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- 1 Treatments and limitations for methicillin-resistant *Staphylococcus aureus*: A review of current literature
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Treatments and limitations for methicillin-resistant *Staphylococcus aureus*: A review of current literature

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) has remained a major threat to healthcare; in both hospital and community settings over the past five decades. With the current use of antibiotics for a variety of infections, including MRSA, emerging resistance is a major concern. Currently available treatments have restrictions limiting their use. These issues include, but are not limited to, side effects, cross-resistance, lack of understanding of pharmacokinetics and clinical pharmacodynamics, gradual increment in minimal inhibitory concentration over the period (MIC creep) and ineffectiveness in dealing with bacterial biofilms. Despite availability of various therapeutic options for MRSA, the clinical cure rates remain low with high morbidity and mortality. Given these challenges with existing treatments, there is a need for development of novel agents for MRSA. Along with prompt infection control strategies and strict implementation of antibiotic stewardship, cautious use of newer anti-MRSA agents will be of utmost importance. This article reviews the treatments and limitations of MRSA management and highlights the future path.

Key words: Methicillin resistant; Methicillin-resistant *Staphylococcus aureus*; Antibiotics; Monotherapy

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Core tip: Methicillin-resistant *S. aureus* (MRSA) remains a major threat despite availability of multiple treatments. Limitations of the current anti-MRSA treatments demand more careful use of these agents. Using antibiotics in combination for MRSA treatment needs further evaluation. Multiple strategies including research and development of new antibiotics and antibiotic stewardship are necessary to contain the MRSA.

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INTRODUCTION

Staphylococci have been involved in human disease for centuries and were identified first as the cause of incurable boils. Sir Alexander Ogston and Friedrich J Rosenbach identified, classified, and contributed to the nomenclature of *Staphylococci*^[1]. *S. aureus* has since evolved as a major infectious pathogen being severely detrimental to the health of millions of patients. *S. aureus* possesses resistance mechanisms to standard agents. The first incidence of penicillin resistance was reported in 1942 which was identified to be due to inducible beta-lactamase. After introduction of methicillin in 1959, methicillin-resistant *S. aureus* (MRSA) was reported in 1961^[2].

Burden of MRSA is high in middle-income countries like India. Amongst all *S. aureus* isolates, Indian Network for Surveillance of Antimicrobial Resistance group reported methicillin resistance in 41% of their isolates^[3]. This high burden of MRSA in India is the cause of significant morbidity and mortality. Additionally, formation of biofilms in MRSA isolates is associated with increased virulence, pose a challenge in clinical management, and may also contribute to the development of resistance^[4,5].

Current treatment strategies have limitations and improper source control may add to that, especially in severe MRSA infections. Thus, we aim to review the current treatment strategies, their limitations, and a way forward for effective management of MRSA infections.

CURRENT TREATMENT RECOMMENDATIONS FOR MRSA INFECTIONS

MRSA infections involve a wide disease spectrum. Common sites include skin/soft tissue, bone/joint, vascular line, native valve/prosthetic valve endocarditis, central nervous system shunt infections and meningitis/brain abscesses. The Infectious Disease Society of America (IDSA) provides treatment recommendations for MRSA infections^[6] (Table 1).

Vancomycin dosing in MRSA

Vancomycin is one of the mainstays of therapy for MRSA infections. In adults, IV vancomycin at a dose of 15-20 mg/kg/dose (max 2 g/dose) every 8-12 h based on renal function is recommended with a loading dose of 25-30 mg/kg in seriously ill patients^[7]. Therapeutic drug monitoring (TDM) is recommended to ensure adequacy of dosing, with most infections necessitating trough concentrations of 10-20 µg/mL, with concentrations at the higher end of this range (*i.e.*, 15-20 µg/mL) reserved for difficult to penetrate sites such as pulmonary and central nervous system. However, in skin and skin structure infections (SSTIs), trough monitoring may not be necessary and vancomycin in a dose of 1 mg every 12 h may be adequate^[6].

