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Review Article

Methicillin resistant *Staphylococcus aureus* - importance of appropriate empirical therapy in serious infections

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ABSTRACT

India has been titled the capital of antimicrobial resistance in the world with the centre for disease dynamics, economics and policy (CDDEP) predicting two million deaths in India by 2050. As per the World Health Organisation's global priority pathogen list of 2017, methicillin resistant *Staphylococcus aureus* (MRSA) has been classified as a 'high priority' pathogen due to its association with increased mortality rate, rising prevalence of resistance and increased burden on healthcare settings. A recent report by Indian Council of Medical Research signifies the exponential rise in the prevalence of MRSA in India, from 29% in 2009 to 39% in 2018. Serious MRSA infections are commonly associated with poor clinical outcomes coupled with increased hospitalisation stay and cost. Therefore, early identification and appropriate empiric treatment of MRSA plays a crucial role in healthcare settings. However, the constant rise in multi-drug resistance to the currently available anti-MRSA agents as well as their compromised safety profile limits its clinical use to manage severe MRSA infections. This review article explores the implications of severe MRSA infections and inappropriate empirical therapy on the clinical as well as economic outcomes. In addition, it also highlights limitations of the currently available anti-MRSA agents and the need for newer agents to manage multi drug resistant (MDR) gram positive infections.

Keywords: Methicillin-resistant *Staphylococcus aureus*, Prevalence, Appropriate empiric therapy, Anti-MRSA agents, Levonadifloxacin

INTRODUCTION

Antimicrobial resistance (AMR) has been on the rise globally posing significant concerns; as per the latest United Nations (UN) report, by 2050, 10 million deaths each year would be attributed to AMR.[1] Among the multi-drug resistant (MDR) gram positive pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a serious threat.[2] In 2017, World Health Organisation's (WHO) global priority pathogen list labelled MRSA as a 'high priority' pathogen owing to its association with higher mortality rate, increasing health care and community burden along with the rising prevalence of resistance.

MRSA is identified with worse clinical outcomes than methicillin-sensitive *S. aureus* (MSSA) and has a mortality risk two-times higher.[3,4] The 2014 report on antimicrobial resistance from WHO highlighted variation in the prevalence of MRSA worldwide: African region (12 to 80%), American region (21 to 90%), European region (0.3 to 60%), South-East Asia region (2 to 81%).[5] In 2018, antimicrobial resistance group of Indian Council of Medical Research reported an overall MRSA prevalence

of 37.3%, ranging from 21% to 45% indicating varied levels of prevalence across the country.[6]

Early identification and appropriate treatment of MRSA is an essential priority in all healthcare settings. However, in treating suspected MRSA infections, initial empirical therapy plays a crucial role. The infectious disease society of America and the United Kingdom practice guidelines recommend various treatments such as vancomycin, linezolid, clindamycin and co-trimoxazole for treating MRSA infections.[7,8] However, the rising resistance to the current anti-MRSA agents render them incapable of managing severe MRSA infections. The Indian network for surveillance of antimicrobial resistance (INSAR) group identified MRSA to be highly susceptible (100%) towards vancomycin and linezolid while exhibiting decreased sensitivity towards clindamycin (53.4%), erythromycin (29.2%) and co-trimoxazole (44.4%).[9] Emerging reports of rising multi drug resistance across the country, also challenge the use of such drugs as empirical therapy.[10-13] Moreover, not only the susceptibility pattern but the selection of the empiric antibiotic especially for critically ill patients is also the key essence for a positive clinical outcome in such patients. Various reports over the years have shown a significantly positive correlation between inappropriate empirical therapy, mortality rates and hospitalisation cost in patients infected with resistant strains. In this review, we explore the current role of empirical therapy, the clinical and economic outcomes of MRSA infections, impact of inappropriate empirical therapy and pitfalls of existing treatments. This article explores newer agents of potential empiric usage in the management of MRSA infections.

