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Healthcare Setting and Methicillin Resistant *Staphylococcus aureus*

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection remains the ever-increasing health care problem. It brings a high rate of morbidity and mortality especially in immunocompromised and hospitalised patients. MRSA infection is most often severe due to the expression of virulence factors, toxins, and immune-modulatory gene products along with limited options for its treatment. MRSA in the healthcare settings is an emerging challenge. Exposure of healthcare personnel to the MRSA environment puts them at increased risk of acquiring the infection. Given the limited options for treatments, there is a need to cautious use the current treatments and quest for research and development of new anti-MRSA agents. For the prevention of MRSA infection in healthcare personnel, adequate implementation of infection and prevention strategies is essential in all healthcare settings. In this article, we discussed the epidemiology of MRSA, current and emerging treatment options along with infection control strategies in the healthcare settings.

Key Words: MRSA, MSSA, Antibiotic resistance, Treatment, Prevention, Epidemiology

INTRODUCTION

For many decades, *Staphylococci* are known to be involved in human disease. They were first isolated as causative pathogens of incurable boils. Two scientists namely, Sir Alexander Ogsto and Friedrich J. Rosenbach, contributed to the nomenclature of *Staphylococci*[1]. *S. aureus* has since evolved as a major infectious pathogen. It is severely detrimental to the health of millions of patients. The emergence of penicillin resistance was reported in 1942 and was due to inducible beta-lactamase. Methicillin first used in 1959, and the methicillin-resistant *S. aureus* (MRSA) was reported within two years of its approval[2]. MRSA is present globally and its burden in middle-income countries like India is especially high with a recent study reporting it high as 41%[3]. MRSA is reported from hospital- as well as community-setting. A recent study from south India reported a prevalence of 20% and 7% being hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA)[4]. In evaluating HCPs, a study from United Kingdom reported that among 198 healthcare workers (HCWs), 37% were *S. aureus* nasal carriers and 4% among them carried MRSA[5]. A meta-analysis of 31 studies reported a pooled MRSA colonization rate of 1.8% with the highest colonization rate for nursing staff (6.9%)[6]. It indicates HCP is at risk of MRSA colonization. HA-MRSA is also associated with an increased risk of mortality and poor prognosis of the patients[7,8]. Therefore, adequate control of MRSA in a healthcare setting is necessary to optimize patient outcomes and reduce exposure risk and colonization among HCPs.

EPIDEMIOLOGY OF MRSA

MRSA is prevalent globally. However, prevalence varies widely within different countries. The study from Europe reported MRSA incidence of 0.5% in Iceland and 44% in Greece[9]. The Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group reported MRSA prevalence of 41%. MRSA isolated from outpatients, ward inpatients, and intensive care unit (ICU) were 28%, 42% and 43% in 2008 and 27%, 49% and 47% in 2009 [3]. In a study by Kaiser et al., the incidence of HA-MRSA was 9% in patients with burns[10]. Another study from Saudi Arabia reported MRSA

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prevalence of 38% [11]. A study from Iraq in hospital staff observed 50.4% *mecA* gene positivity among the isolates of MRSA [12]. On hospital admission, a meta-analysis finds that factors such as healthcare contact, previous healthcare-associated pathogens, and comorbid conditions such as congestive heart failure, diabetes, are associated with MRSA colonization[13]. Thus, early identification of MRSA isolates is essential to prevent adverse outcomes.

LABORATORY METHODS FOR DIAGNOSIS OF MRSA

The present study was conducted in the Dept. of Microbiology at Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi, Wardha in collaboration with Datta Meghe Medical College, Nagpur. Various methods for methicillin (oxacillin) susceptibility testing include the following[14-17].

- Dilution methods: Agar dilution and broth microdilution
- Etest method
- Breakpoint methods
- Agar screening method
- Disc diffusion
- Latex agglutination
- Automated methods: Vitek/Vitek2 (bioMe´rieux), Phoenix (Becton Dickinson) and Microscan (Dade Behring)
- Quenching fluorescence method
- Molecular methods
    - Direct identification of MRSA in blood cultures
        - gel-based and real-time PCR
        - DNA probes
        - Peptide nucleic acid probe
        - EVIGENE kit: colorimetric gene probe hybridization assay for staphylococcus-specific 16S rRNA, *mecA* and *nuc* gene sequences
    - Identification of MRSA in endotracheal aspirates and other clinical samples
        - multiplex PCR procedure (targeting the *femA* and *mecA* genes)

In addition to conventional culture, molecular methods for direct identification of MRSA are being used more commonly. The majority of PCR-methods approved by the USFDA are equivalent. Their sensitivities and specificities range from 82 to 100% and 64 to 99%, respectively[15]. The list of currently approved PCR assays for MRSA detection is as below.