LIMITATIONS OF CURRENT TREATMENTS: MONOTHERAPY

Table 1 Methicillin-resistant *S. aureus* treatment recommendations^[4]

Infections	Antibiotic Treatment
Skin and soft tissue infections (SSTIs)	
Uncomplicated SSTIs	Clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline) (A-II), linezolid
Complicated SSTIs	IV Vancomycin, Linezolid (oral or IV 600 mg twice daily), Daptomycin (4 mg/kg/dose IV once daily), Telavancin (10 mg/kg/dose IV once daily), Clindamycin (600 mg IV or PO 3 times a day)
Recurrent SSTIs	Nasal decolonization - mupirocin twice daily +/- topical body decolonization - skin antiseptic solution (e.g. chlorhexidine) or dilute bleach baths.
Bacteraemia and infective endocarditis	
Native valve endocarditis	Vancomycin; Daptomycin (6 mg/kg/dose IV once daily)
Prosthetic valve endocarditis	Vancomycin + Rifampin (300 mg PO/IV every 8 hour) followed by Gentamicin (1 mg/kg/dose IV every 8 hour)
Pneumonia	
Community acquired, or healthcare associated	IV vancomycin or linezolid (600 mg PO/IV twice daily) or clindamycin (600 mg PO/IV 3 times daily)
Bone and joint infections	
Osteomyelitis or Septic arthritis	Vancomycin; Daptomycin (6 mg/kg/dose IV once daily); TMP-SMX [4 mg/kg/dose (TMP component) twice daily] + Rifampin (600 mg once daily)
Device-related osteo-articular infections (early onset < 2 mo - prosthetic joint infections)	Vancomycin or Daptomycin (6 mg/kg/dose IV once daily) + Rifampin (600 mg once daily) followed by; Rifampin + fluoroquinolone / TMP-SMX / tetracycline / clindamycin
Device-related osteo-articular infections (early onset < 2 mo - spinal implant infections)	Initial parenteral therapy + Rifampin followed by prolonged oral therapy
CNS infections	
Meningitis, Brain abscess, subdural empyema, spinal epidural abscess, Septic Thrombosis of Cavernous or Dural Venous Sinus	IV Vancomycin +/- Rifampin; OR; Linezolid 600 mg PO/IV twice daily or TMP-SMX 5 mg/kg/dose IV every 8-12 hour

SSTIs: Skin and soft tissue infections; TMP-SMX: Trimethoprim-sulfamethoxazole; PO: Per oral; IV: Intravenous; CNS: Central nervous system.

An ideal anti-MRSA agent does not exist; desirable properties in anti-MRSA antibiotics include rapid bactericidal action, excellent penetration in tissue, consistent and predictable pharmacokinetics to support reliable dosing, low probability of resistance development, lower risk of side effects, and good microbiological and clinical cure rates. Biofilm formation with *S. aureus* is known and contributes to antibacterial tolerance by promoting bacterial persistence in biofilms.

Thus, identifying an ideal antibiotic which will also be active against biofilms can be a challenge. Table 2 enumerates some of the limitations of major existing anti-MRSA treatments.

Vancomycin monotherapy

Over the years of vancomycin use, resistance is now beginning to emerge in MRSA isolates^[8]. Vancomycin has several limitations. First is the ratio of minimum bactericidal to inhibitory concentration (MBC: MIC ratio). A study from Sader *et al*^[9] demonstrated that 20.1% of tested MRSA strains ($n = 900$) were vancomycin tolerant defined by MBC: MIC ratio of ≥ 32 . This varied from 10.0% to 43.0% among different centres evaluated^[9]. Secondly, the accessory gene regulator pathway is associated with regulation of quorum sensing and endotoxin production^[10]. Development of polymorphisms or loss of function of accessory gene regulator (*agr*) pathway is associated with failure of vancomycin therapy^[11]. Thirdly, the “MIC creep” phenomenon wherein there is a gradual reduction in susceptibility of *S. aureus* to vancomycin despite concentrations in the susceptible range (≤ 2 mg/L) can develop with continued use of vancomycin^[8]. A study from California by Wang *et al*^[12], demonstrated a gradual shift of MIC from ≤ 0.5 to 1.0 $\mu\text{g/mL}$ over 5 years to vancomycin in MRSA strains ($n = 6002$). The proportion of isolates with MIC 1 $\mu\text{g/mL}$ increased from 19.9% to 70.4% over study duration (Figure 1). Fourth concern is development of hetero-resistance to vancomycin (hVISA). In this phenomenon, from among the isolated MRSA, a subpopulation demonstrates intermediate level of vancomycin resistance, but the colony as a whole remains susceptible. The mechanisms for this remains unclear but may involve thickening of cell wall avoiding penetration of vancomycin, and alteration in *agr* pathway^[10]. A study from Sader *et al*^[9] involving nine hospitals in the United States showed hVISA prevalence of 13.4%. The development of hVISA was more common (45.6%) in MRSA isolates with MIC ≥ 1 mg/L. Fifth, the extensive protein binding of vancomycin leads to variable tissue

