Methicillin-resistant *Staphylococcus aureus* in Intensive Care Unit Setting of India: A Review of Clinical Burden, Patterns of Prevalence, Preventive Measures, and Future Strategies

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ABSTRACT

Aim: The aim of this review article is not only to analyze the clinical burden of methicillin-resistant *Staphylococcus aureus* (MRSA) in intensive care unit (ICU) setting of India, along with the patterns of prevalence and its prevention measures, but also to focus on the new anti-MRSA research molecules which are in late stage of clinical development.

Background: Methicillin resistance is reported to be present in 13–47% of *Staphylococcus aureus* infections in India. Therapeutic options to combat MRSA are becoming less, because of emerging resistance to multiple classes of antibiotics. Intensive care units are the harbinger of multidrug-resistant organisms including MRSA and are responsible for its spread within the hospital. The emergence of MRSA in ICUs is associated with poor clinical outcomes, high morbidity, mortality, and escalating treatment costs. There is an urgency to bolster the antibiotic pipeline targeting MRSA. The research efforts for antibiotic development need to match with the pace of emergence of resistance, and new antibiotics are needed to control the impending threat of untreatable MRSA infections.

Review results: Fortunately, several potential antibiotic agents are in the pipeline and the future of MRSA management appears reassuring.

Clinical significance: The authors believe that this knowledge may help form the basis for strategic allocation of current healthcare resources and the future needs.

Keywords: Antibiotic resistance, Hospital-acquired methicillin-resistant *Staphylococcus aureus*, Intensive care unit, Methicillin-resistant *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* carrier, Methicillin-resistant *Staphylococcus aureus* colonization, Methicillin-resistant *Staphylococcus aureus* pipeline, Methicillin-resistant *Staphylococcus aureus* transmission.

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the *Staphylococcus aureus* isolate which is resistant to all currently available β-lactam antibiotics, namely, penicillins, cephalosporins, and carbapenems. The emergence of MRSA is associated with significantly poor clinical outcomes, high morbidity, mortality, and treatment costs.[1] It is becoming increasingly difficult to combat MRSA because of emerging resistance to other antibiotic classes severely limiting the available treatment options. Methicillin-resistant *S. aureus* is increasing at an alarming rate in both hospital and community settings. Hospital-acquired MRSA (HA-MRSA) is a prominent nosocomial pathogen associated with prolonged hospital stay, indwelling percutaneous catheters, dialysis, mechanical ventilation, tracheostomy, and patients who are debilitated, elderly, and immunocompromised.[2] Its remarkable increase in the intensive care units (ICUs) is a cause of concern even in countries where effective infection control measures are routinely implemented. A World Health Organization review revealed that in low- and middle-income countries the frequency of ICU-acquired infection is at least two to three times higher than in high-income countries.[3] In fact, the prevalence rate of MRSA is recognized as a marker for the quality of care and is considered as the benchmark for hospital infection-control practices.[4]

Methicillin-resistant *S. aureus* causes a wide range of infections commonly involving the skin, soft tissue, bone, joints, bloodstream, urinary tract, respiratory tract, surgical wounds,

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and device-associated infections such as indwelling catheters or prosthetic devices. Its range of clinical manifestations include common skin and soft tissue infection (SSTI) boils, carbuncles, impetigo, cellulitis, and wound infections to the more serious manifestations such as ventilator-associated pneumonia, community-acquired pneumonia, necrotizing pneumonia, necrotizing fasciitis, and sepsis.[5] Methicillin-resistant *S. aureus* can thrive for months in a hostile environment and is thereby transmitted from surfaces long after it is initially deposited. A battery of potent virulence factors contribute to the success of *S. aureus* as a pathogen, including its capacity to persist as a commensal, frequently developing resistance to multiple antimicrobial agents and its multiple virulence determinants.[6] It spreads through cross-infection from colonized patient-contaminated environmental surfaces and the colonized healthcare workers (HCWs) who act as reservoirs for the spread of MRSA to other patients, other HCWs, and the community. The major drivers of the emergence of MRSA resistance include the following:[7]

- Wide availability of antibiotics in India
- Inappropriate and irrational antibiotic use
- Ease of purchasing antibiotics in India
- Suboptimal dosage of antibiotics (and discontinuation of antibiotics by patients on resolution of symptoms)
- Inappropriate administration of antibiotics
- Frequent self-medication by patients.