Methicillin resistant S. aureus: public health concern in India

MRSA is a critical nosocomial gram positive pathogen in the Indian ICUs and the community. It can be categorised into community acquired (CA-MRSA) or hospital acquired (HA-MRSA) infections. CA-MRSA is majorly involved in skin and soft tissue infections (SSTIs) such as wound infection, abscesses or cellulitis. Traditionally, it was thought that HA-MRSA causes infections upon prolonged hospitalisation, in patients with indwelling devices or in patients undergoing dialysis or receiving immunosuppressive therapy. However, it is increasingly being observed worldwide, including in India, that CA-MRSA is gradually resembling HA-MRSA in being more invasive and transmissible than before. However, inappropriate empirical therapy can lead to serious invasive infections like bone and joint infections, necrotizing pneumonia and septicaemia. Furthermore, a recent evolution and global transmission of MRSA has led to the emergence of MDR CA-MRSA lineage from the Indian subcontinent, known as the Bengal Bay clone (ST772). This was first isolated from Bangladesh and India in 2004 and is highly virulent and resistant to multiple classes of antibiotics such as β-lactams, fluoroquinolones, macrolides and aminoglycosides due to the acquisition of Panton-Valentine leukocidin (PVL).[14-16] Its ability to acquire multidrug resistance, to penetrate in hospital settings and association with severe manifestations like necrotizing pneumonia and bacteraemia highlights Bengal bay clone as a major public health concern in the Indian subcontinent.[17]

Risk factors predisposing a serious MRSA infection

A recent study from North India displayed a strong association between MRSA infection and comorbid conditions. The probability of acquiring a serious MRSA infection was increased 3.5-fold with use of invasive devices and 2-fold in cases of previous hospitalisations, as compared with MSSA infected patients.[18] Additionally, Chatterjee et al highlighted prior respiratory infections and bacteraemia as significant risk factors of MRSA in his study.[19] Furthermore, prior antibiotic use or drug abuse is an established threat for multi-drug resistant MRSA, which subsequently may lead to more invasive infections.[20] Older age, diabetes mellitus and chronic kidney disease are commonly seen in association with MRSA infections.[21] Other commonly associated risk factors for MRSA infections are haemodialysis, open wounds and long-term central venous access or long-term urinary catheter.[22]

Clinical outcome in patients infected with MRSA

Mortality with MRSA infection

Over the years, several studies have highlighted the dominating impact of MRSA on the mortality rates when compared with patients infected with methicillin sensitive *S. aureus* strains (MSSA). Additionally, the EPIC II point prevalence study in critically ill patients had reported a 50% higher chance of hospital death in patients with MRSA.[23] Similarly, a study by Chen et al in *S. aureus* bacteraemia patients showed that MRSA was associated with increased mortality risk.[24] A recent comparative review of MRSA and MSSA septic arthritis found that MRSA was associated with increased risk of all-cause mortality which subsequently leads to increased risk of disability.[25]

Hospitalization stay and cost

MRSA not only affects the mortality rates but also has a major impact on the hospital stay, intensive care admission, number of complications and the cost incurred to the patients. Chatterjee et al showed that patients with MRSA infection had longer duration of hospital stay (14 days versus 8 days), antibiotic prescription (20 days versus 14 days) coupled with an increased greater need for ICU care (40% versus 14%) and length of ICU stay (5 days versus 2 days) than patients with MSSA.[17] Additionally, several reports globally have established that MRSA positive patients require longer hospital stay when compared to patients with MSSA infections.[26-28] A recent study from Norway showed that not only was the length of

hospital stay 8 times longer in MRSA group but also the hospitalisation costs were significantly higher as compared to non-MRSA inpatients.[29] A similar study from Swiss university hospital showed that an average bed day cost for MRSA infected patients was 1.5 times higher than non-infected patients admitted in the wards.[30] A multicentre study from China associated MRSA infections to an increased mortality of 0-3.5%, increased hospital stay of 6-14 days and escalated hospital cost ranging from $3,220 to $9,606.[31] Several studies from Europe and US that investigated the MSSA and MRSA investigation found an additional attributable cost of €8,000 to €17,000 and US$13,900 respectively.[32]

