

## Review Article

# Management of acute bacterial skin and skin structure infections in India: are we equipped to meet the challenges of the growing menace of methicillin-resistant *Staphylococcus aureus*?

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**Received:** 02 June 2020

**Revised:** 07 July 2020

**Accepted:** 16 July 2020

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## ABSTRACT

*Staphylococcus aureus* (*S. aureus*) is a Gram-positive facultative anaerobic bacterium that colonizes the skin and nasal passages of humans. The incidence of invasive *S. aureus* infections has increased over the past decades and is associated with poor outcomes and high mortality rates. *S. aureus* is responsible for almost one-third of acute bacterial skin and skin structure infections with methicillin-resistant *Staphylococcus aureus* (MRSA) accounting for a large proportion of these. The *S. aureus* strains prevalent in India are more aggressive and there are recent reports of the emergence of the more virulent multidrug resistant lineages ST2371 and ST8. Management of these infections is complicated by the fact that antimicrobial stewardship is non-existent, the choice of treatment is often empirical and available treatment options are limited due to a high prevalence of resistance strains. Currently available anti-MRSA agents include vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, and clindamycin. However, the emergence of resistant strains and several undesirable features related to the safety and tolerability of these agents have limited the options available for the management of MRSA infections. A newer, safe and efficacious antibiotic is thus an unmet need for the management of MRSA in patients with acute bacterial skin and skin structure infections. In this review we explore the current and future trends in the management of acute bacterial skin and skin structure infections highlighting the challenges in their management in India, and current progress in the development of some novel drugs for the management of MRSA infections.

**Keywords:** Acute bacterial skin and skin structure infections, Methicillin-resistant *Staphylococcus aureus*, Anti-MRSA agents, Multi-drug resistance

## INTRODUCTION

*Staphylococcus aureus*, both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) are

responsible for causing a range of mild to life-threatening infections such as skin and soft-tissue infections (SSTIs), osteomyelitis and endocarditis. *Staphylococcus aureus* is the most common organism isolated in primary and



secondary skin infections. These are usually treated with penicillin and its derivatives but increasing resistance in MRSA has led to a renewed focus on other antibiotics.<sup>1</sup> We reviewed the burden of MRSA focusing on the challenges in the treatment of SSTIs in India. We also reviewed some novel drugs that are under development.

## REVIEW OF LITERATURE

### MRSA and the types of wounds

*S. aureus* is commonly isolated from skin and soft-tissue infections such as impetigo, wounds, furuncles, burns, abscesses and systemic infections especially those of the respiratory and urinary tracts. It has a predilection for the immunosuppressed and those with severe burn wounds. Both superficial infections and severe sepsis are frequently seen in healthcare centres and hospitals, most often in maternity wards where they can cause severe sepsis in babies, abscesses in nursing mothers, and carbuncles in the staff. *S. aureus* infections are also commonly associated with surgical wounds, catheters, implanted feeding tubes or other invasive devices.<sup>2</sup>

### Epidemiology of MRSA in acute bacterial skin and skin structure infections

In the United States, SSTIs account for ~10% of hospital admissions for all infections, of which the majority are MRSA.<sup>1</sup> The increasing number of outbreaks of SSTI around the world results in significant morbidity and mortality along with high direct and indirect costs.<sup>3</sup> Globally, MRSA accounts for a considerable proportion of acute bacterial skin and soft-tissue structure infections and it is now a serious public health issue all over the world with high endemicity in various Western and Asian countries. Both hospital-acquired (HA-MRSA) and community-acquired MRSA (CA-MRSA) have caused epidemics of SSTIs leading to considerable morbidity and mortality since the 1990s.<sup>4</sup> Although MRSA infections have been reported in India since the 1980s, it has only recently been recognized as a serious problem. MRSA is endemic in India with the incidence ranging from 30% to 70% of all *S. aureus* infections - the wide range results from differing infection control policies, varied expertise at healthcare facilities, and the type and efficacy of the antibiotics used in different regions.

