Biospectra : ISSN: 0973-7057, Vol. 18(1), March, 2023, pp. 7-12

An International Biannual Refereed Journal of Life Sciences

Animal Science

ISSN : 0973-7057

A systemic review on mupirocin resistance in *Staphylococcus aureus*: Current status and future prospects

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Received : 15th November, 2022 ; Revised : 20th December, 2022

Abstract- Gram positive *Staphylococcus aureus* bacteria have been identified as prevalent pathogen causing mild tissue infections. In the mid of the 20th century, penicillin and methicillin antibiotics had been widely applied to treat *S. aureus* infection. This widely and ruthless use of these antibiotics resulted into the development of these antibiotic resistant in the *Staphylococcus aureus.* With the increasing demand to treat MRSA, Mupirocin has become the first choice of treatment for the heath service providers worldwide. This is because it is most effective against MRSA and its decolonization. However, large-scale use of Mupirocin antibiotic has resulted in Mupirocin resistant *Staphylococcus aureus* (MuRSA). Conjugative plasmid *mup A gene* which harbors the antimicrobial resistance determinants, mediates higher side Mupirocin resistance in *Staphylococcus aureus* (HL-MuRSA). Mutation in native ileS gene mediates lower side Mupirocin resistance in *Staphylococcus aureus*, which has no medically significant. Reduction in the effectiveness of mupirocin against MRSA has resulted in high risk for invasive infection of MRSA, therefore monitoring of MuRSA is critically needed in present scenario. Keeping this in view, we have discussed mupirocin resistance mechanism, pathological and clinical significance and future perspectives in the current review.

Key words: *Staphylococcus aureus*, Mupirocin, antimicrobial, clinical significance, penicillin

INTRODUCTION

Gram positive *Staphylococcus aureus bacteria* have been identified as the commonest prevalent pathogen causing soft tissue infection, endocarditis, bacteramia, osteomyeliti and nosocomial infections across the globe by the medical professionals Acute pneumonia, septicemia, are some of the acquired infections which prolong the hospital stay and usually are not present at the time of admission.[1-6] In 1940s, penicillin was extensively used to treat of various infectious diseases, which resulted as β lactams resistance in *Staphylococcus aureus.* The gene mec*A,* synthesizes mutated penicillin binding protein PBP2a which shows low affinity with β lactams and allocates methicillin resistance in *Staphylococcus aureus* (MRSA) was first time noted in 1960.[7-9] Later, it was explored that *Staphylococcus aureus* has become resistant to penicillin, Pseudomonic acid A which is also known as Mupirocin, was the only approved antibiotic to treat the methicillin resistance and methicillin sensitive *Staphylococcus aureus* infections.[1,6,10] Mupirocin antibiotics impede protein formation via binding to the Isoleucine residue of tRNA aminoacyl synthetase. The effective clinical data of this antibiotic against MRSA made this antibiotic best bet of clinicians especially to treat the decolonization, bedsore and soft tissue skin lesions. Mupirocin is one of the components of the topical

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antibacterial ointment and nasal formulation used to treat primary and secondary infection caused by *Staphylococcus* and *Streptococcal* species.[11,12] Food and drug administrative (FDA) department of USA has provided the approval for the use of mupirocin in nasal formulations applied to treat *Staphylococcus aureus* in patients and health service providers who are susceptible to MRSA. MRSA infection has become a serious health threat across the globe and associated with higher infection and death rate along with causing high economic burden on the healthcare system.[3,11-13] Multiple drug resistance (MDR) (resistant to ≥ 3 non beta lactum antibiotics) was also observed in methicillin resistance in *Staphylococcus aureus* (MRSA).[14,15] Topical use of mupirocin as ointment and nasal formulation has been found to reduce *Staphylococcus aureus* pathogen related infections in haemodialysis patients and in peritoneal dialysis patients by 80% and 63% respectively. Application of mupirocin and chlorhexidine has been found to reduce 37% MRSA infections and 44% blood infections which were result of secondary infections in Intensive Care Unit admitted patients.[16]

Mupirocin: Resistance and its mechanism

Pseudomonic acid A i.e. Mupirocin antibiotic was derived from *Pseudomonas fluorescens at* first time, and has been found to inhibit translational step at molecular level in bacteria through bacterial *Isoleuyl RNA synthetase* (IleRS).[16] It is widely used antibiotic for the infections causing microbes viz., *Staphylococci*, *Streptococci* and various gram negative bacteria such as Haemophilus influenza, Neisseria gonorrhea.[17] Minimum Inhibitory Concentration (MIC) for higher level resistance for mupirocin is defined as ≥ 512 mg/L and lower level resistance for mupirocin is defined as 8-256mg/L respectively.[18-21] Higher side Mupirocin antibiotic resistance in *Staphylococcus aureus* bacteria (HL-MuRSA) have been associated with conjugative plasmid *mup A gene* which harbours antimicrobial resistance determinants and lower side Mupirocin antibiotic resistance in *Staphylococcus aureus* bacteria due to mis-sense point mutations in *Isoleucyl RNA synthetase* (IleRS) gene.[10,12,22,23] Few studies have shown that plasmid mediated conjugate mupA gene which is present on mobile element of genetic material facilitates in the resistance mechanism. Mupirocin resistant *Staphylococcus* bacterial isolates showed various strains of mutated *Staphylococcus aureus* mediated replicate mupA plasmids in various generations.[24,25] Conjugative plasmid A was identified as the most common factor of higher-level mupirocin resistance during US epidemic caused by *Staphylococcus aureus* strain USA300.[26,27]

Epidemiology:

Mupirocin resistance has been globally reported with different levels of resistance in different countries. In 2009-10, a survey was conducted in 23 hospitals of USA to find out mupirocin resistance in MRSA. 3% bacteria isolated from nasal carriage and 5% from blood cultures were identified as mupirocin resistant MRSA. Between 1995 to 2004, from the 32 hospitals of Canada, out of 4980 MRSA strain, 200 mupirocin resistance *Staphylococcus aureus* were identified.[28,29] The high level of mupirocin antibiotic resistance in *Staphylococcus aureus* bacteria reported in various countries in the various time span has been shown in table 1.