PROPHYLACTIC EMPIRICAL ANTIBIOTIC THERAPY FOR MRSA: CURRENT RECOMMENDATIONS

Table 1 summarizes the recommendation from the Infectious Diseases Society of America (IDSA) guidelines and the Ministry of Health and Family Welfare (MoHFW), India on the prophylactic empirical use of antimicrobials for MRSA infection.[6,33] The UK health practice guidelines also focussed on community associated severe MRSA infections. For SSTIs, these guidelines recommend the use of rifampicin and sodium fusidate or doxycycline for 5-7 days. Trimethoprim combined with rifampicin (5-7 days) and linezolid are also recommended. For pneumonia, linezolid and high-dose clindamycin with or without rifampicin has been advised.[8] From India, the 2019 national guidelines for antibiotic prescription in ICU recommends empiric antibiotic therapy covering MRSA for serious infections like community-acquired pneumonia (CAP), ventilator associated pneumonia, catheter related blood stream infections, bone and joint infections and sepsis of unknown cause. For CAP suspected to be associated with MRSA, vancomycin or teicoplanin are advised in the regimen. Patients resistant to vancomycin or with associated renal failure should be initiated with linezolid therapy. In case of ventilator-associated pneumonia (VAP) with high risk of MDR pathogens (MRSA prevalence of >15% and gram-negative prevalence of >10%), an empirical antibiotic coverage against MRSA and gram negative pathogen is recommended. In treating nosocomial meningitis, vancomycin in combination with cefepime/ceftriaxone/ meropenem is recommended. For brain abscess, vancomycin was advised in cases with suspicion of MRSA. It further recommends piperacillin-tazobactam (pipe-tazo) plus vancomycin/teicoplanin/daptomycin/ linezolid for severe non-purulent SSTIs. Linezolid was recommended to be used restrictively due to its inclusion in the treatment guidelines of tuberculosis in India.[34]

This is reflected in the recommendation from MoHFW, India; where linezolid was not advised in majority of MRSA infections. For most of the MRSA related infections, vancomycin has been identified as a primary empiric antibiotic of choice.[7]

IMPORTANCE OF APPROPRIATE EMPIRIC THERAPY IN MRSA

As the microbiological results take 24-72 hours, an appropriate empiric therapy plays a crucial role in determining a positive clinical outcome of critically ill patients. The choice of empiric therapy is determined by the likelihood of pathogen involved, resistance pattern, severity of illness, site of infection and comorbidities.[35] A SPA-BACT survey from 121 French hospitals emphasized that rapid initiation of appropriate treatment reduces short-term mortality in bloodstream infections.[36]

A meta-analysis conducted to explore the use of inappropriate antibiotic therapy in patients with severe infection showed that the inappropriate usage ranged from 14-79% across various studies with an incidence rate of more than 50%. This was further correlated with significantly increased 28 day and 60 day mortality ($p \leq 0.02$) in patients who received inappropriate antibiotic therapy.[37] Similarly, various reports have highlighted that increased morbidity and mortality rates with inappropriate empiric therapy (IET), have led to clinical and economic outcomes to a higher degree. Table 2 summarizes the studies reporting clinical outcomes with IET in MRSA. In a study involving patients of *S. aureus* bacteraemia (SAB), Kim et al observed that mortality was higher in patients receiving IET than an appropriate empiric therapy (AET) (39% versus 28%, odds ratio (OR)=1.60, p=0.09).[38] Another study from Thailand reported that delayed therapy or IET was significantly associated with increased all-cause mortality ($p<0.001$) and attributable mortality.[39] Similarly, in 510 episodes of MRSA bacteraemia, significantly higher 30-day mortality was observed in IET than AET (49.1% versus 33.3%, OR=2.15, p=0.001).[40] Further, in patients with septic shock, 28-day mortality was significantly higher with IET (61.6% versus 41.9%, p=0.017) than in AET.[41] A systematic review involving 70 prospective studies in patients with sepsis showed that among 46.5% of patients administered with IET, the mortality rate was 35%. IET was associated with significantly higher mortality in both unadjusted (OR=2.11) and adjusted (OR=2.05) comparisons.[42] Another study from Wi et al demonstrated that compared to MSSA bacteraemia, IET in patients with MRSA bacteraemia was associated with a higher mortality rate (56.5% versus 2.6%, $p<0.001$).[43] This evidence clearly suggests an increased risk of mortality with IET in MRSA infections. In addition to mortality, IET in MRSA infections can alter other clinical outcomes. A study from Zilberberg et al in patients with HA-cSSTI (MRSA in nearly 30% cases) demonstrated that IET resulted in a significantly higher frequency of decubitus ulcer, device-related infection, bacteraemia, and increased prolongation of hospital stay.[44] A cohort study from South western India also showed that IET was significantly associated (p=0.006) with adverse outcomes.[19]

Inappropriate therapy is also associated with increased hospital stay which eventually leads to increased cost for

critically ill patients. An initial appropriate therapy was associated with reduced length of hospital stay (7.1 versus 9.3 days, p=0.05) and decreased median crude cost ($13,688 versus $19,427; p=0.01) as compared to patients on initial inappropriate therapy.[45] A similar study on patients with complicated intra-abdominal infection reported an additional 5.3 hospitalised days and $3,287 additional hospital cost incurred to patients with failed initial empirical antibiotic therapy.[46]