- BD GeneOhm MRSA ACP for nares
- BD Gene Ohm Staph SR for positive blood cultures
- Xpert MRSA Cepheid for nares
- Xpert SA Nasal Complete for nares
- Xpert MRSA/SA SSTI for skin and soft tissue infections
- Xpert MRSA/SA BC for positive blood cultures
- Light Cycler MRSA for nares

The use of molecular methods has the advantage of high sensitivity and rapid turnaround time. However, conventional culture methods can provide information on sensitivities. Pourmand et al. compared four different methods in the detection of MRSA. Rates of identification of MRSA was 50%, 50%, 40%, and 45.83% in mecA gene detection, cefoxitin disc diffusion test, oxacillin disc diffusion test, and MIC test strip, respectively. [17]

TREATMENTS OF MRSA

MRSA is associated with a wide variety of infections. Some infections such as bacteraemia, endocarditis, osteomyelitis are serious MRSA infections[19]. The frequency of each type of infection may vary in a hospital setting. In patients with MRSA infection, Madani TA identified surgical site infection (31.1%) as the most common type followed by pneumonia (27%), central venous catheter infection (13.5%), peripheral venous line infection (6.8%), and bacteraemia in 27% cases[11]. The (INSAR) group reported the isolation of MRSA most commonly from the skin and soft tissue infection (64% in 2008 and 61% in 2009) followed by blood (44% in 2008 and 48% in 2009) and respiratory (44% in 2008 and 41% in 2009) samples[3]. A study from South Western India reported among 284 cases with confirmed MRSA, 65% were healthcare-associated MRSA[20]. Given the significant prevalence of MRSA in hospital setting, it needs to be managed effectively.

The Infectious Disease Society of America (IDSA) provides recommendations for treatment of different MRSA infections. The initial choice of antibiotics is summarized in Table 1 [21]. It is quite clear from this table that vancomycin is the first choice in most MRSA infections. Along with vancomycin, linezolid, daptomycin, and clindamycin are also preferred agents. However, the emergence of resistance to these agents calls for their cautious use. The emergence of multidrug-resistant (MDR) MRSA with resistance to linezolid, tigecycline, and vancomycin has also been reported from India[22].

Table 1: Initial treatment options for MRSA infections

MRSA infection	Recommended treatments [21]
Skin and skin structure infections (SSTIs)	Clindamycin, TMP-SMX, Doxycycline/ Minocycline, Linezolid (1-2 weeks)
Complicates SSTIs	Vancomycin, Linezolid, Daptomycin, Telavancin, Clindamycin (1-2 weeks)
Bacteraemia	Vancomycin, Daptomycin (2 weeks)

Table 1: *(Continued)*

MRSA infection	Recommended treatments [21]
Complicated bacteraemia	Vancomycin, Daptomycin (4-6 weeks)
Infective endocarditis	
Native valve	Vancomycin, Daptomycin (6 weeks)
Prosthetic valve	Vancomycin + Rifampicin (6 weeks) followed by Gentamicin (2 weeks)
Pneumonia: Hospital- or community-acquired	Vancomycin, Linezolid, Clindamycin, (1-3 weeks)
Bone and Joint Infections	
Osteomyelitis	Vancomycin, Daptomycin, TMP-SMX + Rifampicin, Linezolid, Clindamycin (8 weeks)
Septic arthritis	Vancomycin, Daptomycin, TMP-SMX + Rifampicin, Linezolid, Clindamycin (3-4 weeks)
Device related	[Vancomycin, Daptomycin, Linezolid, Clindamycin] + Rifampicin (2 week) followed by Rifampicin + [FQ, TMP-SMX, Tetracycline, Clindamycin] (3-6 months)
Central Nervous System Infections	
Meningitis	Vancomycinwith or without Rifampicin (2 weeks), Linezolid, TMP-SMX
Brain or Spinal epidural abscess	Vancomycin with or without Rifampicin (4-6 weeks) Linezolid, TMP-SMX
Septic thrombosis of sinus (dual venous/cavernous)	Vancomycin with or without Rifampicin (4-6 weeks) Linezolid, TMP-SMX

Besides the development of resistance, these initial treatments have certain limitations. Kashyap et al. in their in-depth review provide the limitation of current anti-MRSA agents[23]. Notably, nephrotoxicity, MIC creep phenomenon, variable tissue penetration are reported with vancomycin. Additionally, the risk of red man syndrome is associated with rapid intravenous vancomycin use. With daptomycin, there is a risk of cross-resistance with heteroresistant vancomycin intermediate resistant *S. aureus* (hVISA). It is deactivated by the pulmonary surfactant making it unsuitable for pulmonary MRSA infections. Use of linezolid has risk serious side effects such as thrombocytopenia, optic neuropathy, etc. In India, it has specific limitations as it is one of the drugs in the MDR tuberculosis regimen. Use of trimethoprim-sulfamethoxazole, tetracyclines, and clindamycin are limited by the development of significant resistance[23]. Thus, there is needs to identify newer agents that can be effective in the management of MRSA. Appropriate therapy in MRSA is essential to reduce the mortality outcomes. Paul et al. reported significantly higher mortality at day 30 with inappropriate antibiotic therapy (49.1% vs. 33.3%, p=0.001)in HA-MRSA bacteremia[24]. Thus, newer agents when appropriately used can be effective against the MRSA to improve the outcomes. Table 2 enlists some of the recent anti-MRSA drugs.