Table 2 Limitations of current anti-methicillin resistant *S. aureus* treatments

Treatment	Limitations
Vancomycin	Higher MBC: MIC ratio Polymorphisms or changes in gene function (e.g. <i>agr</i> pathway) MIC creep Development of hetero-resistance (hVISA) Variable tissue penetration AUC: MIC ratio Nephrotoxicity Red man syndrome
Teicoplanin	Therapeutic drug monitoring may be necessary Need to generate evidence on pharmacokinetics and clinical pharmacodynamics
Daptomycin	Resistance development Possible cross-resistance in hVISA Inactivation by alveolar surfactant
Linezolid	Serious adverse drug reactions e.g., thrombocytopenia, optic neuropathy, peripheral neuropathy, lactic acidosis, monoamine oxidase inhibition MIC creep Limited efficacy in bacteraemia or endocarditis
TMP/SMX	High degree of resistance Limited efficacy in bacteraemia Thymidine salvage in presence of pus
Clindamycin	High rates of inducible and constitutive resistance Risk of <i>Clostridium difficile</i> infection
Tetracyclines	Limited utility in severe invasive infections
Tigecycline	Low serum levels with limited efficacy in bacteraemia Poor tissue penetration and AUC: MIC ratio Black box warning from the USFDA for all-cause mortality, Mortality Imbalance and Lower Cure Rates in VAP and pancreatitis
Quinupristin/ Dalfopristin	Limiting side effects like infusion-site inflammation, pain, and oedema, thrombophlebitis, arthralgia, myalgia, nausea, diarrhoea, vomiting, and rash Drug interactions with CYP3A4 inhibitors
Ceftaroline	Risk of agranulocytosis
Telavancin	Risk of nephrotoxicity
Oritavancin and Dalbavancin	Long half-life - delayed hypersensitivity if occurs may persist for weeks Clinical failure may get unnoticed if there is lack of daily follow-up evaluations Effectiveness in bacteraemia, pneumonia, bone and joint infections, and prosthetic infections has not been established Higher occurrence of osteomyelitis reported in clinical studies with oritavancin

AUC: Area under the curve; MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration; TMP/SMX: Trimethoprim-Sulfamethoxazole; USFDA: United States Food and Drugs Administration; VAP: Ventilator associated pneumonia.

penetration which can further be different in comorbidities like diabetes, meningitis, *etc*^[10]. Sixth, the pharmacodynamics of vancomycin has been considered to be an important aspect in determining efficacy. The area under the curve (AUC) and MIC ratio of 400 or more is believed to provide therapeutic effectiveness for which vancomycin trough concentration should reach 15-20 mg/L especially in severe MRSA infections^[7]. For achieving AUC: MIC ratio of 400 or more at MIC of 1 mg/L, dose of 3-4 mg/d is necessary. For MIC of 2 mg/L, achieving target AUC: MIC ratio is not possible even when higher doses are used. This can result in poor clinical and microbiological cure.