The importance of appropriate empirical antibiotic therapy is not restricted to in-patients but is equally vital in the out-patient setting as well. In a study from the ambulatory clinic, Szumowski et al demonstrated that the sensitivity of the pathogen to empiric antibiotic therapy in MRSA-SSTI was associated with better clinical resolution (OR=5.91).[47] Another study reported higher rates of treatment failure in MRSA cellulitis if the strains were not sensitive to the initial empirical antibiotic (71% versus 47%, p<0.001).[48]

LIMITATIONS OF EXISTING ANTI-MRSA AGENTS AS EMPIRIC TREATMENTS

Currently, various agents are available for the initial empirical management of MRSA infections. Vancomycin and Teicoplanin are the most commonly used antibiotic for the empirical management of most MRSA infections. Other agents include clindamycin, TMP-SMX, linezolid, daptomycin and newly approved ceftaroline and telavancin which are used for the treatment of gram positive infections. However, these agents have certain limitations which restrict their clinical use in patients suffering from pneumonia, bone and joint infections, diabetic foot infections (DFI) and blood stream infections (BSI).[49] Table 3 summarizes the common limitations of the currently available anti-MRSA agents approved in India.

NEWER DRUGS FOR MRSA

With increasing resistance to existing antibiotics, there is a need to research and develop novel therapies to manage MRSA infections. There has been substantial progress in identifying newer antibiotics that can effectively manage MRSA. Ideal empiric agent should possess the favorable pharmacokinetic (PK) and pharmacodynamics (PD) profiles, should be active against a wide range of pathogens, be safe and tolerable and available as an oral as well as parenteral formulation. Here, we briefly discuss recent novel therapies with a potential for usage as an empirical antibiotic in MRSA infections.

Newer approved anti-MRSA agents in India

Ceftaroline

Ceftaroline fosamil is an injectable fifth generation cephalosporin which has been approved for the treatment of adult patients with acute bacterial skin and skin-structure infections, community-acquired bacterial pneumonia (CABP) and concurrent bacteremia in India (year: 2016). Ceftaroline has activity against MRSA, penicillin resistant streptococcus spp. and respiratory gram negative pathogens like *Haemophilus influenzae* and *Moraxella catarrhalis*. It has potential benefit in the treatment of severe and refractory MRSA infections of various organ systems and is well tolerated. However, recent safety studies have shown agranulocytosis as an adverse event complicating 13% of treatment courses and long term therapy is associated with increased risk of neutropenia.[50] Ceftaroline has poor lung tissue concentration, with only 23% of the initial dose reaching the epithelial lining fluid and being a β-lactam agent, it does not have activity against atypical respiratory pathogens and hence, cannot be used as monotherapy in CABP patients with suspected involvement of atypical pathogens.[51]

Levonadifloxacin

Of all the newer anti- MRSA agents, Levonadifloxacin is the only one that has been indigenously researched, developed and approved in India. Levonadifloxacin (intravenous) and alalevonadifloxacin (oral prodrug) are broad spectrum, benzoquinolizine subclass of quinolones which have potent antimicrobial activity against quinolone-resistant *S. aureus* (QRSA), MRSA and hVISA isolates. It has recently been granted approval for indications; ABSSSI, diabetic foot infections (DFI) and concurrent bacteraemia. Spectrum of activity against MDR gram-positive, quinolone‑susceptible gram-negative, anaerobes and atypical pathogens suggest their potential utility in resistant polymicrobial infections. It has rapid bactericidal activity against MRSA and QRSA even under high bacterial density. In a comparative study, levonadifloxacin exhibited anti-biofilm activity where it showed consistent killing of MRSA and QRSA embedded biofilms when compared with other agents which showed static or variable cidal action.[52] Additionally, unlike other fluoroquinolones that deteriorate in acidic conditions, levonadifloxacin exhibited enhanced activity in a pH of 5.5 which increases its therapeutic potential in intracellular infections and other clinical conditions with acidic environment.[53]

Levonadifloxacin has been reported to have excellent lung tissue penetration along with superior PK/PD profile coupled with immunomodulatory property where it attenuates TNFα and IL-6 production.[54,55] This characteristic property bestows levonadifloxacin with favourable clinical outcomes in MRSA pneumonia. Moreover, narrow mutant selection window and not being a substrate of NorA efflux pump, imparts levonadifloxacin with an enhanced resistance suppression potential. Therefore, levonadifloxacin has a strong potential for empiric management of serious infections with suspected MRSA. Table 4 elucidates efficacy and adverse events between currently available anti-MRSA agents-levonadifloxacin, vancomycin, teicoplanin, linezolid, daptomycin and ceftaroline.

