Review Article

Recent developments in methicillin-resistant *Staphylococcus aureus* (MRSA) management and potential antimicrobial alternatives to combat the antibiotic resistance challenge: A review

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Abstract

The global emergence of Methicillin-resistant *Staphylococcus aureus* (MRSA) strains is causing a serious increase in mortality and morbidity rates both in hospitals and in community settings. The high incidence of MRSA associated bacteremia can potentially cause infective endocarditis, septic arthritis, osteomyelitis and complications such as septic shock which are becoming a high challenge for clinicians to treat. The multi-resistance acquisition of MRSA against currently available antibiotics has significantly reduced their efficacy against related infections. To overcome this global health concern of the rapidly spreading antibiotic-resistance phenomenon among bacterial pathogens, particularly MRSA, implementation of effective management strategies and the need for rapid identification and practical application of potential antimicrobial alternatives has become crucial. Herein, we have provided a brief description of potential antimicrobial alternatives i.e., phytochemicals from plant extracts, bacteriocins, antimicrobial peptides, bacteriophage therapy, nanoparticles and some other approaches that can be used as monotherapy or in combination with currently effective antibiotics to combat MRSA infections. An overview of MRSA infections and developments in MRSA management has also been presented in the initial section of this review.

Keywords: Antibiotic-resistance; Antimicrobial alternatives; Bacteremia; Nosocomial infections; Phytochemicals, *Staphylococcus aureus*

Introduction

Staphylococcus aureus is a leading nosocomial Gram-positive bacterium and responsible for several infectious diseases such as bacteremia, pneumonia, endocarditis, skin infections, and food poisoning [1]. Originally, *Staphylococcus aureus* (*S. aureus*) was thought to be a major nosocomial pathogen but

epidemiologically different clones have also been identified in community settings [2].

S. aureus has developed resistance against multiple antibiotics which makes this bacterium a challenging pathogen to treat [3]. Therefore, *S. aureus* is termed methicillin-resistant *Staphylococcus aureus* (MRSA) which is highly resistant to

methicillin and causes high morbidity, high mortality rate, and expensive treatment approaches [4]. Vancomycin was a standard drug to treat MRSA for years but bacteria also have developed resistance against it and restricted its clinical efficacy [5].

Nosocomial infections present a serious threat to patients globally. The decision and timing of antibacterial treatment extraordinarily influence treatment results in MRSA [6]. For *S. aureus* infection, β -lactam treatment is viewed as the highest quality standard to treat infection [7]. The 2011 Infectious Diseases Society of America rules suggest treatment with vancomycin or daptomycin for MRSA [8]. Nonetheless, every antimicrobial formulation has restrictions [9]. Many cases reported that the utility of vancomycin possesses slow bactericidal activity, low tissue penetration, and increasing findings related to resistance and failure [10]. Although, Daptomycin was found to be effective against MRSA bacteremia treatment-emergent non-susceptibility is concerning and experimental evidence showed that prior vancomycin treatment may facilitate daptomycin resistance in *S. aureus* [11]. Given the significant morbidity and mortality related to MRSA and the limits of presently affirmed treatments, there is a need to explore different approaches and agents for the treatment of MRSA bacteremia [12]. Time to efficacious treatment is to a great extent reliant on the identification of the pathogen. Delays in the identification of pathogen lead to ineffective clinical results [13]. Standard microbial recognition procedures take somewhere in the range of 48 and 72 hours, while advanced methods which have been developed recently give fast results within 3 hours of sample collection [14]. By adopting advanced identification techniques, optimized antibacterial therapy, fast diagnostic procedures may bring down mortality, hospitalization, and expenses.

Prevalence

The predominance of MRSA infections, particularly bacteremia, varies around the globe. In 2014, the population-weighted mean of Europe was 17.4% in Netherlands and Romania, and the percentages of invasive MRSA isolates were from 0.4% in the Netherlands to 56% in Romania. A high proportion of resistant isolates of MRSA prevail in southern countries in the Europe region. Invasive *S. aureus* isolates of MRSA in Europe have decreased over time but 7 of the 29 European Union countries still report more than 25% of MRSA isolates [13].

