percentage of your ICU patients with suspected infection, do you give empirical gram positive cover?
5.	What are the major indications in which you give empirical gram positive cover?
6.	What is your preferred anti-MRSA agent?
7.	Is nephrotoxicity a limitation of usage of vancomycin in your clinical practice?
8.	Do you feel that the bacteriostatic nature and thrombocytopenia caused by Linezolid is a major drawback for its use in bacteraemia?
9.	Biofilm formation is a problem in device related infections, line related infections, bone and joint infections and diabetic foot infections. Do you think that limited biofilm penetration of current anti-MRSA agent is a challenge in management of these infections?
10.	Currently available ant-MRSA agents have a narrow spectrum of coverage. Do you feel that a new agent which has a coverage on gram positive including MRSA, gram negative, anaerobe and atypical coverage will be useful in your clinical practice for empiric therapy?

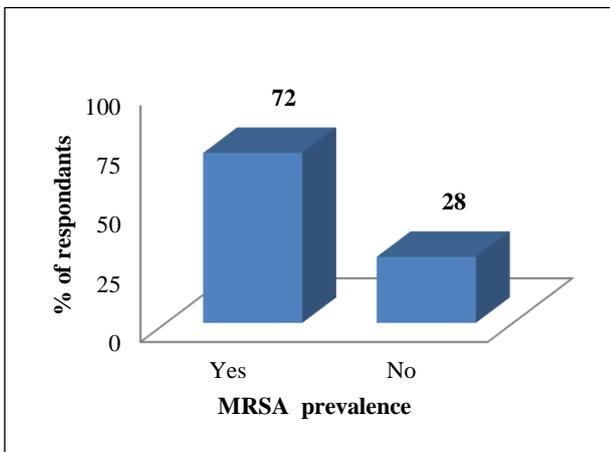
With MRSA prevalence being exponentially rising in India, the first survey question asked was to determine the prevalence of MRSA across different critical care set ups across India. 30% of the delegates observed the MRSA prevalence from 20-40%, while 66% said that the prevalence varied between 10-20% (Figure 1).

Data from Centre for Disease Dynamics, Economics & Policy, 2015 reported a steep rise in the MRSA prevalence from 29% in 2009 to 47% in 2014.

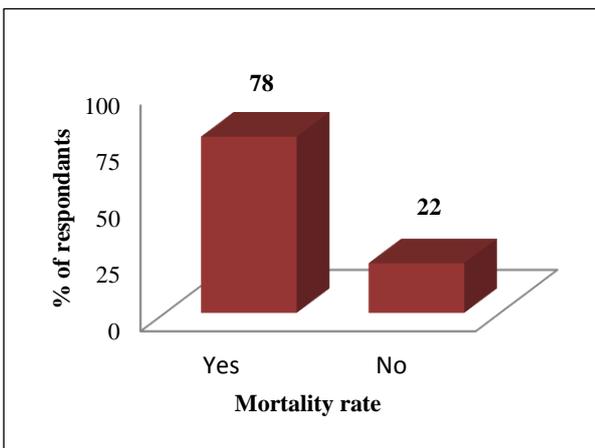
Moreover, a multi-institutional observational study across India had reported the mortality rate among patients with multi drug resistant GPIs in ICU settings to be as high as 16%. Similar to these trends, majority of the specialists agreed that the MRSA prevalence (Figure 2a) and the mortality rates (Figure 2b) have increased over the years in the ICU settings.



**Figure 1: What is the prevalence of MRSA in your ICU setup? (Question 1).**

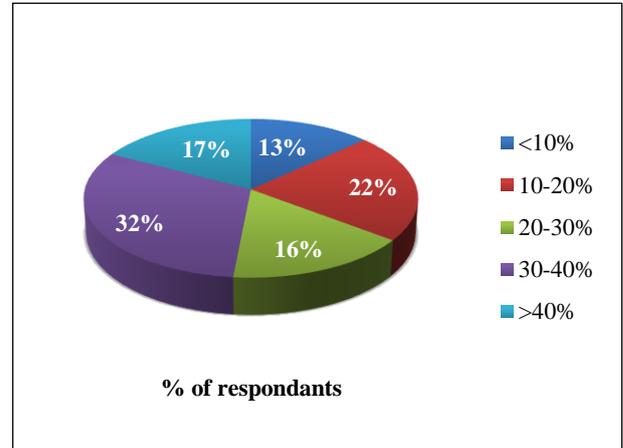


**Figure 2 (a): Centre for Disease Dynamics, Economics and policy data shows that there is an increasing trend in the prevalence of MRSA in India. Do you see a similar trend in your hospital? (Question 2).**