Table 1: Guideline recommendations on initial antibiotic therapy for MRSA in adults.

MRSA infection	IDSA[7]	MOHFW, India[33]
SSTIs		
SSTIs	Clinda, TMP-SMX, Doxy/Mino, Linez (1-2 weeks)	-
cSSTIs	Vanco, Linez, Dapto, Telavan, Clinda (1-2 weeks)	-
Bacteraemia		
Uncomplicated	Vanco, Dapto (2 weeks)	-
Complicated	Vanco, Dapto (4-6 weeks)	-
Infective endocarditis		
Native valve	Vanco, Dapto (6 weeks)	Vanco (6 weeks)
Prosthetic valve	Vanco + Rifa (6 weeks) + Genta (2 weeks)	Vanco + Genta (only 2 weeks) + Rifa (6-8 weeks)
Pneumonia		
HA or CA-MRSA	Vanco, Linez, Clinda (1-3 weeks)	Vanco + Cefta, Vanco + Pipe-Tazo (1 week)
Bone and joint infections		
Osteomyelitis	Vanco, Dapto, TMP-SMX + Rifa, Linez, Clinda (8 weeks)	Vanco, TMP-SMX + Rifa (4-6 weeks)
Septic arthritis	Vanco, Dapto, TMP-SMX + Rifa, Linez, Clinda (3-4 weeks)	Vanco, TMP-SMX + Rifa (4-6 weeks)
Device related	[Vanco, Dapto, Linez, Clinda] + Rifa (2 week) f/b Rifa + [FQ, TMP-SMX, Tetra, Clinda] (3-6 months)	Based on actual sensitivity (6 weeks-6 months)
CNS infections		
Meningitis	Vanco±Rifa (2 weeks), Linez, TMP-SMX	Vanco (7-10 days)
Brain/spinal epidural abscess	Vanco±Rifa (4-6 weeks), Linez, TMP-SMX	
Septic thrombosis of sinus (dual venous/cavernous)	Vanco±Rifa (4-6 weeks), Linez, TMP-SMX	

SSTI: Skin and soft tissue infections; cSSTI: complicated skin and soft tissue infections; Clinda: clindamycin; TMP-SMX: trimethoprim-sulphamethoxazole; Doxy/Mino: doxycycline/minocycline; Linez: linezolid; Vanco: vancomycin; Dapto: daptomycin; Telavan: telavancin; Rifa: rifampicin; Genta: gentamycin; Cefta: ceftaroline; Pipe-Tazo: piperacillin-tazobactam; FQ: fluoroquinolones; Tetra: tetracyclines

Table 2: Clinical outcomes with inappropriate empirical therapy in MRSA infections.

Author (year)	Population	Groups	Outcomes
Kim et al (2006)[38]	*S. aureus* bacteraemia (n=238)	IET versus AET	Mortality Unmatched, univariate: 39% versus 28% (p=0.09) Matched, multivariate: 32% versus 28% (p=0.42)
Paul et al (2010)[40]	MRSA bacteraemia (n=510)	IET versus AET	30-day mortality: 49.1% versus 33.3% (p=0.001)
Zilberberg et al (2010)[44]	HA-cSSTI (n=717) (MRSA~30%)	IET versus AET	Decubitus ulcer: 29.5% versus 10.9% (p<0.001) Device-associated infection: 42.6% versus 28.6% (p=0.004) Bacteremia: 68.9% versus 57.8% (p=0.028) Increased length of hospital stay by 1.8 days Hospital mortality: 7.4% versus 6.4% (p=0.710)
Andersson et al (2019)[56]	Community-onset sepsis and septic shock (n=90)	IET versus AET	28- day mortality was 46.4% among the high-risk patients who received IET compared with 12.5% with AET

MRSA: Methicillin resistant *Staphylococcus aureus*; IET: inappropriate empirical therapy; AET: appropriate empirical therapy; cSSTI: complicated skin and soft tissue infections

Table 3: Limitations of the currently available anti-MRSA agents approved in India.

