

## Review Article

# Methicillin resistant *Staphylococcus aureus*: a review of the present Indian scenario and drug treatment

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## ABSTRACT

Methicillin-resistant strains of *S. aureus* cause infections that are associated with higher mortality rates and increased length of hospital stays, than infections caused by methicillin-susceptible strains. The mechanism by which MRSA strains develop resistance is by the production of an altered penicillin-binding protein (PBP), which has a decreased affinity for most semisynthetic penicillins. MRSA has increased in prevalence and has become endemic in the Indian subcontinent, with incidence varying from 25% in Western regions to 50% in Southern India. A multi-centric study conducted across 15 tertiary care centers in India from 2008 to 2009 showed overall prevalence of MRSA infection to be 41% among *S. aureus* isolates, and recent Indian studies from 2014 and 2018 have also suggested an increasing prevalence of MRSA. Transmission is mainly horizontal and concerns high risk populations (patients with prolonged hospital stay, on haemodialysis, receiving cancer treatment or specific medications that affect immune function, intravenous drug users and individuals who have had surgery in the recent past). Community Acquired MRSA has emerged as significant pathogen responsible for potentially fatal infections including life-threatening pneumonia, necrotizing fasciitis, endocarditis, osteomyelitis, severe sepsis, and toxic shock syndrome. Diagnosis is mainly by gram stain, culture and quantitative PCR. Newer techniques include Multi-locus sequence typing (MLST), Pulsed-field gel electrophoresis (PFGE), Bacteriophage typing, spa locus typing and SCCmec typing. Although Vancomycin was previously considered the definitive treatment for serious MRSA infections, the emergence of less-susceptible strains, poor clinical outcomes, and increased nephrotoxicity with high-dose therapy have deterred its use as first-line therapy in many cases. Although a number of new and effective antimicrobial agents are now available for the treatment of MRSA, their exact role and choice of agent needs to be well-defined.

**Keywords:** Altered penicillin-binding protein, Endocarditis, Linezolid, Methicillin-resistant *S. aureus*, Toxic shock syndrome

## INTRODUCTION

*Staphylococcus aureus* is a gram-positive and coagulase-positive spherical bacterium of approximately 1 µm in diameter, which forms grape-like clusters. It is a body commensal, which is often present asymptotically on skin and mucous membranes of nose and gut of healthy individuals.<sup>1</sup> Nearly 20% of individuals are persistent nasal carriers of *S. aureus*, 30% are intermittent carriers,

and 50% cases are non-carriers.<sup>2</sup> Most affected cases are infected by these indigenously carried commensal *S. aureus* strains.<sup>3</sup>

Recently, *S. aureus* has shown a high level of resistance against multiple antibiotic classes. This resistance first emerged in 1942, within two years of the introduction of penicillin.<sup>4</sup> Methicillin, a semisynthetic antibiotic was developed in the late 1950s, and in 1960, the first case of

methicillin-resistant *S. aureus* (MRSA) was clinically identified.<sup>5</sup> Although these “archaic” MRSA strains were first found in the United Kingdom and parts of Europe, new cases started to emerge after 1980, slowing spreading and transforming into a global catastrophe.

Methicillin-resistant strains of *S. aureus* cause infections that are associated with higher mortality rates and increased length of hospital stays, as compared to infections caused by methicillin-susceptible strains.<sup>6-8</sup> The mechanism by which MRSA strains develop resistance is by the production of an altered penicillin-binding protein (PBP), which has a decreased affinity for most semisynthetic penicillins. The protein is encoded by an acquired gene, *mecA*, which is carried on a mobile genetic element (MGE) designated as staphylococcal cassette chromosome *mec* (SCC*mec*).<sup>9-11</sup> The insertion of these mobile genetic elements into the chromosomes of susceptible strains causes the emergence of methicillin resistance. These strains are a major concern due to their high morbidity and mortality, as they are responsible for almost 25 to 50% of *S. aureus* infections in the hospital setting.<sup>12</sup>