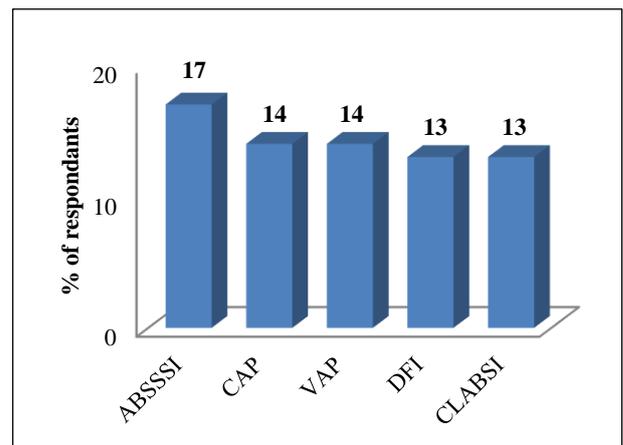
**Figure 2 (b): A recently published multi-institutional observational study across India concluded that the mortality rate among patients with multi-drug resistant gram positive infections in ICU settings are as high as 16%. Do you find a similar trend in your ICUs? (Question 3).**

The next set of questions was structured to get insights on the practicing behaviour of the critical care specialists in the management of MRSA infection. The first was to determine the empirical gram positive cover being given to patients in ICU, where the delegates responded that they were more likely to add a gram positive empiric agent in 30-40% of ICU patients with suspected infections (Figure 3).



**Figure 3: In what percentage of your ICU patients with suspected infection, do you give empirical gram positive cover? (Question 4).**

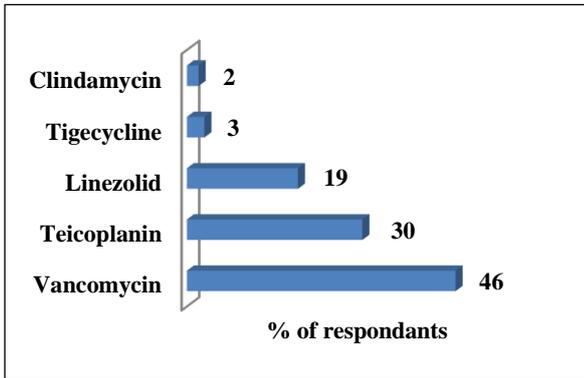
Also, Acute bacterial skin and skin structure infections (ABSSSI) was the most frequent infection for which empirical gram positive cover was given. A large proportion (45-50%) of delegates also found community acquired pneumonia (CAP), ventilator acquired pneumonia (VAP), diabetic foot infection (DFI) and central line related blood stream infections (CLBSI) to be major indications for gram positive cover in ICU patients (Figure 4).



**Figure 4: What are the major indications in which you give empirical gram positive cover? (Question 5).**

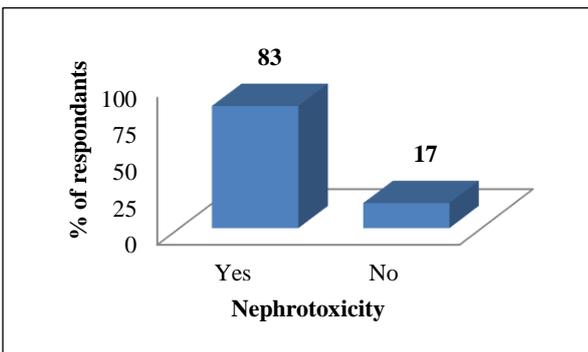
In the survey, 46% of the delegates listed vancomycin as their preferred choice for the empirical treatment of

MRSA infection, followed by teicoplanin (30%) and linezolid (19%) (Figure 5).