Furthermore, health sector in India is under-resourced, which leads to conditions favorable for perpetuation of drug resistance.

The scope of this literature review article is HA-MRSA, with a focus on the ICU infections. The authors believe that knowledge pertaining to its prevalence, risk factors, and emerging treatment modalities may help form the basis for strategic allocation of the healthcare resources, at present and in the future. The objectives of this review article are as follows:

- To review the clinical burden of MRSA in ICU setting in India
- To understand the patterns of prevalence
- To review knowledge on prevention measure of MRSA in the ICU setting, and
- To gauge the ongoing research aimed at combatting the impending rise of MRSA

Evolution of MRSA

Methicillin was developed in the late 1950s and is a semisynthetic derivative of penicillin. It was developed by modifying the penicillin structure which conferred resistance to penicillinase. The mechanism of methicillin is inhibition of bacterial cell wall synthesis, like other penicillins. Methicillin-resistant *S. aureus* isolates were notified within 1 year of its introduction. Since then, the introduction of other antibiotics has provided a selective pressure for the evolution of new and diverse MRSA clones. In 1968, the United States recorded the first outbreak of MRSA and soon thereafter resistant strains were recovered from other parts of the world. Since 1987, the prevalence of MRSA is reported to have increased close to 25-fold in the ICUs of the United States.

Some theories have been proposed for evolutionary descent and population biology of MRSA. Robinson et al.[8] have postulated that all the major MRSA clones could have evolved from one common ancestor, *S. aureus* phage type 80/81. Kreiswirth et al.[9] proposed a similar theory of single ancestral origin of *S. aureus*

strain that acquired *mecA*, but few other studies[10] have shown that some MRSAs are very divergent, implying that SCC*mec* has been transferred between different *S. aureus* lineages. Enright et al.[11] demonstrated that MRSA clones evolved from five different groups of related genotypes or clonal complexes, each arising from a distinct ancestral genotype. The drug resistance of MRSA still continues to evolve. Historically, this infection was confined only to the healthcare setting, then the community-acquired MRSA emerged, and the current status is that the boundary between hospital-onset and community-acquired MRSA infections has become blurred.

Prevalence of MRSA in the ICUs of India

Methicillin-resistant *S. aureus* is associated with poor clinical outcomes in ICUs. It poses a significant burden on hospital infection control practices. Furthermore, the ICU is a critical place for the wider dissemination of MRSA, since patients are admitted from and discharged to different healthcare settings such as wards and other hospitals. Methicillin resistance is reported to be 13–47% of *S. aureus* infections in India. Patients in an ICU, especially a surgical ICU, have wounds, drains, and invasive monitoring devices that cause skin breach which further increases the risk of developing infections. Additionally, impaired neutrophil properties due to conditions such as chronic liver disease, diabetes, or steroid therapy may render these patients susceptible to MRSA. Furthermore, specific defects associated with granulocyte function, such as decreased chemotaxis and impaired phagocytosis-associated burst activity, have been documented with liver disease and diabetes. Table 1 shows the prevalence of MRSA (as a percentage of all *S. aureus* infections) in ICUs reported by different studies in India. Different rates reported from different regions may be due to varying proportions of underlying condition: for instance, MRSA rates are reportedly higher in oncology patients owing to higher antibiotic usage, differing local infection control practices, and pathogen-specific characteristics of the circulating clones. Table 2 depicts the percentage of MRSA isolates from various clinical specimens reported by studies in India.