An analysis of 15 studies reports that in the range of 13 to 74% of global *S. aureus* infections are MRSA [17]. Publications and national surveillance data from the countries of South and East Asia and the Western Pacific identify *S. aureus* as an important pathogen, with MRSA infections ranging from 2.3 to 69% [18]. In 2005, a survey conducted in the US reported that the rate of invasive MRSA infections was 31.8 per 100,000 individuals after adjustment for gender, age, and race, and from this data, it was deduced that 75% of these MRSA infections involved *S. aureus* bacteremia [19]. The percentage of rate of MRSA bacteremia is higher than the rate of MRSA bacteremia in Canada, where from 2000 to 2004 the rate of infection was 2.1, 3.6, and 1.6 per 100,000 individuals for Calgary, Sherbrook, and Victoria [20]. In Europe, from 2011-2012, 12.3% of all healthcare-associated infections were due to *S. aureus*. More than 60% of healthcare-associated infections were caused by *S. aureus* in Italy, Cyprus, Romania, and Portugal [21].

The source of MRSA infections-hospital acquired, community-acquired, or healthcare-associated community-onset-has been evolving. The rate of invasive MRSA cases in the US has been going down (Fig. 1) [21, 22], with healthcare-associated community onset-infections currently being the major cause of MRSA infections. Patients with healthcare-

associated community-onset MRSA infections often have complications, for example, diabetes, decubitus, ulcers, renal sickness, earlier stroke, or dementia [23]. Information from Canada, Australia, and Scandinavia show an increase in the percentage of MRSA bacteremia in the years 2000 to 2008, principally brought about by an increment in community-acquired infections. In Pakistan, staphylococcal infections are identified and most of them are resistant

infections (MRSA). In one study, a total of 350 staphylococcal clinical specimens were obtained out of which 194 were found out to be methicillin-resistant *Staphylococcal aureus* (MRSA) infections [24]. In one more study, 280 clinical specimens of *S. aureus* were taken out of which 36% were identified as MRSA. *S. aureus* infection was more prevalent among 50-59 years age group patients (Table 1) [25].

Figure 1. The public assessed number of MRSA related infections in the United States (US), separated by disease setting. Adjusted from information revealed by the Center for Disease Control and Prevention [21]

Table 1. Studies of clinical specimens of MRSA in Pakistan

Study	Location	Specimens analyzed	Specimens proved to be MRSA	References
1	Rawalpindi	350	55%	[24]
2	Peshawar	280	36%	[25]

Infections caused by *Staphylococcus aureus*

Staphylococcus aureus infects the skin, soft tissue, respiratory tract, bones, joints, and endovascular system [26]. The debate

beneath is restricted to perilous staphylococcal infections. Most of these infections happen in people with various peril factors for infection. A more definite debate on the clinical signs of

staphylococcal infections can be found in a few late reports [27].

Bacteremia

Staphylococcal bacteremia cause 11 to 43% deaths [28]. Several factors are associated with increased mortality including the age of more than 50 years, eradicable foci of infection, and life-threatening underlying respiratory, cardiac, and neurologic disease. Methicillin-resistant strains causing bacteremia are not associated with an increased death rate. The change in the Acute Physiology and Persistent Health Evaluation (APACHE) score from the day preceding to the day of *S. aureus* bacteremia was as of late found to foresee the clinical course and outcome [29]. Staphylococcal bacteremia causes a high frequency of complications, ranging from 11 to 53%. Patients with bacteremia who do not have endocarditis can develop metastatic infection [30].

Catheterization is associated with an increased level of staphylococcal bacteremia [31]. The frequency of complications is lower for catheter-related infections than for all other causes of bacteremia (24%), similar to the general death rate (15%) [32]. Patients with bacteremia or fever that endures for more than 72 hours after the catheter has been taken out may have a high level of complications [33]. The rate of endocarditis in patients with catheters, assessed based on clinical signs, is likewise low, extending from 0 to 18%. Some examinations, in any case, propose that the occurrence of endocarditis might be higher. Twenty-five percent of chose patients with staphylococcal bacteremia (26 of 103) and 23% of those with catheters as the essential center had trans-esophageal echocardiographic proof of endocarditis without clinical or transthoracic echocardiographic findings [34, 35].