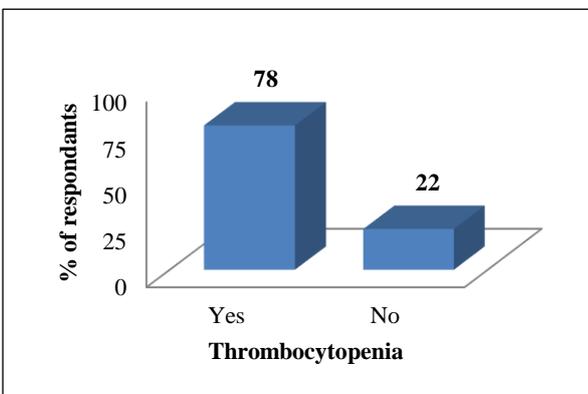


**Figure 5: What is your preferred anti-MRSA agent? (Question 6).**

However, 78% of the delegates agreed that the use of vancomycin as an anti-MRSA agent has been associated with increased risk of nephrotoxicity in ICU patients (Figure 6a). Further, Linezolid too has notable side effects; with 78% doctors listing thrombocytopenia and the bacteriostatic nature as major drawbacks for its effective use in bacteraemia and endocarditis (Figure 6b).

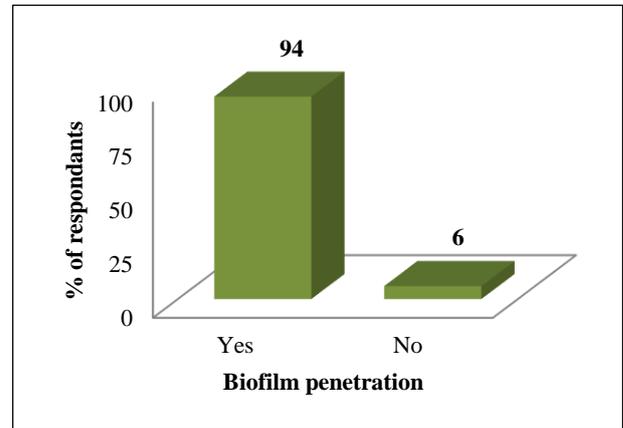


**Figure 6 (a): Is nephrotoxicity a limitation of usage of vancomycin in your clinical practice? (Question 7).**



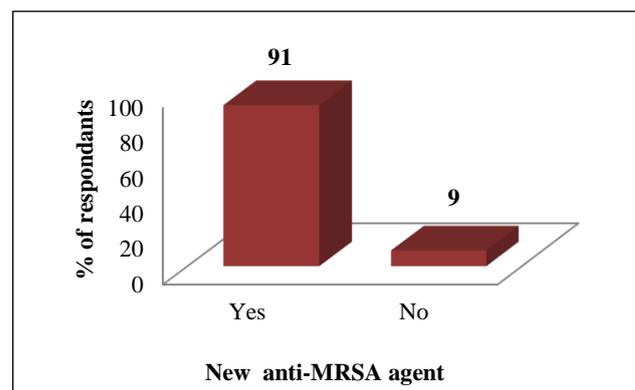
**Figure 6 (b): Do you feel that the bacteriostatic nature and thrombocytopenia caused by Linezolid is a major drawback for its use in bacteraemia? (Question 8).**

Biofilm production by *S. aureus* species provides a niche for the growth of potential multi drug resistant strains thereby making the treatment more challenging. There was a broad agreement among the delegates that limited biofilm penetration of current anti-MRSA agent is a major challenge in the management of device related infections, line related infections, bone and joint infections and diabetic foot infections (Figure 7).



**Figure 7: Biofilm formation is a problem in device related infections, line related infections, bone and joint infections and diabetic foot infections. Do you think that limited biofilm penetration of current anti-MRSA agent is a challenge in management of these infections? (Question 9).**

The last question of the survey was to address the unmet need for a new agent to which more than 90% of the specialists unanimously agreed that there is an urgent need for a new agent (Figure 8) which has a broad spectrum coverage on gram positive including MRSA, gram negative, anaerobe and atypical along with enhanced safety profile which will be useful as an empiric therapy in their clinical practice.



**Figure 8: Currently available ant-MRSA agents have a narrow spectrum of coverage. Do you feel that a new agent who has coverage on gram positive including MRSA, gram negative, anaerobe and atypical coverage will be useful in your clinical practice for empiric therapy? (Question 10).**

## DISCUSSION

The European Prevalence of Infection in Intensive Care (EPIC) 2 reported an increased mortality rate in infected ICU patients as compared to non-infected patients. Further, out of 47% GPIs, 20% were resistant staphylococci species which were associated with longer ICU stay.<sup>19</sup> In India, poor antimicrobial stewardship along with an inappropriate usage of the antibiotic regimen has contributed extensively to the burden of MDR anti-microbial resistance (AMR) in the ICUs. Various reports across India have documented variations in MRSA prevalence which ranges from 17.6% to 80.4% depending on the geographical area.<sup>20-24</sup> Similarly, the survey identified 34% of the delegates who observed 10-20% of MRSA prevalence; while, another 30% delegates identified 20%-40% of MRSA in their respective ICU settings. This variation in prevalence rates could be attributed to the different ICU settings, patient profiles and local antibiotic regimen that could impact the overall prevalence.