MRSA Transmission

The potential agents for MRSA transmission are colonized HCWs and contaminated hand-touch surfaces.[27] The main mode of transmission is through direct contact with discharge, soiled areas, wounds, or physical contact with MRSA-afflicted patients, carriers, and their environment. Factors increasing the chances of transmission are close skin-to-skin contact, breaks in the skin (indwelling catheters or wounds), crowded ICUs, and poor personal hygiene. In the resource-poor settings such as India, MRSA poses a serious threat whereby the associated morbidity and mortality are more than that seen in resource-rich setting of the developed nations. When an infection occurs after a breach of the body's defence of the skin, the pathogen is often endogenous. *Staphylococcus aureus* from a nasal colonization can be transferred to skin and other body areas. Hence, colonization with MRSA often precedes infection by MRSA. The connection between transmission of MRSA from an exogenous source via hands, equipment, and the hospital environment and subsequent endogenous carriage of MRSA is the primary consideration of infection prevention and control consideration for the elimination of MRSA transmission in hospital setting.[28]

Data pertaining to MRSA transmission dynamics continue to be scarce. An Indian study explored the MRSA transmission dynamics

Table 1: Prevalence of MRSA infection in ICUs in India

Serial number	Region	Year	Study design	Sample size	Prevalence (%)	Author
1	Pan India	2008	Retrospective	13,975	43	INSAR Group[12]
2	Pan India	2009	Retrospective	12,335	47	
3	Delhi	2010	Surveillance		43	Wattal et al.[13]
4	Punjab	2012	–	248	20.7	Jindal et al.[14]
5	Punjab	2013		248	13	
6	Bengaluru	2013	Prospective	70	23	Eshwara et al.[15]
7	Chennai	2010	Retrospective		40–50 of all *Staphylococcus aureus* isolates	Gopalakrishnan and Sureshkumar[16]
8	Punjab	2013	Prospective	400	22.5	Datta et al.[17]
9	Tamil Nadu	2006	Retrospective	906	31.1	Rajaduraipandi et al.[18]
10	Mumbai, Delhi, and Bengaluru	1996	Surveillance study	13,610	32	Mehta et al.[19]

MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit

Table 2: Percentage of MRSA isolates from various clinical specimens reported by studies in India

Clinical specimen	Tsering et al.[20] (Sikkim) (n = 827) 2011 (%)	Tiwari et al.[21] (Bhubaneshwar) (n = 204) 2011 (%)	Khan et al.[22] (Lucknow) (n = 350) 2017 (%)	Arora et al.[23] (Punjab) (n = 6,743) 2010 (%)	Pai et al.[24] (Mangaluru) (n = 237) 2010 (%)	Kaur et al.[25] (Pune) (n = 335) 2015 (%)	INSAR study[26] (n = 26,310) 2013 (%)
Pus	27.05	45	24	51.2	27.07	13.56	40
Blood	50	–	4.29	31.6	22.22	5.56	48
Urine	45.83	20.5	43.71	10.8	42.8	5.32	52
Sputum	56.52	–	11.14	0.02	29.4 (respiratory samples)	7.69	41 (respiratory samples)
Throat	41	–	–	–	–	–	–

MRSA, methicillin-resistant *Staphylococcus aureus*

in ICU using mechanistic statistical models. Methicillin-resistant *S. aureus* infection data were collected for 50 months retrospectively. A total of 72 MRSA infections were observed during this study period, corresponding to an average of 1.44 cases/month, and nearly 78% of these infections were nosocomial. Only 4.2% of the patients were MRSA-positive when admitted. The transmission rate was estimated to be 0.094/day using the structured hidden Markov model. Thus, high transmission rates are prevalent in ICUs in India. Another method of measuring transmission is MRSA ICU-acquisition rates, which are calculated as the total number of imported or ICU-acquired cases divided by the total number of ICU admissions over the same time period, respectively. Koessler et al.[29] reported an MRSA acquisition rate of 3.8% during the hospital stay.

Carriage Status among HCWs of India

Healthcare providers working in proximity with MRSA-infected patients are colonized in the course of their work. Methicillin-resistant *S. aureus* colonization is the most important risk factor for subsequent MRSA infection. Furthermore, if MRSA carriage is present at more than one site, then it strongly predicts the development of MRSA infection during ICU admission. Methicillin-resistant *S. aureus* carriage rates among professionally exposed individuals can diminish the efficacy of hospital infection control programs.