Treatment	Mechanism of action	Spectrum/cidality	Limitations
Vancomycin[57, 58]	Targets cell wall synthesis (Bind to terminal D-ala-D-ala chains on peptidoglycan in the cell wall, preventing further elongation of peptidoglycan chains)	Narrow spectrum coverage	Nephrotoxicity
		Slow bactericidal	Redman syndrome
			MIC creep, hVISA development
			Variable tissue penetration
			Dose adjustment required in renal patients
			Therapeutic drug monitoring (TDM) is recommended
Teicoplanin[59,60]	Inhibits cell wall synthesis	Narrow spectrum coverage	Nephrotoxicity
		Slow bactericidal	MIC creep
			2–3 days required to reach therapeutic levels, even with loading dose
			Variable tissue penetration
			Dose adjustment required in renal patients
			Therapeutic drug monitoring (TDM) is recommended
Linezolid[61,62]	Inhibits protein synthesis by binding to 50s ribosomal subunit	Narrow spectrum coverage	Thrombocytopenia
		Bacteriostatic	Bone marrow suppression
			Peripheral and optic neuropathy
			Serotonin syndrome
			Limited efficacy in bacteraemia or endocarditis
Daptomycin[63, 64]	Disrupts cell membrane, leading to rapid depolarization and cell death	Narrow spectrum of coverage	Inactivated by pulmonary surfactant
		Bactericidal activity	Skeletal muscle toxicity
			Potential for cross resistance with hVISA
			Dose adjustment in renal patients
Tigecycline[65,66]	Inhibits protein synthesis by binding to 30s ribosomal subunit	Broad spectrum coverage	Not useful for lung and blood stream infections
		Bacteriostatic	Black box warning from the USFDA for all-cause mortality
			Low serum levels
			Poor tissue penetration
Clindamycin[67, 68]	Inhibits protein synthesis by binding to 50s ribosomal subunit	Broad spectrum coverage	Increased constitutive and inducible resistance
		Bacteriostatic	Clostridium difficile colitis
			Antibiotic associated diarrhoea
Rifampicin[69,70]	Inhibits bacterial DNA dependent RNA polymerase thereby inhibiting bacterial transcription	Broad spectrum coverage	Increased risk of drug interactions
		Bacteriostatic/ bactericidal activity	Hepatotoxicity
			Rapid development of resistance
			Restriction due to TB in third world countries
Ceftaroline[71,72]	Binds to penicillin binding protein (PBP2a) and inhibits the synthesis of the peptidoglycan layer of bacterial cell walls	Narrow spectrum coverage	Poor intracellular concentration
		Bactericidal activity	Dose adjustment in renal patients
			Cannot be used as monotherapy in CABP
			Clostridium difficile-associated diarrhea

Table 4: Comparative efficacy and safety parameters between anti-MRSA agents.[57-72]

Properties	Levonadifloxacin	Vancomycin/teicoplanin	Linezolid	Daptomycin	Ceftaroline
Dose	800mg BID (I.V) 1000 mg BID (oral)	Vancomycin: 0.5g QID or 1g BID Teicoplanin: 400 mg BID (loading dose); 400 mg OD (maintenance dose)	600 mg BID	500 mg OD	600 mg BID
Spectrum	Broad	Narrow	Narrow	Narrow	Broad
Formulation	IV and Oral	I.V only	IV and Oral	I.V only	I.V only
Bacterial killing	Cidal	Slow bactericidal	Static	Cidal	Cidal
Major adverse effects	None	Nephrotoxicity	Bone marrow suppression	Muscle toxicity	Diarrhoea, nausea, and rash
Lung tissue concentration	Excellent	Poor	Good	Not active	Poor
Biofilm action	Potent	No	Moderate	No	No
Dose adjustment in RI	No	Yes	No	Yes	Yes
Dose adjustment in HI	No	No	Yes	No	No

CONCLUSION

MRSA remains a serious threat globally and necessitates timely management. Appropriate empiric therapy is a strong pillar of antibiotic stewardship in decreasing mortality, morbidity and hospitalization costs. Limitations of current antibiotics call for new and effective anti-MRSA antibiotic which can potentially be used in severe invasive infections as well as on outpatient basis. Newer antibiotics, ceftaroline and levonadifloxacin cater to the unmet clinical needs and hold promise to be considered as an appropriate initial antibiotic therapy for invasive MRSA infections. However, watchfulness will be necessary to avoid unmonitored use to prevent the development of resistance to these novel antibiotics. We look forward to more studies in these areas, especially from those countries where hospital acquired infection burden is high.

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