Nephrotoxicity is an important adverse effect associated with vancomycin. The reported incidence varies from nearly 14% in children to 35% in adults. In adults, trough concentration beyond 15 µg/mL is associated with increased risk of renal injury. Attaining AUC: MIC ratio of ≥ 400 is therefore harmful especially wherein the

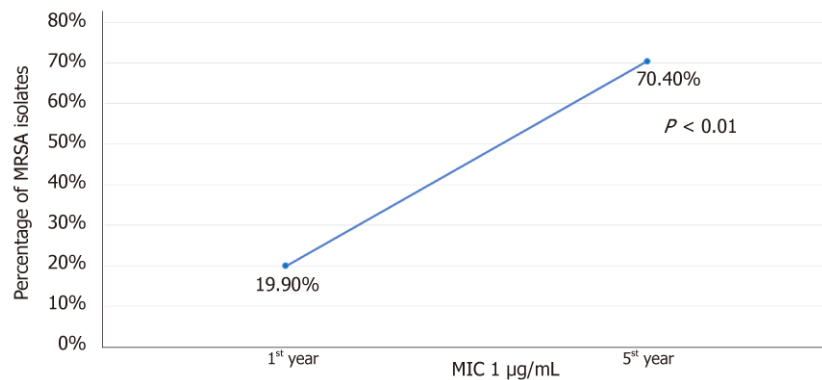


Figure 1 Minimal inhibitory concentration creep - Proportion of MRSA isolates with vancomycin minimal inhibitory concentration of 1 µg/mL^[12].

isolate MIC is > 2 mg/L. In such cases, use of alternative agents is advised^[13].

Daptomycin

Daptomycin, a branched cyclic anionic lipopeptide exerts bactericidal action *via* calcium-dependent modification in membrane potential causing leaking of intracellular ions and cell death^[14]. It has shown similar efficacy to vancomycin in MRSA bacteraemia, endocarditis, complicated SSTIs, but not in pneumonia due to inactivation by alveolar surfactant^[10]. However, point mutation in *MprF* gene (L431F substitution) identified in clinical isolates was associated with reduced negative cell membrane charge, thicker cell wall, and longer doubling time. This was found to confer increased resistance to daptomycin and vancomycin^[15]. Daptomycin-non-susceptible (DAP-NS) phenotype has also been reported in MRSA infections. Among 2.4% DAP-NS strains ($n = 208$), one was sequence type 72 (ST72) and other four were ST5. Three of these strains were also found to be hVISA. The resistance mechanism in ST72 was charge repulsion, ST5 showed charge independent mechanisms. Changes in cell wall thickness were not found in any of the DAP-NS strains^[16]. DAP-NS isolates were not sensitive to high-dose of daptomycin^[17]. Increased MIC of daptomycin was found to be associated with increased mortality in patients with MRSA bacteraemia^[18]. Finally, daptomycin has been associated with elevated creatine kinase and rhabdomyolysis, which is problematic in critically ill patients already at risk of such increases and sequelae thereof, such as renal injury^[19].

Linezolid

Linezolid, a synthetic antibiotic, binds to ribosomal RNA on both 30S and 50S subunits and thereby inhibits protein synthesis. Additionally, it inhibits formation of initiation complex and reduce the rate of translation process^[20]. Occurrence of serious adverse drug reactions like thrombocytopenia, optic neuropathy, peripheral neuropathy, lactic acidosis, and potential serotonin syndrome through monoamine oxidase inhibition have important therapeutic limitations resulting in poor adherence to therapy^[21]. MIC creep with linezolid similar to that of vancomycin has also been reported^[22]. Being a bacteriostatic agent, its first line use in severe invasive infections especially bacteraemia and endocarditis is avoided^[10].

In persistent MRSA bacteraemia (> 7 d) despite therapy with glycopeptides like vancomycin or teicoplanin, shifting to linezolid failed to show superiority in microbiologic response, treatment success, and mortality compared to the patients who continued glycopeptides^[23].

Limitations of other agents

Teicoplanin: TDM may be necessary in ascertaining the teicoplanin concentrations as daily dosages of 4 mg/kg have been reported to result in treatment failure compared to a 6 mg/kg dose. Also, trough concentrations of > 10, > 20, and > 30 mg/L have been reported to be necessary for successful treatment of *S. aureus* septicemia, MRSA endocarditis, and MRSA osteomyelitis, respectively^[24]. Also, given its important role in MRSA management, there is more need to generate evidence on pharmacokinetics and clinical pharmacodynamics^[24].

Trimethoprim-sulfamethoxazole (TMP-SMX): In MRSA infections, its utility is limited by development of resistance and poor efficacy^[25,26]. Therefore, TMP-SMX is mainly confined to treatment of uncomplicated skin and skin structure infections

from an MRSA standpoint^[27].