Due to the opportunistic nature of *S. aureus*, carriage may evolve into a wide range of infections. Singh et al.[30] reported carriage rates from North India and showed a higher proportion of MRSA carriage among the nurses (73.3%) as compared with laboratory technicians, doctors, and ward attendants, although the difference between these groups was statistically insignificant. This finding is similar to the result reported by Kalyani et al.[31] Furthermore, a study from Northeast India[32] showed that carriage rates were highest from the orthopedics department, followed by those in the surgery and the gynecology departments.

The incidence of nasal carriage among HCWs as reported by various studies from India is enumerated in Table 3. The high carriage rates reported from India reflect the irrational usage of antimicrobials in our community.

Risk Factors for MRSA

Effective control of MRSA infection necessitates a thorough knowledge and analysis of its risk factors. This knowledge can also help guide the empirical antibiotic choices, enhance infection control, prevent delay in prescribing the suitable antibiotic, thereby reducing mortality and morbidity in the ICU. It also prevents overuse of empirical broad-spectrum antibiotics which can perpetuate MRSA and contribute to antibiotic-related complications. Callejo-Torre et al.[37] had reported in a multicenter cohort study of 69,894 patients that the risk factors on ICU admission included male gender, urgent surgery, trauma critical patient, immunosuppression, admitted from other ICUs, hospital ward or long-term facility, and SSTI. However, they also mentioned that clinical and demographic risk factors should not be used to accurately prescribe empirical anti-MRSA treatment.

Table 3: Incidence of nasal carriage among HCWs as reported by various studies from India

Serial number	Region	Year	Sample size	Carriage prevalence (%)	Author
1	Punjab	2017	200	7.5	Singh et al.[30]
2	Assam	2013	315	Males—54.28	Rongpharpi et al.[32]
				Females—45.71	
3	South India	2009	200	1.8	Mathanraj et al.[33]
4	Madurai	2009	100	13	Vinodhkumaradithyaa et al.[34]
5	Manipal	2005	205	22	Shobha et al.[35]
6	Mangaluru	2013	200	2.5	Radhakrishna et al.[36]

HCW, healthcare worker

A dose–effect relationship has been established between the prescription of antimicrobial drugs and MRSA infections.[38] Having said that, the local epidemiology and resistance profile of bacteria causing infections is important while making the choice of empirical antibiotics. Following is the list of risk factors for developing MRSA infections:

- Compromised immune system
- Infants
- Elderly
- Chronically ill
- Burn survivors
- Organ transplant recipients
- Cancer patients receiving chemotherapy agents
- Steroid users
- Diabetic patients
- Intravenous drug users
- HIV
- Length of stay in hospital
- Exposure to antibiotics
- Exposure to people infected with MRSA
- Duration of hospitalization in ICU
- Simultaneous MRSA colonization in another patient in the ICU
- Prior use of antibiotics
- Presence of central line
- Breech in skin continuity and skin lesions
- Smokers
- Illicit drug users
- COPD
- Liver disease
- Patients who had received inpatient antibiotics within the past 3 months.

ANTIBIOTIC RESISTANCE PATTERNS AMONG MRSA IN INDIA

The resistance patterns of prevalent MRSA strains in any setup are liable to continuous changes over a period, owing to changes in antibiotic prescription patterns, infection control measures, and awareness among HCWs. As a result of increasing antibiotic pressure in hospitals, new strains with higher antibiotic resistance emerge and they replace the previous strains. Different patterns of antibiotic resistance have been reported from different regions of India. Table 4 depicts the antibiotic resistance rates (percentage) of MRSA as reported from India.

Arora et al.[23] reported the percentage of multidrug-resistant (MDR) strains among MRSA to be 73%. In the various reports from different parts of India, the burden of such strains ranged from 23.2% to 63.6%.