Endocarditis

S. aureus endocarditis has increased with time and now 25 to 35% of patients get infected by it [36]. People which take intravenous drugs, aged patients, and

hospitalized patients with prosthetic valves are at high risk to contract *S. aureus* endocarditis. In all three groups, the initial symptoms are only limited to malaise and fever, which make diagnosis difficult. Usually, endocarditis is not much fatal disease but *S. aureus* endocarditis cause rapid onset of high fever involves cardiac valves and the loss of physical stigmata [37]. In one study, 13% of patients with febrile intravenous drug users were admitted to an emergency room and the diagnosis could not be done based on available laboratory data [38].

Intravenous drug users have right-sided endocarditis and the patients are young and the death rate among them is very low. Intravenous drug users with Human Immunodeficiency Virus (HIV) infection have a poor prognosis as compared to patients without HIV infection [39]. Patients who do not use drugs have left-sided endocarditis and these patients are old and the mortality rate is high among them [40]. A study states that embolic and neurologic complications are common in left-sided *S. aureus* endocarditis.

aureus is quite possibly the most well-known pathogen in nosocomial and prosthetic-valve endocarditis, and intravascular catheters are the most regular source of bacterial inoculation. The death rate for nosocomial endocarditis, paying little mind to the microbe, is 40 to 56%, and the rate is considerably higher when the microbe is *S. aureus* [41]. In a large number of these cases, the conclusion is clouded by different conditions or the administration of anti-microbials. Prosthetic-valve endocarditis, particularly in the early postoperative period, is frequently fulminant and is portrayed by the formation of myocardial abscesses and the development of valvular scarcity. Forty-three percent frequency of endocarditis in patients with prosthetic valves who had nosocomial bacteremia, the most involved bacterium was *S. aureus* [42].

Metastatic infections

Staphylococcus aureus tends to spread to specific locations, including the bones, joints, kidneys, and lungs. Suppurative samples collected from these locations of infections are the source of potential foci for repetitive infections. Patients who have constant fever conditions even after taking proper treatment should be evaluated for the presence of suppurative locations in the body.

Sepsis

Few bacteremic or local infections can lead to sepsis. Old age, immunosuppression, chemotherapy, and invasive clinical procedures are the risk factors for sepsis. Staphylococcal sepsis includes fever, hypotension, tachypnea, and tachycardia. *S. aureus* is a gram-positive pathogen and it is the most common one in the cases of sepsis [43]. If the sepsis leads to a severe condition then infection can progress to dysfunctioning of many organs, intravascular coagulation, lactic acidosis, and ultimately death [43]. In both gram-positive and gram-negative sepsis, the

degrees of flowing tumor necrosis factor-alpha, interleukin-1, as well as, interleukin-6 are prescient of the outcome [44].

Toxic shock syndrome

Several cases of staphylococcal toxic shock syndrome were reported from 1980 to 1981 due to the use of superabsorbent tampons during menstruation. The disease is characterized by a sudden onset, frequently in formerly healthy persons. Staphylococcal toxic shock syndrome includes multiorgan damage, hypotension, high fever, and erythematous rash. The toxic shock syndrome develops from a site of colonization as opposed to infection [45]. 90% of cases are related to menstruation but 50% of cases are unrelated to menstruation (Table 2). One-third of total cases are nonmenstrual and also these cases are increasing. These nonmenstrual cases are associated with localized infections, surgery, or insect bites. Patients with nonmenstrual toxic shock syndrome have a higher death rate than those with menstrual toxic shock syndrome [46].

Table 2. Comparison of rate of infection, mortality rate and signs and symptoms of *S. aureus* infections

Infections	Incidence of infection	Mortality rate	Signs and symptoms	References
Bacteremia	11-53%	11-43%	Fever, skin rashes and fast heart rate	[30]
Endocarditis	25-35%	>40-56%	Malaise, fever and loss of physical stigmata	[37]
Metastatic infections	11-53%	11-43%	As for bacteremia	[30]
Sepsis	20-25%	10-30%	Fever, hypotension, tachypnea and tachycardia	[43]
Toxic shock syndrome	39%	3-5%	Multi organ damage, hypotension, high fever, erythematous rash	[45]