Table 2: Recent approved and investigational drugs against MRSA[25-32]

Group	Drug name
Oxazolidinedione	Tedizolid, Radezolid and Delpazolid
Lipoglycopeptide	Oritavancin and Dalbavancin
Cephalosporins	Ceftaroline and Ceftobiprole
Quinolone	Delafloxacin, Levonadifloxacin, Gepotidacin and Lascufloxacin
Peptidomimetic	Brilacidin

Among the various drug in this class, tedizolid is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults[25]. Radezolid and Delpazolid are currently under investigation[26].

Oritavancin and dalbavancin are the lipoglycopeptide antibiotics that are approved for use in ABSSSI in adults. Dalbavancin has potential utility in MDR-MRSA isolates[27].

Both Ceftaroline and Ceftobiprole offer not only Gram-negative but also Gram-positive coverage and are active against MRSA. Ceftaroline is approved for use in ABSSSI and community-acquired bacterial pneumonia (CABP). Ceftobiprole is active against VISA, and vancomycin-resistant *S. aureus* (VRSA) isolates[28,29].

Delafloxacin is a quinolone recently approved by the US-FDA for the treatment of ABSSSI caused by MRSA[30]. Levonadifloxacin is a novel, benzoquinolizine subclass of quinolone having potent anti-MRSA activity that was recently approved in India for treatment of ABSSSI caused by MRSA[31]. Lascufloxacin was approved in Japan for respiratory and ENT infections[32].

Brilacidin is a peptidomimetic antibiotic. It mimics naturally occurring proteins and has strong activity against MDR MRSA isolates. It is under evaluation for use in ABSSSI and serious skin infections[26].

MRSA infection control and preventive strategies

In a healthcare facility, hand contamination is one of the predominant modes of bacterial pathogen transfer. In taking of patients with MRSA infection, healthcare personnel are at increased risk of harbouring infections. MRSA has been isolated from hands, gloves, aprons, and other instruments that healthcare staff utilized in the care of such patients. Furthermore, MRSA were isolated from the keyboards of com-

puters used by the doctors [33]. Since MRSA is increasing in incidences at a rapid rate it can be better controlled by understanding its colonization dynamics risk factors for progression of colonization dynamics, routes of transmission, and conditions which enhances the emergence of resistance [34]. For effective control and prevention of MRSA in hospitals, recommended strategies are briefly discussed.

Standard precautions such as hand hygiene should be practiced after examining every patient. The use of gloves is not a replacement for hand washing.

Contact precautions need to be practiced in all patients where MRSA colonization is suspected or confirmed. In asymptomatic patients who serve as MRSA reservoirs, rapid detection tests should be undertaken to identify MRSA to reduce contact transmission.

Active surveillance cultures to identify MRSA carriers at the time of hospital admission (carriers) and periodic screening of admitted patients (cases) need to be undertaken to detect for colonization of MRSA. Studies indicate that without active surveillance, MRSA prevalence can increase gradually in a healthcare setting[35,36]. Nasal swab is the most effective sample with a negative predictive value of 98% [37]. Besides culture, PCR can be a point of care testing method for the screening of MRSA with the advantage of the lesser time for results[38]. Recent studies identify 7-fold higher rates of MRSA colonization in hospitalized patients than community population[39]. It indicates the active surveillance of hospitalized patients for MRSA colonization is necessary. Besides patients, active surveillance of HCWs is necessary as they have been identified as carriers of MRSA[40-42]. Surveillance need to be prioritized in HCWs and those working in high-risk areas should be screened. One problem with the screening of HCWs is that majority of them do not have persistent colonization [43].

Decolonization with *t*opical antimicrobial or antiseptic for suppression and eradication of MRSA from the colonized person is necessary, especially, in persistent MRSA carriers. This will help the establishment of infection in a colonized person, as well as help, prevent the transmission to others. Further research is required to determine the effectiveness of decolonization in reducing MRSA transmission in a hospital setting [44].

Evidence indicates the disinfection of environmental surfaces and education of the service staff reduces the MRSA contamination [45].

Controlling the antibiotic use is another strategy to reduce MRSA infection. Controlling antibiotic use helped to reduce the development of antibiotic resistance. Limiting unnecessary and optimizing efficient antibiotic use should be the usual approach. Good antibiotic stewardship can help establish rational antibiotic use. In recent years, better control of MRSA by involving the number of small molecule potentiators for antibiotics has been proposed. These small molecule potentiators are not actually bactericidal by themselves but function by reversing the resistance mechanisms, interfering with quorum sensing activity, and able to attenuate *Staphylococcus aureus* virulence[46].

CONCLUSION

In a hunt for controlling MRSA, humans have developed a number of diagnoses and preventive techniques but still, MRSA remained dominant in pathogenicity.

Research in the field of diagnosis certainly has reduced the challenge of detection of MRSA and that provides a small window of better treatment by early control of MRSA. With the range of antibiotics such as vancomycin in recent time, new antibiotics therapies also become available which can provide effective alternatives for strains that have acquired resistance to acting drugs. Nevertheless, need always remain alive in terms of vigilance and effective MRSA prevention strategies by regular monitoring and hygiene concepts which will assist in handling the challenge of MRSA with better treatment.

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