## REVIEW OF LITERATURE

### Prevalence, risk factors and sub-types

In a recent European survey, the most common organisms in Skin and Soft Tissue Infections (SSTIs) were *S. aureus* (71% cases) with 22.5% being MRSA. MRSA prevalence varied widely among these European countries as well.<sup>13</sup> In a US study spanning over 10 years<sup>14</sup>, incidence of *S. aureus* increased overall, with an increase in community onset MRSA infections. Presently, Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most commonly implicated agents in nosocomial infections in the US intensive care units, and is one of the leading causes of surgical site infections in North American tertiary care hospitals.<sup>15,16</sup>

MRSA has increased in prevalence and has become endemic in the Indian subcontinent, with incidence varying from 25% in Western regions to 50% in Southern India.<sup>17,18</sup> A multi-centric study conducted across 15 tertiary care centers in India from 2008 to 2009 showed overall prevalence of MRSA infection to be 41% among *S. aureus* isolates.<sup>19</sup> The prevalence of MRSA in a study from Chennai<sup>18</sup> was reported as 40-50 per cent, and a high prevalence of MRSA (35% in ward and 43% in ICU) was observed from blood culture specimens in a study from Delhi as well.<sup>20</sup> Patel et al reported a change in the blood stream infections with *S. aureus* emerging as the predominant pathogen in recent years, with MRSA strains becoming increasingly common among them.<sup>17</sup>

The prevalence of MRSA varies between regions, and between hospitals in the same region as seen in a study from Delhi<sup>21</sup> where the MRSA prevalence in nosocomial infections varied from 7.5 to 41.3 per cent between three

tertiary care hospitals. Community acquired-MRSA (CA-MRSA) isolates are now being increasingly reported from India, which are mainly isolated from skin and soft tissue infections. D’ Souza et al studied 412 confirmed cases of MRSA and found that 54 per cent were true CA-MRSA possessing the SCC*mec* IV and SCC *mec* V genes. Chatterjee et al found the overall prevalence of *S. aureus* nasal colonization was 52.3 per cent and that of MRSA was 3.89 per cent in the community.<sup>22,23</sup>

In a 2014 study in Central India, out of 192 coagulase positive strains, a total of 112 (58.33%) strains showed resistance to methicillin, and of the remaining 93 coagulase negative strains, 12 (12.9%) showed methicillin resistance.<sup>24</sup> In a 2018 study done by Singh et al in 300 school-going children of age 5-15 years from North India, nasal carriage of *S. aureus* was found in 140 (46.67%) children, whereas MRSA colonization was found in 23 (7.67%) children.<sup>25</sup> The male children were found to have a slightly higher nasal colonization with both *S. aureus* and MRSA, as compared to the female children.

In recent years, Methicillin-resistant *Staphylococcus aureus* (MRSA) strains have emerged as a cause of nosocomial infections responsible for rapidly progressive, potential fatal diseases.<sup>26</sup> Independent risk factors for MRSA include old age, extended hospital stay, immune-suppression, hemodialysis, inadequate antimicrobial therapy, peripheral hypo-perfusion, diabetes and multiple indwelling devices.<sup>27</sup>

New genetically distinct reservoirs of MRSA strains, including Healthcare-associated/Hospital acquired methicillin-resistant *S. aureus* (HA-MRSA), Community-acquired MRSA (CA-MRSA) and livestock-acquired MRSA (LA-MRSA) have now been described.<sup>28</sup> Rapid evolution of new genetic lineages/clonal complexes (CC) and resistance to multiple classes of antibiotics, has worsened the MRSA led health crisis.<sup>29,30</sup>

### Transmission

Transmission of methicillin resistance to *Staphylococcus aureus* is mainly horizontal in hospital and community settings, and presents a significant clinical challenge to the management of MRSA led infections. CA-MRSA strains occur in people who have not been recently hospitalized/low risk populations such as children, prisoners, athletes, soldiers and adults presenting to the emergency department with a positive contact/travel history. HA-MRSA strains first appeared, and are prevalent in high risk populations such as patients with prolonged hospital/ICU stay, undergoing haemodialysis, receiving cancer treatment or specific medications that affect immune function, intravenous drug users and individuals who have had surgery in the recent past.<sup>31</sup>

MRSA infections present a highly variable course, and may progress substantially within one to two days of

initial symptom onset; rapidly taking hold in human tissues and eventually become resistant to treatment.<sup>32,33</sup> Transmission occurs through crowding and close contact, open wounds and via clothing such as cotton towels and wash cloths, privacy drapes and curtains, splash aprons, scrub suits and lab coats.<sup>34</sup> The 5 Cs are used to remember transmission of MRSA: Crowding, Contact (skin-to-skin), Compromised skin (open wounds), Contaminated (items and surfaces) and lack of Cleanliness.<sup>31</sup>

### ***Clinical manifestations and disease spectrum***

CA MRSA and HA MRSA have emerged as significant pathogens responsible for potentially fatal infections which have been tabulated below.<sup>32,34</sup> These infections are seen to be more prevalent in high risk groups.