Development of antibiotic resistance in MRSA

Methicillin is known to put forth its antimicrobial activity by preventing the cross-linking of peptidoglycan via inhibition of transpeptidase enzyme's activity. It does so, by first binding with cell-wall's Penicillin binding proteins

(PBPs) [47]. However, MRSA has adopted ways to prevent itself from methicillin's lethal action, MRSA strains are now identified based upon their acquisition of *mecA* gene which is present on staphylococcal cassette chromosome *mec* (SCC*mec*). This *mecA* gene is responsible for expression PBP2 homolog protein

known as PBP2a or PBP2'. At least 6 different types of *mecA* gene have been reported [48, 49]. SCCmec region is incorporated into the *S. aureus* chromosome at a specific position (*attBsc*), located nearby *orfX* region (near the origin of replication) [50]. Based upon the type of SCCmec, this DNA fragment can range in size from 21-67Kb [49]. There is a constant rapid increase in discovery of new types of SCCmec region in MRSA chromosome, currently 11 types have been found. Surprisingly, all types contain low-affinity (for beta-lactams) possessing PBP2a gene, *mecA*.

Expression of *mecA* gene is generally inducible and regulated by *mecI*, *mecRI* and other genes like *blaI*, *blaRI*, *femB*, *aux* [51]. The *mecA* gene encoded PBP2a has low affinity for β -lactams due placement of its active site in a deep location not accessed by methicillin and other β -lactams antibiotics as a result of this, resistance is attained against Methicillin [52]. A pictorial representation of mechanism of *mecA* gene activation is shown (Fig. 2). SCCmec DNA region is also found to contain *ccr* genes that are responsible for amalgamation and excision from the chromosome and aid in mobility of element [49, 50]. Other regions of SCCmec may vary depending upon the particular type, but some of them contain additional resistant genes against other antibiotics [52]. In a novel research finding this region is also found to harbor virulent

gene, *Psm-mec*, that encodes peptide toxin and is located in close proximity to *mecA* gene in different SCCmec types [53]. From a drug-discovery perspective it is logical to synthesize alternatives (small molecule-inhibitors) that work in synergy with β -lactams for particularly targeting *mecA* and associated *fer* (factors essential for the expression of methicillin-resistance) genes expression. One such report regarding efficiency of synthetic tripeptide, LY301621 have also appeared in which it is found to potentiate the activity of methicillin against MRSA strain [54].

Recent developments in MRSA management

MRSA infections are frequently prevailing in our societies affecting and killing many people of different age groups worldwide. Most of the infections which are a risk to the community are blood infections (bacteremia) which is a more threatening and more lethal condition. Since MRSA infections are more frequent in old people so there is a need to control infection by efficient management in the community as well as in hospitals for that old people are more susceptible to infections due to their weak immunological state. Efficient management in hospitals includes effective measures to prevent contact transmission of infections, rapid and effective methods to diagnose and detect infections, and to treat infections by antimicrobial alternatives to combat resistance issues as shown in the below flow chart (Fig. 3).

Figure 2. Schematic overview of regulation of *mecA* gene in MRSA. a) In absence of β lactams *mec* operator is inactivated by binding of repressor protein *mecI* to its promotor site. b) β -Lactams are detected in external environment by their binding to the penicillin-binding domain (PBD) of *MecR1* Protein. c) This binding triggers the activation of the intracellular metalloproteinase domain (MPD) (L3) of *MecR1* protein. Whether this activation directly lead to proteolytic degradation of *MecI* repressor protein is unclear. d) B-lactams induced disruption of cell-wall biosynthesis leads to formation of cell-wall fragments in cytoplasm that act as co-activator and disrupt association of *mecI* repressor protein with *mec* operator and performs its proteolytic degradation. e) B-lactams also induce transcription of *mecR2* gene that form another repressor protein *MecR2*, that also binds to *Mec I*, leading to its proteolysis. f) Ultimately, through proteolytic activities of these three degradation mechanisms, *MecI* induces transcription of *mecA*, that causes PBP2a production (having lower affinity for β -lactams), hence the expression of methicillin resistance is executed