When linezolid was launched, researchers predicted that resistance would never develop to this molecule owing to its unique mechanism of action (prevention of 50S subunit of prokaryotic ribosome to complex with the 30S initiation complex, thus inhibiting protein synthesis at the initiation step). But Rajaduraipandi et al.[18] reported 2.4% of linezolid-resistant *S. aureus* from South India in 2006. Furthermore, Thool et al.[42] reported a 24% incidence of linezolid resistance in the orthopedic patients (12 of 50 patients), which reflected the nosocomial spread and abuse of this antibiotic. Similarly, multiple studies across India have also reported linezolid resistance among enterococcus.[43] The highly emerging resistance of linezolid is a matter of great concern as it was considered to be the last resort for MDR bacteria. On similar lines, high resistance to vancomycin has been reported from different parts of the country. A study conducted in Northeast India[44] evaluating 827 clinical specimens (including pus, sputum, urine, blood, and throat) screened for MRSA reported high resistance to vancomycin (79.83% resistant) as well as imipenem (64.60% resistant).

D'Souza et al.[45] performed antibiotic susceptibility testing and correlated it with SCC*mec* characterization. They found that of the SCC*mec* III strains, 38% were MDR and the rest were susceptible only to chloramphenicol, rifampin, vancomycin, and linezolid. Among the SCC*mec* IV strains, 83% were susceptible to many antimicrobial classes, and the rest were susceptible to three classes, none of them being MDR. Among the SCC*mec* V strains, 64% were susceptible to many antimicrobial classes, 24% were susceptible to three classes, and 12% were MDR. Furthermore, as community and hospital strains intermingle, there is a growing concern that highly virulent community strains that affect healthy individuals will become less susceptible to antibiotics.

CURRENT THERAPEUTIC APPROACH

Havey et al.[46] identified in their retrospective cohort study ($n = 100$) that infection with *S. aureus* was one of the predictors of prolonged duration of treatment among ICU admitted patients who have bloodstream infections. The virulence determinants of MRSA have continually evolved, and hence the surveillance of clinical and microbiological parameters have become an essential component of infection control practices including the choice of empirical antibiotic. The factors driving the choice of antibiotic in treating MRSA include comorbidities, allergies, local epidemiology, antibiotic susceptibility pattern, safety of antibiotic, and drug interactions.

Antibiotic selection must be based on host, microbiological, and pharmacological factors. Institution-specific data, such as susceptibility patterns and local antibiotic use, also need to be evaluated. The antimicrobial therapy should be individualized based upon culture and sensitivity results.

Table 4: Antibiotic resistance rates of MRSA as reported from various studies in India

Serial number	Antibiotic	Kaur et al.[25] (n = 36)	INSAR study[26] (n = 26,310)	Kali et al.[39] (n = 102)	Saikia et al.[40] (n = 96)	Abbas et al.[26] (n = 143)	Arora et al.[23] (n = 250)	Bhutia et al. (n = 15)
1	Gentamicine	100	58.3	66.1	91.5	46.15	72.2	20
2	Rifampin/ rifampicin	27.78	–	–	–	–	–	0
3	Ceftaroline	0	–	–	–	–	–	–
4	Oxacillin (cefoxitin)	100	–	–	100	–	–	–
5	Ciprofloxacin	100	79.3	80.6	91.5	54.54	67.8	–
6	Moxifloxacin	100	–	–	–	–	–	–
7	Trimethoprim/ sulfamethoxazole	25	55.6	85.4	96.88	32.16	–	100
9	Vancomycin	0	–	–	–	–	–	–
10	Teicoplanin	0	–	–	–	16.08	–	–
11	Telavancin	0	–	–	–	–	–	–
12	Tigecycline	0	–	–	–	–	–	–
13	Clindamycin	97.22	46.6	–	56.25	46.15	–	–
14	Daptomycin	5.56	–	–			–	–
15	Erythromycin	100	70.8	–	81.25	62.93	61.7	33.33
16	Linezolid	2.78	–	–	–	–	–	–
17	Quinupristin/ dalfopristin	5.56	–	–	–	–	–	–

MRSA, methicillin-resistant *Staphylococcus aureus*

Glycopeptides, including vancomycin, are the mainstay of the treatment of MRSA. But evidence suggests toward a phenomenon of higher vancomycin minimum inhibitory concentrations (MICs), also known as "MIC creep." The CLSI recently reduced the cutoff value of vancomycin sensitivity toward MRSA from an MIC of ≤4 to an MIC of ≤2. Thereafter, much data have emerged demonstrating increasing rates of treatment failure and higher mortality among patients treated with vancomycin when MICs are higher, even if those MICs are within the currently accepted range of susceptibility (≤2).[47]