Laboratory detection of Mupirocin antibiotic resistance:

Conventional microbiological studies based on Agar dilution, broth micro dilution and E-test[30-32] are most commonly used laboratory techniques to detect minimum inhibitory concentration (MIC) threshold of mupirocin antibiotic.[30,33] Disc diffusion test for the assessment of high side mupirocin antibiotic resistance in *Staphylococcus*

Table 1: High level mupirocin resistance in *Staphylococcus aureus* prevalence rate reported among various countries

Sl. No.	Time duration of the survey	Geographical area of the survey	Mupirocin resistance among identified MRSA in specific survey	References
1	2009-10	23 hospitals in USA	3% from nasal Carriage and 5% from blood cultures	(Dadashi *et al.* 2020) (Eum *et al.* 2021).
2	2009-10	32 Canadian Hospitals	4%	
3	2006-2007	Ireland	3%	
4	2011-12	France	1%	
5	2011-12	Spain	13%	
6	2011-12	Turkey	47%	
7	2006-2009	England	5%	
8	2008-2011	USA	12%	

aureus bacteria was recommended by the international organizations namely European Committee for antimicrobial Susceptibility Testing (EUCAST), Clinical and Laboratory Standards Institute (CLSI), and British Society for Antimicrobial Chemotherapy (BSAC). The CLSI and EUCAST recommended 200µg discs to detect mupirocin resistance whereas 20 µg discs were recommended by BSAC. Thresholds and interpretation of mupirocin sensitivity test were recommended by EUCAST, CLSI and BSAC have been shown in table 2.

Table 2: Thresholds and interpretation of mupirocin susceptibility testing

Organization	Laboratory Method	Thresholds and interpretation		
		Susceptible	Intermediate	Resistant
European Committee for antimicrobial Susceptibility Testing (EUCAST)	Disc diffusion tablet: 200µg MIC	≥ 30 mm	18-29 mm	< 18mm
Clinical and Laboratory Standards Institute (CLSI)	Disc diffusion tablet: 200µg MIC	≥ 27 mm	7-26 mm	< 7mm
British Society for Antimicrobial Chemotherapy (BSAC)	Disc diffusion tablet: 20µg MIC	≤ 1 mg/L	2-256mg/L	> 256mg/L

Clinical implication and relevance of mupirocin antibiotic resistance:

Increased and inadequate use of mupirocin antibiotic to cure the various infections caused by *Staphylococcus aureus* bacteria have been resulted into the development of mupirocin antibiotic resistance. It has been well established that higher side mupirocin antibiotic resistant in *Staphylococcus aureus* bacteria resulted in the failure of mupirocin decolonization. However, lower level of mupirocin resistance was not demonstrated to inhibit mupirocin decolonization.[11,12,34] In Swiss, Brazilian and Dutch hospitals, mupirocin was broadly used for the eradication of MRSA due to hospital wide policies.[33,35-37] In New Zealand, during 1991 to 2000, Mupirocin was extensively used for the treatment of tissue infection at the end of this decade, 28% mupirocin resistant isolates of *Staphylococcus aureus* had been identified.[38] As a result of higher level mupirocin resistance in *Staphylococcus aureus*, Australian government's health department issued a guideline to regulate the use of mupirocin to minimum, which resulted in 0.3% reduction in resistance rate during the period of 4 years.[39] In some studies, it was found that lower level mupirocin resistant was not found insignificant with decolonization of MRSA carriage.[15,40-42] Overall, both higher and lower level mupirocin resistance in *Staphylococcus aureus* directly connected to fail with decolonization.[12]

Future perspectives:

In many cases, only the Real Time PCR method was effectively found to confirm mupirocin exposed staphylococcus aureus. It is cost effective to screen all the patients with this PCR based technique instead of culture-based technique.[43,44] Decolonization of all patients undergoing surgery would be another cost-effective approach better than PCR screening.[12] Noticeably, universal decontamination of all the patients is also unnecessary application of mupirocin, where approximately 80% of the patients are not carrying *Staphylococcus aureus*. This could again direct towards the resistance for *Staphylococcus aureus*. Therefore, mupirocin prophylaxis should be carefully considered before its application and mupirocin resistance statistics for *Staphylococcus aureus* should be considered. The recommendation of the international organization "European Committee for antimicrobial Susceptibility Testing" (EUCAST), intermediate threshold > 1 and ≤ 4 mg/L should be undertaken for the determination of resistance mechanism and clinical relevance in mupirocin exposed *Staphylococcus aureus* bacteria.

CONCLUSION

Large-scale use of mupirocin application to cure soft tissue infections, nasal decolonization and bed sores due to *Staphylococcus aureus* resulted in increased mupirocin resistance. Higher and lower level mupirocin antibiotic resistant strain is the basis of epidemiology of mupirocin resistance in *Staphylococcus aureus* which has enormously affected the health sector. Therefore, it should be focused on the use of mupirocin, closely monitored to avoid development of mupirocin antibiotic resistance in

Staphylococcus aureus bacteria in health care setup of the country. It is also suggested that, to treat soft skin tissue infection and bed sores, use of mupirocin should be avoided as much as possible and alternatives of mupirocin should be used.

DECLARATION OF INTEREST

Authors declared that they have no conflict of interest.

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