#### ***Common clinical presentations***<sup>32,34</sup>

- Acute bacterial skin and skin structure infections such as folliculitis, furuncles (boils), carbuncles, styes, abscesses, impetigo, paronychia, wound infections and cellulitis.
- Osteomyelitis
- Endocarditis
- Pneumonia and Urinary tract infections/ Cystitis
- Meningitis
- Infections in Pacemaker Pockets/ Implants
- Acute food poisoning due to toxins
- Toxic shock syndrome and staphylococcal scalded skin syndrome.

TSST-1 or other enterotoxin producing strains cause the Staphylococcal toxic shock syndrome, in which the patient presents with a constellation of fever, hypoperfusion and shock, a red rash and multi-organ failure. Risks include tampon use, nasal packing and surgical wounds. Ingestion of preformed Staphylococcal enterotoxin causes an acute, self-limited gastroenteritis with an incubation period of 2-6 hours.<sup>35</sup>

Infection may occur without an apparent focus or entry site, and the patient should be evaluated for endocarditis, mycotic aneurysms or vertebral infection. Skin/soft tissues infections include folliculitis, cellulitis, furuncles, carbuncles, abscesses, impetigo (may occur in combination with *Streptococcus pyogenes*), Breast mastitis, abscesses of the spleen, kidney, epidural space; visceral or deep abscesses occurring almost always due to hematogenous seeding from bacteremia.<sup>36,37</sup>

Nearly 6-25% of patients present with endocarditis due to *S. aureus* bacteremia, affecting both the native and prosthetic valves.<sup>38,39</sup> Bone involvement is evidenced by osteomyelitis (most commonly vertebral osteomyelitis secondary to bacteremia/discitis and epidural abscess), and infections in the prosthetic joints/implants.<sup>32,34</sup>

CA-MRSA strains are also responsible for Nosocomial necrotizing pneumonia, and for right-sided endocarditis via septic pulmonary emboli.<sup>40,41</sup> The release of TSST1 toxin is mainly responsible for toxin associated gastroenteritis and the subsequent toxic shock syndrome. CNS manifestations may present as post-operative or bacteremia associated meningitis.<sup>42</sup>

### ***Diagnosis and rapid identification techniques***

An appropriate specimen is obtained depending upon the type and site of infection, and analyzed either by using biochemical or enzyme-based tests. A Gram stain would show typical gram-positive cocci in clusters, and a culture on mannitol salt agar (selective medium with 7-9% NaCl) produces yellow-colored colonies as a result of mannitol fermentation and a decrease in the pH. For differentiation on the species level, the tests done are Catalase (positive for all *Staphylococcus species*), Coagulase (positive for *S. aureus*), DNase, Lipase and Phosphatase tests. Phage typing can be performed in cases of staphylococcal food poisoning to determine the source of infection.<sup>43</sup>

Rapid and reliable techniques have now been developed due to recent genetic advances, which support infection control strategies to limit bacterial spread and ensure the appropriate use of antibiotics.