Linezolid, tigecycline, and daptomycin are the other alternatives to vancomycin in the event of adverse reactions or resistance. On the contrary, newer drugs such as tedizolid, telavancin, and dalbavancin, which are being used for the treatment of MRSA infections also possess higher efficacy. However, linezolid resistance has already been reported from India. It is important that treating physicians utilize these options judiciously and de-escalate to β-lactams once the culture sensitivity results reveal a methicillin-sensitive *S. aureus* isolate instead of MRSA. Preservation of glycopeptides and linezolid for use only in MRSA cases should be encouraged. Table 5 mentions various options currently available in India for managing MRSA.

Reviving Research and Boosting the Pipeline[41]

The swift evolution of MRSA has created new challenges for drug development, healthcare systems, and for governments. There is a sense of urgency to augment the existing antibiotic pipeline. The late-stage clinical pipeline for MRSA worldwide includes an array of treatments aimed at acute bacterial skin and skin-structure infections and community-acquired bacterial pneumonia. Few of these are first-in-class agents. The others belong to drug classes such as quinolones, macrolide derivative, and a tetracycline derivative. One such promising pipeline compound is levonadifloxacin, belonging to a novel subclass of quinolone. It

is unique because it is a broad spectrum bactericidal anti-MRSA drug derived from benzoquinolizine fluoroquinolone. It has a differentiated mechanism of action against MRSA. It targets key bacterial enzyme DNA gyrase along with topoisomerase IV leading to high potency even against those MRSA which are levofloxacin and moxifloxacin resistant. It also inhibits a staphylococcal efflux pump Nor A, which causes resistance to quinolones. In this manner, levonadifloxacin overcomes three well-known mechanisms of resistance to quinolones in MRSA, namely, Nor A, mutations in Topo IV, and DNA gyrase. Furthermore, levonadifloxacin is also active against MRSA biofilms . The various investigational drugs in the late phase of clinical development for MRSA are presented in Table 6.[55]

Conclusion

Antimicrobial resistance is a phenomenon inevitably related to microbial evolution and antibiotic use. In this context, the evolutionary success of MRSA has been remarkable. Methicillin-resistant *S. aureus* has been considered the prototype of multiresistant nosocomial pathogens. It is considered a major public health issue worldwide and is associated with considerable morbidity and mortality. In developing countries such as India, it is being increasingly reported in both healthcare and community-associated infections. The prevalence of MRSA is reported to be as high as 13–47% in various regions of India. It tends to fast acquire resistance to the newest antibiotics by virtue of new antibiotic-resistance determinants and new virulence traits. Despite an array of antibiotics, MRSA continues to pose therapeutic dilemma and remains the most feared multiple-antibiotic resistant pathogen in the ICUs. The main reason behind it is that the existing therapeutic options to treat MRSA infections are becoming limited. Resistance to vancomycin and linezolid has already been reported from different parts of India. The research efforts for antibiotic development need to be at par with it. Newer antibiotics are needed to combat the impending threat of untreatable MRSA infections.