Figure 3. Management system for effective control of MRSA related infections

Advancements in detection and diagnosis methods

Identification of causative agents for infections can be very difficult and challenging when the strains involved are resistant as in the cases of MRSA. Old cultural techniques and susceptibility testing methods are too much time-consuming and take between 48 and 72 hours to conclude a decision [16]. The time to detect MRSA has been greatly reduced by the development of advanced molecular and nonmolecular testing approaches [16]. These techniques are rapid and effective to

control infections and decrease costs. Rapid tests for MRSA are low cost and reduce the length of stay of the patient in the hospital. In this way, identification can happen rapidly and the switch from empiric to targeted therapy can be 1.6 days shorter. Rapid molecular tests for diagnosis can also reduce the rate of mortality among patients with bacteremia [55]. Rapid molecular testing and antibiotic management program should be collaborated to further decrease the risk of mortality [55]. There should be a proper management system [15] in every hospital to consider the factors like

specificity, sensitivity, price, turnaround time, and proficiency needed for each test [56]. The (Table 3) presents a comparison of tests that can be used to detect and diagnose MRSA more efficiently and rapidly.

Chromogenic media tests

Advancement to the old cultural techniques is the use of chromogenic agar, which involves the production of color in bacterial cultures [16]. Chromogenic media involves the use of antibiotics which only allow the resistant bacteria to grow and flourish [16]. By this method, MRSA can be detected within 20 to 26 hours. A series of experiments showed that the sensitivity of the test was 78.3% after 18 to 24 hours and it was increased after 48 hours, specificity of the test was 97% at 18 to 24 hours and it was decreased by 94% after 48 hours. Both sensitivity and specificity factors of the test were higher than the traditional culture methods. Chromogenic media test has also reduced the time by 12 hours to treat MRSA [57].

Real time polymerase chain reaction (PCR)

Another important molecular technique in the detection of MRSA is the real-time polymerase chain reaction (PCR) test. PCR test can detect genes that are specific to *S. aureus* [16]. PCR test targets a portion of DNA where the SCCmec gene responsible for MRSA meets the *S. aureus* orfX gene [16]. Samples for PCR test can be taken from blood or a nasal or wound swab and the test can be performed directly on these samples giving the results within only 1 to 3 hours [16]. Although the PCR test is very rapid as compared to other tests but time is required to transport samples, perform the test and deduce the results [58]. Nevertheless, the overall time required to

run the PCR test is much shorter as compared to the chromogenic media test [58]. The sensitivity and specificity for PCR are 92.5% and 97%, respectively [56]. The sensitivity of PCR is significantly higher than that of the chromogenic media test, and specificity is significantly higher than that of old cultural methods [56].

Immunochromatographic test

The immunochromatographic test is another detection approach for MRSA. In this test, antibodies that are specific for bacterial proteins, bind to these proteins and produce color in the test medium. An example of an immunochromatographic test is the latex agglutination test. This test involves the use of a monoclonal antibody against a protein (PBP2a) produced by the *mecA* gene [59]. Firstly, the latex particles are sensitized by the antibody and then they are allowed to react with PBP2a and they clump together showing agglutination [16]. The sensitivity and specificity for this test are 97% and 100%, respectively [60]. Another PBP2a antibody test showing 97% sensitivity and 100% specificity [60], includes fewer steps than the latex agglutination test [61]. This test takes under 6 minutes to complete, and results show up as hued lines on test strips [61].

BinaxNOW *Staphylococcal aureus* test

The BinaxNOW *Staphylococcus aureus* Test detects *S. aureus* and helps to escape from false-positive results. The time required for this test is less than 30 minutes, sensitivity is 95.8% and specificity is 99.6%. This test is not specific for MRSA but it can eliminate out other staphylococci. Because of the minimal cost and speed of results, it could be a valuable test to perform before sending tests for PCR testing [59].

Table 3. Comparison of tests and techniques which can be used to detect and diagnose MRSA more efficiently and rapidly

S. No.	Tests and techniques	Detection time	Sensitivity	Specificity	References
1	Chromogenic media test	20-26 hours	86%	95%	[57]
2	Real time PCR	1-3 hours	92%	97%	[56]
3	Immunochromatographic test	> 30 minutes	97%	100%	[60]
4	BinaxNOW <i>Staphylococcal aureus</i> test	< 30 minutes	95.8%	99.6%	[59]

Potential antimicrobial alternatives to combat the MRSA antibiotic resistance crisis