Outbreaks of MRSA infection are being increasingly identified by quantitative PCR.<sup>43,44</sup> “Band-based” or “sequence-based” methods are now employed to observe the evolution pattern and adaptability of *Staphylococcus aureus* to existing and new antibiotics.<sup>45</sup>

Multi-locus sequence typing (MLST), Pulsed-field gel electrophoresis (PFGE), Bacteriophage typing, Spa locus typing and SCC mec typing are also used to determine the origin of MRSA strains.<sup>46</sup>

### ***Drugs and management strategies***

The Principle Characteristics of Current US Food and Drug Administration–Approved Anti-infective Agents for MRSA have been given in Table 1.<sup>41,47,48</sup>

- Vancomycin remains the mainstay of treatment for the management of MRSA ever since 1958. No drug to date has shown superiority to vancomycin in the treatment of MRSA infections with the possible exception of Linezolid in hospital-acquired pneumonia (HAP). Vancomycin has been recommended in consensus guidelines to predict successful therapy, and continuous infusion has been associated with lower rates of nephrotoxicity.<sup>48,49,50</sup>
- Teicoplanin is a glycopeptide with a similar mode of action as vancomycin. Recent data has concluded that teicoplanin (at higher and appropriate dosing) is not inferior to vancomycin and may be associated with a lower rate of adverse events.<sup>32,48</sup>

**Table 1: Principle characteristics of US-FDA approved drugs against MRSA.**<sup>41,47,48</sup>

Agent	Bacterial effect and mechanism of action	Route of administration and dosing recommendations	Dosage adjustment for renal and hepatic impairment	Adverse events	Advantages	Disadvantages
Vancomycin	“Slow” Bactericidal activity (concentration independent); cell wall inhibition	IV: 500 mg q6h or 1000 mg q12h; high-dose therapy (15 to 20 mg/kg total body weight q8 to 12 h) currently recommended when MIC values are 1 µg/mL	Renal: Dosing adjustments are necessary Hepatic: no adjustment needed	Nephrotoxicity, red man syndrome	Inexpensive; >50 years of clinical experience	Resistance - development of VRSA; increasing MIC values associated with poor outcomes; nephrotoxicity with higher doses
Linezolid	Bacteriostatic; Protein synthesis inhibition (23S RNA at 50S ribosomal subunit)	IV or PO: 600 mg q12h	Renal: None Hepatic: No specific recommendations	Thrombocytopenia and anemia; peripheral and optic neuropathy; lactic acidosis; serotonin syndrome	100% bioavailable oral formulation; good lung penetration; active against Vancomycin Resistant Enterococci	Bacteriostatic; serious adverse events with longterm use (>14 d); increasing linezolid-resistance; high drug cost
Daptomycin	Bactericidal (concentration dependent); membrane depolarization (Ca <sup>++</sup> dependent)	IV: <i>S. aureus</i> bacteremia: 6 mg/kg (total body weight) q24h; some experts recommend higher doses (8 to 10 mg/kg) for bacteremia/ infective endocarditis indications	Renal: For Creatinine Clearance <30 mL/min, q48h Hepatic: No specific recommendations	CPK elevation; myopathy; peripheral neuropathy; reports of rhabdomyolysis and eosinophilic pneumonia	Rapidly bactericidal; effective for MRSA bloodstream infections and right-side endocarditis; active against VRE	Inactivated by pulmonary surfactant and should not be used to treat pneumonia;; suboptimal clinical outcomes in patients with reduced renal function; high drug cost
Tigecycline	Bacteriostatic; Protein synthesis inhibition (at 30S ribosomal subunit)	IV: loading dose of 100 mg followed by 50 mg q12h	Renal: None Hepatic: Child-Pugh class C, 100 mg single dose, maintenance 25 mg q12h	GI side effects (nausea and vomiting are common)	Active against VRE	Bacteriostatic; high rates of GI adverse events; higher risk of mortality than comparator agents; high drug cost
Telavancin	Bactericidal (concentration dependent); cell wall inhibition and membrane depolarization	IV: 10 mg/kg (total body weight) q24h	Renal: CrCl 30-50 mL/min, 7.5 mg/kg q12h; CrCl 10 to <30, 10 mg/kg q48h; CrCl <10, limited data Hepatic: No specific recommendations	GI side effects (including dysgeusia); mild QT prolongation; Nephrotoxicity	Rapidly bactericidal against MRSA, VISA, and VRSA; active against MRSA strains resistant to vancomycin, linezolid, and daptomycin	Nephrotoxicity; lower clinical outcomes in patients with reduced renal function; Avoided during pregnancy
Ceftaroline	Bactericidal (time dependent); cell wall inhibition	IV: 600 mg q12h	Renal: CrCl 31-50 mL/min, 400 mg q12h; CrCl 15-30, 300 mg q12h; CrCl <15, 200 mg q12h Hepatic: No specific recommendations	Well tolerated (<5% incidence of diarrhea, nausea, rash)	Bactericidal; well tolerated; moderately expensive	Limited reports on treatment of MRSA infections