**Table 1: List of few studies reported previously for the skin infections caused by MRSA.**

Study	Objectives	Study design	Key findings
Joshi et al <sup>6</sup>	To evaluate prevalence and susceptibility pattern of MRSA in India	Survey report	<ul style="list-style-type: none"> <li>Sensitivity to ciprofloxacin was low in both MSSA (53%) and MRSA (21%).</li> <li>The study showed a high level of MRSA (41%) prevalence</li> </ul>
Nagaraju et al <sup>7</sup>	Prevalence of MRSA in community acquired pyoderma in south India	Prospective study	<ul style="list-style-type: none"> <li>The study showed 59.7% of the patients with <i>S. aureus</i> nasal colonization</li> <li>MSSA strains showed higher resistance towards commonly used antimicrobials</li> </ul>
Hsiao et al <sup>8</sup>	Evaluation of role of MRSA in ocular infection	Retrospective, observational study	<ul style="list-style-type: none"> <li>274 patients identified with MRSA ocular infections, which comprised 181 CA-MRSA and 93 HA-MRSA isolates</li> <li>The annual ratio of CA-MRSA in ocular MRSA infections averaged 66.1% and tended to increase over the 10-year interval</li> </ul>
Schmitz et al <sup>9</sup>	Evaluation of role of TMP-SMX for uncomplicated skin abscesses in patients at risk for community-associated MRSA infection	Clinical trial	TMP-SMX treatment decreased the formation of subsequent lesions after uncomplicated abscess incision. However, it does not reduce treatment failure.

MRSA: methicillin-resistant *Staphylococcus aureus*; *S. aureus*: *Staphylococcus aureus*; CA-MRSA: community-acquired MRSA; HA-MRSA: hospital-acquired MRSA; TMP-SMX: trimethoprim-sulfamethoxazole.

A large study from 15 Indian tertiary care centres published in 2013 reported the overall prevalence of MRSA as 41%. A more recent study by the Antimicrobial Research And Surveillance Initiative of the Indian Council of Medical Research (ICMR-AMRSN) conducted in four premier institutes in India found the prevalence of MRSA to be 37.3% (range 21% to 45 %).<sup>5</sup> Various studies of the incidence of MRSA infections in India and globally are detailed in Table 1.

### Evolution of MRSA isolates in India

A rapid increase in the incidence of MRSA is due to the emergence of specific clones with different genotypic characteristics. All the MRSA strains carry the *Staphylococcal cassette chromosome mec* (SCCmec), but while HA-MRSA strains carry SCCmec types I, II, or III, CA-MRSA have SCCmec IV. Recently a novel *staphylococcal cassette chromosome mec* (SCCmec)



element was found in an ST152 methicillin-resistant *Staphylococcus aureus* (MRSA) and multiple SCCmec types exist in individual MRSA.<sup>10,11</sup>

The majority of HA-MRSA isolates carry SCCmec type III while CA-MRSA mostly belong to ST22 (SCCmec IV), ST772 (SCCmec V), and ST672 (SCCmec V) genotypes. Recently a study had reported the emergence of a more aggressive multidrug resistant MRSA lineages ST2371 and ST8 strains.<sup>12</sup> CA-MRSA tend to be more virulent than HA-MRSA and often carry genes that encode the Panton-Valentine leucocidin (PVL), as well as many exotoxins that are associated with tissue necrosis and greater severity of disease.<sup>13</sup> Many variants of

epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA)-15 have been reported over the years.<sup>14,15</sup>

#### **Clinical profile of patients with acute bacterial skin and skin structure infections and importance of MRSA**

Acute bacterial skin and skin structure infections frequently occur in patients with compromised skin integrity, such as maceration, ischemia, immunosuppression, or erosions and wounds that enhance cutaneous colonization. Other factors include trauma, pre-existing skin conditions such as tinea pedis, various chronic skin lesions, and edema due to venous insufficiency.<sup>16</sup>

**Table 2: Anti MRSA agents indicated for the treatment for ABSSSI.**

Drug	Recommended Dosage
Vancomycin	500 mg q6h or 1 g q12h IV
Teicoplanin	6 mg/kg q12h IV for 3 doses followed by 6 mg/kg once daily IV for 7-14 days
Linezolid	600 mg IV/oral twice daily, for 10-14 days
Daptomycin	4–6 mg/kg administered IV every 24 h for 7–14 days
Tigecycline	100 mg IV once, then 50 mg IV every 12 h for 5-14 days
Telavancin	10 mg/kg IV every 24 hours for 6 days
Ceftaroline	600 mg every 12 h for 5–14 days
Clindamycin	600 mg IV q 8h or 300 mg oral q8h
TMP-SMX	1-2 DS tabs twice daily PO
Dalbavancin	1000 mg for 7 days followed by 500 mg
Oritavancin	1200 mg IV single dose
Tedizolid	200 mg IV/oral OD for 6 days

ABSSSI: acute bacterial skin and skin structure infection; MRSA: methicillin-resistant *S. aureus*; IV: intravenous.