The development of the first antibiotic penicillin in 1929 significantly raised the quality and probability of human life. Later on, a number of effective antibiotics were produced against previously lethal bacterial infections. Thus, about a half-century ago, antibiotics significantly brought a golden revolution in the medicine field. But unfortunately, an unregulated and careless attitude towards over antibiotic utilization into medicine, agricultural, aquaculture, poultry and veterinary medicine practices has brought disastrous side-effects in the form of world-wide emergence of the multiple drug resistance (MDR) and extensively drug-resistant (XDR) clinical strains. The antibiotic resistance even against core and potent antibiotics has brought us towards the beginning of the post-antibiotic era where millions of lives are being threatened and suffering, morbidity, and mortality rates are continuing to increase.

The widespread presence of MRSA in hospital-settings, community, and food and feed sectors is raising life-threatening concerns. The first case of MRSA emerged in 1961 during the clinical use of “Methicillin” against Penicillin-resistant *S.aureus*. Surprisingly, resistance against Methicillin was developed within 1 year of its first use [62]. Globally, 90-95% strains

of *S.aureus* have attained resistance against Penicillin, while 70–80% of them are known to be resistant against most potent methicillin antibiotic in Asian countries [63]. Currently, MRSA infections are treated by Vancomycin, Teicoplanin, Linezolid and Daptomycin antibiotics. However, the progression of resistance mechanisms in MRSA against these only available therapeutic drugs is quite distressing. A sporadic rapid emergence of vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-intermediate *Staphylococcus aureus* (VISA), and an increase in MIC values of glycopeptides clearly indicate a reduction in MRSA susceptibility to these drugs. Also, the increased resistance and scarceness of any other potent anti-MRSA therapy is observed to further limit the treatment options in near future [47]. A rapid increase in practical utilization of alternative or combinatorial approaches for prevention and cure for MRSA infections must come to the rescue. Owing to this dire need, a brief overview of such antimicrobial alternatives against MRSA infections has been presented with the particular discussion on their relevant research findings and their future prospects. The (Fig. 4) represents an overview of such anti-MRSA alternatives that can exert an antimicrobial effect on MRSA alone or can potentiate the effects of existing antibiotics in combinatorial approaches.

Figure 4. Schematic overview of potential alternative therapies against MRSA infections

Phytochemical approach

The utilization of various plant regions i.e., leaf, stem, bark and roots, etc. for preventing diseases, relieving the symptoms and regression of abnormalities that arise due to various reasons has a long history [64]. Many communities across the world (about 60% of the total world's population and 80% of developing countries) still rely on and consider this traditional herbal-therapeutic approach as the preferable primary solution to their medical issues [65]. Due to the rapid emergence of antibiotic resistance in many clinical isolates all around the globe, the need to find substitute antimicrobial agents has become paramount than in previous years. Owing to this fact, research interest

has been invigorated in searching for suitable bioactive anti-microbial compounds from plants.

Plants have been found to act as a natural source of harboring a wide variety of valuable bioactive compounds, that have extra-ordinary potential to combat currently problematic antibiotic resistant-bacterial infections. And it is an accepted fact that numerous commercially available modern medicines were successfully used in their crude forms in traditional healing practices too. Plant-derived medicines also offer profound clinical benefits due to their comparatively safer nature than synthetic drugs [66]. The antimicrobial traits of plants are attributed to their phytochemicals synthesized primarily

during their secondary metabolism. These secondary metabolites are produced as defense mechanisms against microbes, insects, and other predators, while some aid plants in communication with other organisms in their eco-systems [67]. Among these secondary metabolites, tannins, flavonoids, phenolic compounds and alkaloids are the most potent antimicrobial bioactive compounds [68]. Due to the incomparable chemical-diversity existence in natural extracts and their novel mechanisms of actions, they open new avenues and unlimited opportunities in the development of new drugs against resistant strains [69]. It was reported by Wilkins & Board in 1989 that more than 1340 plants are known that have potential antimicrobial effects [70] while the total number of plant species on Earth is estimated to be about 250,000 to 500,000 species [71].