**Table 2: Recommendations for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>31,33,41</sup>**

Manifestation	Treatment	Adult dose
<b>Skin and soft-tissue infection (SSTI)</b>		
Abscess, furuncles, Carbuncles	Incision and drainage	
Purulent cellulitis (defined as cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess)	Clindamycin	300-450 mg PO TID
	TMP-SMX	1-2 DS tab PO BID
	Doxycycline	100 mg PO BID
	Minocycline	200 mg 3 1, then 100 mg PO BID
	Linezolid	600 mg PO BID
Nonpurulent cellulitis (defined as cellulitis with no purulent drainage or exudate and no associated abscess)	beta-lactams (eg, cephalexin and dicloxacillin)	500 mg PO QID
	Clindamycin	300-450 mg PO TID
	b-lactam (eg, amoxicillin) and/or TMP-SMX or a tetracycline	Amoxicillin: 500 PO mg TID. See above for TMP-SMX and tetracycline dosing
	Linezolid	600 mg PO BID
Complicated SSTI	Vancomycin	15-20 mg/kg/dose IV every8-12 h
	Linezolid	600 mg PO/IV BID
	Daptomycin	4 mg/kg/dose IV QD
	Telavancin	10 mg/kg/dose IV QD
	Clindamycin	600 mg PO/IV TID
<b>Bacteremia and infective endocarditis</b>		
Bacteremia	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
	Daptomycin	6 mg/kg/dose IV QD
Infective endocarditis, native valve	Vancomycin and Daptomycin	
Infective endocarditis, prosthetic valve bacteremia	Vancomycin and gentamicin and Rifampin	15-20 mg/kg/dose IV every 8-12 h 1 mg/kg/dose IV every 8 h 300 mg PO/IV every 8 h
	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
	Linezolid	600 mg PO/IV BID
Persistent bacteremia	Clindamycin	600 mg PO/IV TID
	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
	Daptomycin	6 mg/kg/day IV QD
Bone and joint infections Osteomyelitis Septic arthritis	Linezolid	600 mg PO/IV BID
	Clindamycin	600 mg PO/IV TID
	TMP-SMX and Rifampin	3.5-4.0 mg/kg/dose PO/IV every 8-12 h
	Vancomycin	15-20 mg/kg/dose IV every8-12 h
Septic arthritis Prosthetic joint, spinal implant infections	Daptomycin	6 mg/kg/day IV QD
	Linezolid	600 mg PO/IV BID
	Clindamycin	600 mg PO/IV TID
	TMP-SMX	3.5-4.0 mg/kg/dose PO/IV every 8-12 h
	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
<b>Central nervous system infections</b>		
Meningitis Brain abscess, subdural empyema, spinal epidural abscess	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
	Linezolid	600 mg PO/IV BID
	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h
Brain abscess, subdural empyema, spinal epidural abscess	Vancomycin	15-20 mg/kg/dose IV every 8-12 h
	Linezolid	600 mg PO/IV BID
Septic thrombosis of cavernous or dural venous sinus	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h

- Lipoglycopeptides such as Oritavancin, Telavancin, and Dalbavancin are semi-synthetic lipopolypeptide analogues of vancomycin with activity against MRSA. In common with vancomycin, they also act by inhibition of cell wall synthesis.<sup>48,49</sup>
- Anti-MRSA Cephalosporins namely Ceftriaxone and ceftobiprole have in-vitro activity against MRSA due to their affinity for the penicillin-binding protein PBP2a, and offer great promise in the treatment of MRSA.<sup>41,48</sup>