Table 5: Therapeutic options for managing MRSA infections

Serial number	Drug name	Drug class	Mechanism of action	Bacteriostatic/ bactericidal	Route of administration	Indications	Major adverse effects
1	Vancomycin	Glycopeptide	Vancomycin inhibits the cross-linking within peptidoglycan layer of bacterial cell wall	Bactericidal (variable)	IV	MRSA, *Staphylococcus endocarditis*, and *Diphtheroid endocarditis*	Infusion-related ana-phylactoid reactions, nephrotoxicity, pseudomembranous colitis, ototoxicity, neutropenia, and phlebitis
2	Linezolid	Oxazolidinone	Inhibits bacterial protein synthesis	Bacteriostatic	IV and oral	SSTI, vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia	Diarrhea, vomiting, headache, nausea, and anemia
3	Tigecycline	Glycylcycline	Bacteriostatic: inhibits protein translation in bacteria by binding to the 30 S ribosomal subunit	Bacteriostatic	IV	Complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections, and community-acquired bacterial pneumonia	Nausea, vomiting, diarrhea, abdominal pain, headache, and increased serum glutamic pyruvic transaminase (SGPT)
4	Teicoplanin	Glycopeptide	Inhibits bacterial cell wall synthesis	Bactericidal	IM or IV	Skin and soft tissue infections, urinary tract infections, lower respiratory tract infections, joint and bone infections, septicemia, endocarditis, and peritonitis related to continuous ambulatory peritoneal dialysis	Local reactions, hypersensitivity, increased transaminases, eosinophilia, thrombocytopenia, increase in serum creatinine, blood urea, renal failure, hearing loss, and tinnitus
5	Daptomycin	Cyclic lipopeptide	Bacterial cell membrane lysis	Bactericidal	IV	cSSSI, *Staphylococcus aureus* bloodstream infections (bacteremia), right-sided infective endocarditis	Diarrhea, headache, dizziness, rash, abnormal liver function tests, elevated creatine phosphokinase (CPK), urinary tract infections, hypotension, and dyspnea
6	Ceftaroline	Cephalosporins	Bactericidal: binds to essential penicillin-binding protein	Bactericidal	IV	ABSSI and CAP	Diarrhea, nausea, rash, vomiting, and pyrexia
7	Ceftobiprole	Cephalosporins	Has high affinity for PBP2a of MRSA	Bactericidal	IV	HAP, VAP, and CAP	Hypersensitivity reactions, *Clostridium difficile*-associated, direct Coombs' test seroconversion
8	Clindamycin	Lincosamide antibiotic	Inhibits bacterial protein synthesis at the level of the 50S ribosome	Bacteriostatic	IV or oral	Skin and skin structure infections, gynecological infections, intra-abdominal infections, septicemia, and bone and joint infections	Pruritus, rash, urticarial, abdominal pain, diarrhea, and esophagitis

MRSA, methicillin-resistant *Staphylococcus aureus*; IV, intravenous; IM, intramuscular; ABSSI, acute bacterial skin and skin structure infections; HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia; VAP, ventilator-associated pneumonia; SSTI, skin and soft tissue infection

Table 6: Various investigational drugs in the late phase of clinical development for MRSA

Molecule	Class	Potential clinical use	Phase of clinical development	Route of administration
Levonadifloxacin[48]	Benzoquinolizine quinolone	ABSSI, DFI, HAP, CAP, and BJI	Phase III	IV/oral
Radezolid[49]	Oxazolidinone	SSTI and CAP	Phase II	Oral
Eravacycline[50]	Tetracycline; synthetic fluorocycline	Intra-abdominal infections and UTI	Phase III IGNITE (investigating Gram-negative infections treated with eravacycline)	IV and oral
Omadacycline[51]	Tetracycline; aminomethylcycline	SSTI and CAP	Phase III	IV and per oral
Lefamulin[52]	Pleuromutilin	SSTI and CAP	Phase III	IV and per oral
Brilacidin[44]	Defensin-mimetic	ABSSSI	Phase II b	IV, per oral and oral rinse for oral mucositis
Debio 1450 Afabicin[53]	Fabl enzyme inhibitor	ABSSSI	Phase II	IV and per oral
CEM-102 Taksta[54]	Fusidic acid	ABSSSI	Phase III	IV and per oral

MRSA, methicillin-resistant *Staphylococcus aureus*; ABSSI, acute bacterial skin and skin structure infections; DFI, diabetic foot infections; HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia; BJI, bone and joint infection; IV, intravenous; SSTI, skin and soft tissue infection; UTI, urinary tract infection; ABSSSI, acute bacterial skin and skin structure infections

Clinical Significance

Several potential antibiotic agents are in the pipeline and, therefore, the future of MRSA management seems reassuring. Furthermore, the hospitals need to implement MRSA surveillance, stricter hand hygiene measures besides developing a strong antibiotic stewardship program which includes development of antibiotic policies based on local microorganism flora and the sensitivity patterns, prescription audit, and pharmacovigilance.

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