Clindamycin: Clindamycin has bacteriostatic activity and high rates of inducible and constitutive resistance, limiting its utility for MRSA infections^[28,29]. Further, risk of *Clostridium difficile* infection (CDI) might deter use of clindamycin as sole agent for MRSA as duration of exposure has been identified as an important determinant of CDI^[30].

Tetracyclines: Tetracyclines such as doxycycline and minocycline are limited to uncomplicated SSTIs by community-acquired MRSA. Bacteriostatic activity and limited spectrum limits utility in severe invasive MRSA infections^[10].

Fucidin (fusidic acid): Fusidic acid inhibits bacterial protein synthesis *via* action on RNA. As a topical agent, it has been used for treatment of skin infection, though there has been recent interest in rectifying its use in combination with rifampicin for infected joint prostheses. This however has been limited by significant drug-drug interactions resulting in ineffective fusidic acid exposure^[31].

Tigecycline: Tigecycline has shown promise in MRSA infections equivalent to vancomycin^[32]. It is effective in SSTIs and complicated intraabdominal infections^[33]. However, high protein binding can result in low serum levels thereby limiting effectiveness in MRSA bacteraemia. Black box warning issued from the US Food and Drug Administration for all-cause mortality, mortality imbalance and lower cure rates in VAP and pancreatitis is a concern with tigecycline^[34].

Quinupristin/Dalfopristin: Quinupristin/Dalfopristin is considered among the effective agents in *Staphylococcal* infections and may be effective in MRSA bacteremia^[35]. However, occurrence of side effects like infusion-site inflammation, pain, and edema, thrombophlebitis, arthralgia, myalgia, nausea, diarrhoea, vomiting, and rash limit its use. Also, inhibition of cytochrome P450 3A4 with quinupristin/dalfopristin warrants caution with use of drugs metabolized through this enzymatic pathway^[36]. Interference with other drugs metabolism may result in QTc prolongation with use of quinupristin/dalfopristin.

Ceftaroline: Ceftaroline is an effective agent for severe MRSA infections and provides clinical cure in nearly 74% cases. The major concern with this agent is development of agranulocytosis. Prolonged therapy (≥ 21 d) increases risk of leukopenia and therefore treatment with ceftaroline should be closely monitored in these situations^[37].

Telavancin: It is another effective agent in MRSA with resistance to vancomycin, linezolid and daptomycin. However, nephrotoxicity is an important limitation. An increased mortality has been observed in hospital or ventilator associated pneumonia^[38].

Oritavancin and Dalbavancin: These lipoglycopeptides have ultra-long half-life upwards of 346 h making them attractive as single-dose antibiotics. This and the inability to remove *via* dialysis, however also raises a concern as injury resulting from delayed hypersensitivity (if occurs) or other adverse effects may persist for weeks. It's effectiveness has not been established in bacteraemia, pneumonia, bone and joint infections, or prosthetic infections^[39]. While these agents have potential for ambulatory infectious diseases management, particularly in areas of poor clinic access for frequent intravenous infusions, their utility in acute and critical care remains to be proven.

LIMITATIONS OF CURRENT TREATMENTS: COMBINATION TREATMENTS

With development of resistance and limitations of individual agents discussed above, combination therapy is suggested for most severe and invasive MRSA infections. The objectives are to broaden the coverage, prevent or reduce development of resistance, improve the effectiveness of individual agents, enhance capacity to penetrate biofilms, and to reduce toxin production^[40].

Vancomycin + Rifampicin

Rifampicin is bactericidal to *S. aureus*, achieves high intracellular concentration, and penetrates biofilms. A systematic review in 2008 reported that *in-vitro* findings identified with rifampicin combination did not relate to *in-vivo* findings^[41]. Another review in 2013 reported limited evidence to support adjunctive use of rifampicin in MRSA infections. The increased risk of drug interactions, adverse effects with

rifampicin and development of rifampicin resistance are possibilities with use of rifampicin in combination^[42]. Latter is especially important in Indian context where the rifampicin is the primary drug against tuberculous infection and burden of tuberculosis is enormous. Currently, IDSA guidelines recommend use of rifampicin in combination only in prosthetic valve endocarditis and in osteoarticular infections associated with prostheses^[6]. Rifampicin should not be used as monotherapy for the treatment of MRSA infections.