**Table 3: Mechanism of action and limitations of drugs used in the management of MRSA ABSSSI.**

Antibiotics	Mechanism of action	Limitations
Clindamycin	Inhibits protein synthesis by binding to 50s ribosomal subunit	Abdominal pain, diarrhea, nausea, rash, agranulocytosis, elevated liver enzyme levels, erythema multiforme, jaundice, pseudomembranous enterocolitis Inducible resistance can be missed if D-testing not performed on clinical isolate
Vancomycin	Inhibits bacterial cell wall synthesis	Red man syndrome, nephrotoxicity MIC creep, and potential for nephrotoxicity at higher concentrations and in combination with other nephrotoxic agent
Teicoplanin	Inhibits cell wall synthesis	Nephrotoxicity, MIC creep, 2–3 days required to reach therapeutic levels, even with loading dose, variable tissue penetration, dose adjustment required in renal patients
Daptomycin	Disrupts cell membrane, leading to rapid depolarization and cell death	Inactivated by pulmonary surfactant, Skeletal muscle toxicity, Potential for cross resistance with hVISA, dose adjustment in renal patients
Linezolid	Inhibits protein synthesis at 50S subunit with prolonged use	Myelosuppression usually related to prolonged therapy >2 weeks, peripheral neuropathy, serotonin syndrome Serious side effects like marrow suppression, lactic acidosis have been reported especially with prolonged use
Tigecycline	Inhibits protein synthesis at 30S subunit	Nausea, vomiting, Low serum levels, Poor tissue penetration, Black box warning

Continued.



Ceftaroline (fifth-generation cephalosporin)	Inhibits bacterial cell wall synthesis Used in combination with daptomycin (synergism) for salvage therapy	Poor intracellular concentration, dose adjustment in renal patients, clostridium difficile-associated diarrhoea
Telavancin (lipoglycopeptide)	Inhibits bacterial cell wall synthesis	Have higher nephrotoxicity rates than vancomycin renal dysfunction associated with its use, propensity to cause QTc prolongation, and alteration of laboratory values of prothrombin time (PT) and activated partial thromboplastin time (aPTT)

MIC: minimum inhibitory concentration; PT: prothrombin time; aPTT: activated partial thromboplastin time.

## TREATMENT MODALITIES

### Traditional agents for MRSA

Older drugs used for the treatment of acute bacterial skin and skin structure infections caused by MRSA were clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and minocycline. The use of clindamycin is limited by its bacteriostatic nature, the high rate of resistance (both inducible and constitutive), as well as a high incidence of *Clostridium difficile* associated colitis. Tetracyclines and TMP-SMX have limited activity against *S. aureus*.<sup>17</sup> Vancomycin is the most frequently used antibiotic for the empiric and definitive therapy of systemic MRSA infections as outlined in the Infectious Diseases Society of America (IDSA) treatment guidelines.<sup>18</sup>

### Present treatment modalities for MRSA

Anti-MRSA agents indicated for the treatment for ABSSSI are listed in Table 2.

The mechanism of action and limitations in the treatment of acute bacterial skin and skin structure infections caused by MRSA are elucidated in Table 3.

## CHALLENGES IN TREATMENT

### Inappropriate management

Vancomycin has remained the drug of choice to treat MRSA infections over the past 50 years. The usual dose is 1 g every 12 h, but this may need to be modified according to the glomerular filtration rate in patients with compromised renal function. Administration may be intermittent based on the susceptibility of strains, but lately the increasing MICs of MRSA strains to vancomycin has led a recent reduction in its usage.<sup>19</sup> Vancomycin is mildly nephrotoxic and ototoxic when used at conventional dosages but the toxic potential increases at higher dosages especially if other nephrotoxic drugs are used concomitantly.<sup>20</sup>

The clinical practice guidelines published by the Institute of Medicine Committee to advise the Public Health

Service, the Surgical Infection Society, and the World Society of Emergency Surgery recommends empiric antibiotic therapy. The guidelines emphasize the importance of surgical source control.<sup>21,22</sup>

Inappropriate choice of initial antibiotic or treatment duration leads to treatment failure in a large proportion of patients (range: 16.6%–34.1%) irrespective of source of infection (community or hospital).<sup>23</sup>