- Daptomycin belongs to a new cyclic lipopeptide class of antibiotics and has a unique mechanism of action, with calcium-dependent binding to the cytoplasmic membrane resulting in rapid membrane depolarization and efflux of potassium. This results in the arrest of DNA, RNA, and protein synthesis and leads to rapid cell death. Although effective, daptomycin is inactivated by pulmonary surfactant and cannot be used in the treatment of pneumonia.<sup>34,49,50</sup>
- Linezolid is an oxazolidinone class antibiotic that inhibits bacterial protein synthesis by preventing the formation of the 70S initiation complex with activity against MRSA. Unlike, vancomycin, linezolid achieves high levels in the epithelial lining fluid of the lungs, making it a promising candidate for treatment of patients with MRSA associated HAP.<sup>48,49,50</sup> Tedizolid is a new oxazolidinone that has been specifically engineered to improve bioavailability and efficacy, and reduce the toxicity as compared with linezolid. It is dosed once daily and its potency is 4 to 16 times greater than linezolid.<sup>48-50</sup>
- Quinupristin/Dalfopristin (QD) is a combination of two semi-synthetic streptogramin antibiotics which acts by binding to the 50S bacterial ribosome in two sequential steps, and thus inhibits bacterial protein synthesis. Each drug alone is bacteriostatic against susceptible gram-positive organisms including MRSA, but the combination is synergistic and bactericidal.<sup>32,48</sup>
- Tigecycline is a parenteral glycylicycline antibiotic, with in vitro activity against many gram-positive bacteria, including MRSA. The main treatment-limiting adverse effect of tigecycline is nausea and vomiting, which occurs in 30 to 40% of treated patients.<sup>48-50</sup>

Many of these agents with activity against drug-resistant gram-positive pathogens are being developed primarily for treatment of MRSA infections, including tedizolid, dalbavancin, and oritavancin.<sup>51</sup> The current recommendations for treatment of MRSA have been summarized in Table 2.

### **Prevention and screening**

Patient screening with nasal cultures upon hospital admission prevents the co-habitation of MRSA carriers with non-carriers.

Alcohol has been proven to be an effective surface sanitizer against MRSA, and can be used in conjunction with quaternary ammonium to extend the longevity of the sanitizing action. Some important prevention measures as recommended by the CDC have been mentioned below.<sup>31</sup>

- Hand washing, alcohol-based and chlorhexidine based handrubs remain somewhat effective.

- Prevention for health care workers by wearing gloves when examining or treating body areas with a suspected cutaneous lesion; and proper hand washing following examination or treatment is required, including proper hand hygiene; gloving; wearing eye, mouth, and nose protection; gowning; cleaning equipment with disinfectant; and the appropriate cleaning of laundry.
- The CDC recommends that surfaces and floors be cleaned with disinfectants approved by the Environmental Protection Agency using List-H on the Environmental Protection Agency's list.

### **Resistance trends and need for newer drugs**

Better treatment of this evolving organism requires a better understanding of it by both the researchers and the treating clinicians. Vancomycin remains a viable option, but there still remains uncertainty about the best dosing strategy. Lipoglycopeptides as a class, all the agents show in vitro potency greater than Vancomycin.<sup>48-50</sup> However, their long half-life and complex pharmacokinetics may preclude the use of these agents in critically ill patients. Anti-MRSA cephalosporins (Ceftobiprole and Ceftaroline) show greater promise in the treatment of MRSA.<sup>32,48</sup>

Daptomycin is currently the only antibiotic to have shown non-inferiority to Vancomycin in the treatment of MRSA bacteremia.<sup>48,49</sup>

Vancomycin resistance has become evident in select clinical settings through rising MICs, growing awareness of hetero-resistance and emergence of intermediate-resistant and fully resistant strains.<sup>49</sup> Although the resistance to linezolid and daptomycin remains low, some cases have shown development of resistance through point mutations and horizontal transmission of cfr-mediated resistance to linezolid.<sup>49,50</sup> These points highlight the ongoing need for new and more potent antimicrobial therapies for MRSA.

### **DISCUSSION**

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be associated with significant morbidity and mortality. Although Vancomycin was previously considered the definitive treatment for serious MRSA infections, the emergence of less-susceptible strains, poor clinical outcomes, and increased nephrotoxicity with high-dose therapy have deterred its use as first-line therapy in many cases.<sup>49,50</sup> Few drugs till date have shown superiority to Vancomycin in the treatment of MRSA with possible exception of Linezolid in HAP.<sup>48</sup> Although a number of new and effective antimicrobial agents are now available for the treatment of MRSA, their exact role and choice of agent needs to be well-defined.

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