Vancomycin + Gentamicin

In vitro studies have demonstrated increased bactericidal activity of vancomycin and animal studies have shown to shorten the duration of bacteraemia. Nephrotoxicity associated with gentamicin can add to the nephrotoxic potential of vancomycin^[40].

Vancomycin + Quinupristin/Dalfopristin

Laboratory analyses have shown synergism with this combination^[10]. However, clinical evidence is restricted to case reports.

Daptomycin + Rifampicin or Gentamicin

Similar to other combination treatments, the evidence from *in-vitro* studies shows synergistic activity with this combination as well^[43,44]. However, clinical evidence is restricted to case reports^[45-47]. In time-kill study, addition of gentamicin rather than rifampicin has been shown to provide synergism with daptomycin^[48].

Daptomycin + Beta-lactams

With beta-lactams active against MRSA (*e.g.* ceftaroline), daptomycin has shown synergistic activity^[49]. In MRSA strains from endocarditis, ceftaroline in addition to daptomycin also cleared daptomycin non-susceptible strains. Daptomycin at 6 mg/kg every 48 h was and ceftaroline at 200 mg every 12 h enhanced bacterial killing^[50]. The finding from this single study demands further careful determination of optimal dosing regimen for effective utilization of active agents like ceftaroline. Another study reported rapid clearance of bacteraemia with addition of high dose nafcillin or oxacillin (2 mg IV every 4 h) to high-dose daptomycin (8-10 mg/d) in 7 cases of vancomycin and daptomycin resistant MRSA^[51]. Though this points to enhanced efficacy of beta-lactams, further evaluation in prospective studies is necessary.

Daptomycin + Linezolid

An *in-vitro* study involving pharmacokinetic/pharmacodynamic model of biofilm for 3 d showed greater activity with combination of daptomycin and linezolid than either agent alone suggesting potential for biofilm associated MRSA infections^[52]. However, there is lack of clinical studies to substantiate the findings of *in-vitro* studies.

Linezolid/Tedizolid + Rifampicin

In combination with rifampicin, time kill studies of linezolid did not show synergism or antagonism but linezolid prevented emergence of mutant resistance in rifampicin^[53]. One major issue with this combination is that rifampicin can reduce the linezolid concentration which can be well below the MIC₉₀ for *Staphylococci* and effect may persist longer than 3 wk even after withdrawal of rifampicin^[54,55]. With tedizolid and rifampicin combination, activity is increased but synergy observed was not found to be universal^[56].

Trimethoprim/Sulfamethoxazole + Rifampicin

Poor efficacy, development of resistance and side effects and drug interactions as mentioned above in their individual discussion, render this regimen redundant.

Triple antibiotic combination

The evidence is very limited for effectiveness and utility of triple drug combinations including beta-lactams, aminoglycosides, and vancomycin, barring isolated case reports^[57].

FUTURE DIRECTIONS

Despite availability of multiple treatment options for MRSA, burden of MRSA remains substantial. While choosing an effective therapeutic strategy, multiple factors play a vital role in antibiotic selection. Development of resistance with anti-MRSA antibiotics has led to the use of antibiotics in combinations. There is no concrete evidence as to decide on specific combination neither there are any comparative data with different combinations. Success of new molecules like ceftaroline, tedizolid, and

plazomicin should stimulate further research and development of new anti-MRSA therapies.

A number of anti-MRSA molecules are in different phases of development. But, to identify truly novel anti-MRSA agent that will act on new targets in the pathogen, there is need to invest further.

CONCLUSION

Current therapeutic management of MRSA is mainly focused on vancomycin and it still remains an effective therapy either alone or in combination. However, development of intermediate level of resistance, MIC creep, adverse effects, and vigilant TDM have been path-blockers for the sole use of vancomycin in MRSA. At present, selecting an individual agent that can provide the best synergy and minimal adverse effects remains the frontline therapeutic option against MRSA. Stimulating and supporting new and ongoing research for development of effective anti-MRSA therapies and implementation of infection control strategies are of urgent necessity. A collaborative action from policy makers, prescribers, and consumers is essential to safeguard the judicious use of newer agents in the management of MRSA infections.

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