Inappropriate categorization of patients with acute bacterial skin and skin structure infections is a major problem in the management of MRSA as antibiotic selection varies with the type and severity of the infection. In wound infections the decision as to whether Gram-positive or Gram-negative bacteria or anaerobes are the cause would clearly alter therapy. The type of discharge may be an important clue, with staphylococcal infections being associated with a purulent discharge while streptococcal infections often produce a watery (non-purulent) discharge. The anatomical location of the wound may also influence management - infections in the perianal area, extensive cellulitis, or rapidly spreading

purulent infections in the neck, hand, face, and genitalia almost always require hospitalization.<sup>24</sup>

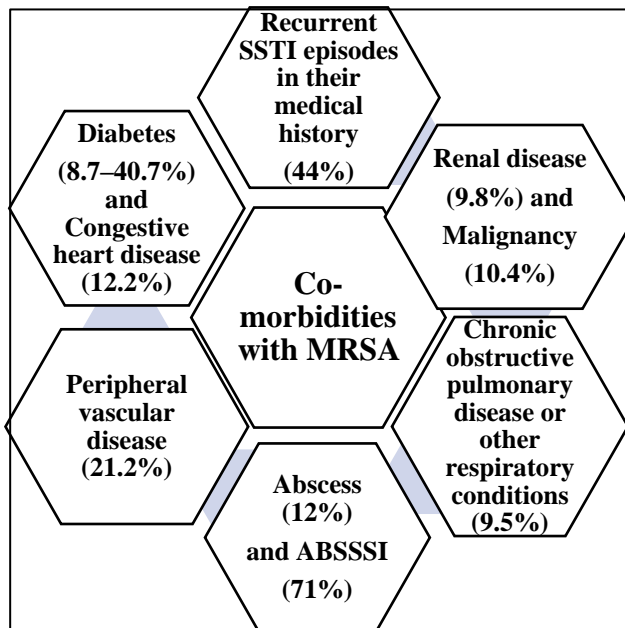
### Comorbidities

Comorbidities such as diabetes, cardiovascular disease and stroke, peripheral vascular disease, chronic obstructive pulmonary disease, renal failure, and cancer are commonly associated with MRSA infections and pose an additional challenge in management.<sup>7</sup> Hospitalized patients with a history of such comorbidities or a prior history of intravenous (IV) drug use, recent surgery, and chronic alcoholism may not only interfere with antibiotic selection<sup>25</sup> but may elevate the risk of drug interactions (especially when multiple antibiotics are prescribed) and increase the total duration of treatment.<sup>26</sup>

Patients hospitalized with acute bacterial skin and skin structure infections also suffer with diabetes.<sup>27</sup> Antibiotic treatment in these patients is often prolonged to several weeks and the chances of recurrence are higher. Osteomyelitis as a complication of SSTIs also occurs



more than twice as frequently in diabetic patients (13.3%) as compared to non-diabetics (5.2%).<sup>28</sup>



**Figure 1: Comorbidities with MRSA ABSSSI.**

ABSSSI: acute bacterial skin and skin structure infections, MRSA: methicillin-resistant *Staphylococcus aureus*, SSTI: skin and soft-tissue infection.

### Global financial burden of MRSA

MRSA infections are responsible for a huge financial burden worldwide. There are few studies of the cost analysis of MRSA infections. Lee *et al.* used an economic simulation model to estimate that CA-MRSA infections could cost annually an average of  $\geq$ \$560 million to a third party, from \$834,848 to \$874,797 to the society and from \$737,618 to \$780,354 in direct medical costs.<sup>29</sup> The CDC estimates that 323,700 hospitalized patients are infected by MRSA annually with at least 10,600 deaths imposing additional costs for US\$ 1.7 billion each year.<sup>30</sup> Other comparative cost analysis studies have concluded that the economic burden imposed by CA-MRSA is far greater than many other acute infectious diseases with the annual economic burden of CA-MRSA infections being 2–13 times higher than that of pertussis and 8–17 times higher than that of Lyme disease.<sup>31,32</sup> The overall cost of treatment for acute bacterial skin and skin structure infections with MRSA is high due to the frequent need for hospitalization involving the administration of IV antibiotics and the also the cost of treating the associated comorbidities. The estimated mean cost of an acute bacterial skin and skin structure infections hospitalization in the United States is \$8023 with a 4.9-day length of stay.<sup>3</sup>