Data from the National Nosocomial Infection surveillance system has shown an increased incidence of MRSA infection, which has contributed to >60% of the ICU admissions in the United States.<sup>25</sup> On the similar lines, the Indian data generated by Centre for Disease Dynamics, Economics & Policy (cddep.org) also shows an increasing trend in the prevalence of MRSA which has escalated from 29% in 2009 to 47% in 2014.<sup>6</sup> With 72% of the delegates agreeing on the similar escalating trend in their ICU settings, MRSA infection has therefore, acquired a dominating presence in the ICU setup.

A recently published multi-institutional observational study across India concluded that the mortality rate among patients with multi drug resistant Gram positive infections in ICU settings is as high as 16%.<sup>26</sup> GPIs especially MRSA infections have been associated with more invasive disease and worse clinical outcomes than hospitalised patients with non-MRSA infection in bacteraemia and ABSSSI.<sup>27</sup> In the survey also, 78% of the delegates found a similar trend of increased mortality which is attributed to the growing menace of MRSA infection among ICU patients.

The global scenario shows gram positive infections to be predominant in western ICU, while gram negative pathogens are more prevalent in Indian ICUs.<sup>28</sup> However, variations within the health care community (rural/urban), healthcare set up (government/private) and wards of the hospital (various wards in a hospital) lead to various infections caused by different pathogens. Therefore, this makes it vital for the physicians to combine antibacterial agents covering both gram positive and gram negative pathogens. In line with this, majority of the critical care specialists surveyed agreed that they give 30-40% gram positive empirical cover to their ICU patients.

For over five decades, vancomycin has been used as a standard therapy to treat MRSA infections. Even 46% of the delegates surveyed mentioned vancomycin as their preferred anti-MRSA agents. However, reports have emphasized the rising MIC creep along with its association with nephrotoxicity at high serum concentrations, to be a major challenge for extensive use of vancomycin in MRSA treatment.<sup>29-31</sup> According to 83% of the delegates surveyed, nephrotoxicity is a limitation of usage of Vancomycin in their clinical practice.

Limitation with vancomycin treatment have paved the way for other antimicrobial drugs like linezolid and daptomycin, which according to the surveyed delegates are the preferred anti-MRSA agents after vancomycin. However, they too come with their own shares of limitations. The serious adverse drug reactions like thrombocytopenia, optic and peripheral neuropathy with linezolid limits its usage for longer duration.<sup>17,31</sup> Moreover, 78% of the delegates agreed that the bacteriostatic nature of the drug is a major drawback for its use as a front line treatment for bacteraemia and endocarditis.

Biofilm production is a virulence factor of MRSA infection. Biofilm production involves microbial adhesion, colonisation, cell proliferation and accumulation forming a matrix like coating which provides a niche for the growth of potential multi drug resistant strains.

Bacteria in the biofilm have reduced susceptibility to the antibiotics which can be explained by the reduced penetration of the antibiotics, high bacterial density, slow growth and altered gene expression of the bacteria in the biofilm. Majority of the surveyed delegates (94%) also agreed that the limited biofilm penetration of the current anti-MRSA agents aids in the protection of bacteria in the biofilm, thereby making the treatment more challenging for patients with catheter related or device related infections, bone and joint infections and diabetic foot infections.

## CONCLUSION

In conclusion, the survey highlighted the increasing trend in the prevalence and associated mortality in GPIs in clinical care settings in India. Despite the dominance of gram-negative pathogens in Indian ICUs, the rising incidence of multi drug resistant MRSA is a major cause of concern for the clinicians. Further, due to the limitations associated with the existing anti-MRSA agents, there is an urgent need for a new anti-MRSA agent which has a potent broad spectrum anti-bacterial activity along with improved safety profile and effective biofilm penetration, which can be used as a suitable alternative empiric therapy in the management of GPIs in the ICU settings.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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