There is a paucity of cost analysis studies in India, but a cross-sectional study conducted in a tertiary healthcare centre estimated the median hospitalization cost for MRSA infection was INR 16,383 and for MSSA it was

INR 11,481 with a median 10 day hospital stay for MRSA and 7.5 days for MSSA infections. Prolonged hospital stay further escalates the treatment costs and morbidity owing to acquisition of nosocomial infections.<sup>33</sup>

### NEED OF NEW THERAPIES

Before the emergence of MRSA,  $\beta$ -lactam antibiotics were the drugs of choice for skin infections. In 2013, the US FDA redefined acute bacterial skin and skin structure infections and issued recommendations and guidance based on the identification of specific infections. The objective was to rationalize antibiotic choice through quantifiable parameters, such as improvement in the lesion size and systemic signs of infection.<sup>34</sup>

Over the past couple of decades there has been a significant decrease in the development of new anti-infective agents, especially those with a novel mechanism of action. Many derivatives of older antibiotic classes currently used to treat MRSA (Glycopeptides, oxazolidinones, cephalosporins, tetracyclines) and several investigational agents<sup>35</sup> for treatment of MRSA infections have been in development for several years.

Some newer approaches to enhance the activity of older antibiotics have been explored. Vancomycin–d-octaarginine conjugate (V-r8) has been shown to eradicate the MRSA biofilm and persister cells *in vitro* thus outperforming vancomycin.<sup>36</sup> Recently, scientists observed that clavulanic acid was highly effective in protecting against beta-lactamase degradation of both penicillin and amoxicillin and found that both cefuroxime and dicloxacillin were highly stable against staphylococcal beta-lactamase degradation.<sup>37</sup> However, these novel approaches are still under development and long-term effects have not been studied.

A new benzoquinolizine subclass of quinolone derivatives, Levonadifloxacin its oral prodrug, alalevonadifloxacin have been shown to have an established antimicrobial spectrum against clinically significant gram positive and gram negative, atypical, and anaerobic pathogens. The well differentiated mechanism of action primarily towards the DNA gyrase has led to a distinctive potent activity of levonadifloxacin against MRSA, QRSA and hVISA strains.<sup>38</sup> Moreover, the dual action on DNA gyrase and topoisomerase IV gives levonadifloxacin an added efficacy advantage in topoisomerase IV resistant *S.aureus* strains. Attractive features such as resistance to NorA efflux pump, effective cidal action against high density cultures, low mutant prevention concentration confers levonadifloxacin with resistance suppression features. Levonadifloxacin has a superior bactericidal action which is observed even in acidic pH, intracellular environment and biofilms thereby retaining its potency and tackling difficult-to-treat MRSA infections.<sup>39</sup>



Levonadifloxacin also retains a potent antibacterial activity against respiratory pathogens such as macrolide- and penicillin –resistant *S. pneumonia*, *S. pyogenes*, *H. influenza* and *M. catarrhalis*. It provides best in class epithelial lung fluid concentration, thereby promising potential in the treatment of lower respiratory tract infections.<sup>40</sup> Unlike other anti-MRSA agents, no dosage adjustments are required for levonadifloxacin/alalevonadifloxacin in renal and hepatic impaired patients. Both the molecules have recently been approved by DCGI (Drug Controller General of India) for the treatment of acute bacterial skin and skin structure infections (ABSSSI), concurrent bacteraemia and diabetic foot infections.

## CONCLUSION

In the recent years, MRSA resistant to multiple antibiotics have become endemic in many countries. However, the FDA approvals of newer antibiotics for treatment of acute bacterial skin and skin structure infections have been on the decline. There is an urgent need not only to develop novel anti-MRSA agents to curb already resistant MRSA strains but also to develop stringent infection control guidelines and strong antibiotic stewardship programs. This approach could help manage MRSA infections with a considerable reduction in morbidity, mortality and hospitalization costs.

*Funding: No funding sources*

*Conflict of interest: Dr. Jaishid Ahdal and Dr. Rishi Jain are employees of Wockhardt Ltd, Mumbai, India*

*Ethical approval: Not required*

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**Cite this article as:** Mahakalkar C, Padhye D, Nandagawali VR, Takale S, Ahdal J, Jain R. Management of acute bacterial skin and skin structure infections in India: are we equipped to meet the challenges of the growing menace of methicillin-resistant *Staphylococcus aureus*? Int Surg J 2020;7:3172-9.