Different parts of plants (from seeds to roots) have been extensively studied for their anti-infection properties. A number of research findings on different plant extracts and essential oils have been conducted to combat the challenge of MRSA [72]. For a plant-extract, the appropriate Minimal Inhibitory Concentration (MIC) value considered to exhibit anti-MRSA effect is 250 mg/mL to 1 µg/mL. Concentrations of extracts > 1 mg/mL are not considered inhibitory because bacteriostatic/bactericidal effects can be due to osmotic stress applied by solutes on cell-walls of bacteria [73]. 62.5–250 µg/mL of *Bauhinia kockiana* Korth flower-extract showed anti-MRSA potential [74]. Examination of ethanolic extraction of 10 traditional medicinal plants against MRSA activity also showed promising results [75]. Also, a detailed literature review of medicinal plants against MRSA has been presented by Li et al., 2019 and Ramírez Rueda, 2013 [76,77].

Anti-MRSA potential of essential-oils

The antibiotic activity of many plants-extracts is mainly due to essential-oil fraction or due to Sulphur containing

compounds in aqueous phase [78]. Essential oils are complex volatile mixtures of 20-80 components present essentially in plants in very minute concentrations. Their extraction from plants can be done through various methods i.e., via solvent extraction, super-critical CO₂ and subcritical water extraction, steam-distillation hydro-diffusion as well as via solvent-free microwave and combination (solvent + steam) methods [79]. Plants store their essential oils in various cell-compartments that include secretory cells, cavities and glandular trichomes [80]. Chemical composition of essential oil depends upon harvesting period, climatic, seasonal, geographical situations, and upon particular distillation technique used. Other potential properties of essential oil include their diverse chemical compositions, wide antimicrobial spectrum, least toxicity and broad pharmacological activities. Particular kind, composition, concentration, storage condition of essential-oil as well as nature and inoculum size of target bacteria are the influencing factors of their antibacterial activities [81].

Melaleuca alternifolia essential oil is considered the first essential oil that demonstrated anti-MRSA activity [82]. In a research finding, a combination of citricidal and geranium oil exhibited the highest antibacterial potential against MRSA. This finding also showed that essential-oils work best in vapour form and in combinatorial forms than single oils used alone. However, in dressing method, with Flamazine presence, these vapors were failed to obstruct the growth of *S.aureus* strains, the thick coating of Flamazine might prevented the antibacterial effects of volatile vapors on *S.aureus* strains [83]. Similarly, in another study the anti-MRSA effects of 10 essential oils were examined, the essential oils of cinnamon and thyme were found to be the most powerful ones against MRSA, 25 µl/ml was the lowest concentration that formed effective 9±0.085mm and 8±0.051mm clear zones of inhibition around MRSA culture. Also,

increased antibacterial activity of Amoxicillin was observed when used in combination with active components of essential oils of oregano and pennyroyal mint. No effective outcome was obtained when the latter two essential oils were used alone against MRSA [84]. Cold-pressed orange essential oil is also potent anti-staphylococcal agent for topical MRSA

infections [85] (Table 4) lists some other essential oils that have been studied for their anti-MRSA potential. The combination of essential oils with one another and with antibiotics increase not only the antibacterial activities but also reduced the MIC of antibiotics than if they were used alone [86].

Table 4. Potential essential oils effective against Methicillin-resistant *Staphylococcus aureus* (MRSA)

Essential oil	Amount of Essential oil used	Diameter of Zone of inhibition(mm)	MIC ¹	MBC ²	Mechanism of action	Ref
Lemongrass oil	10 □L/6mm disc	20-29mm	NA ³	NA	NA	[87]
Eucalyptus oil		8-14mm			NA	
Tea Tree oil		9-15mm			cause degradation of the bacterial cell wall and reduction in osmotic tolerance	
<i>Melaleuca alternifolia</i> (Tea Tree oil)	NA	NA	0.50 (%v/v)	2 (%v/v)	Eucalyptol found as main antimicrobial component, might contribute in permeabilization of target-bacterial membranes and thus facilitate the entry of other active components	[88]
<i>Eucalyptus globulus</i> (Southern blue gum)	12 □l/disc	8mm	85.6 µg/mL	NA	Eucalyptol (47.2%) was found as the main component of essential oil.	[89, 94]
<i>Thymus vulgaris</i> (thyme)	12 □l/disc	12mm	18.50 µg/ml	NA	Thymol (48.1%) was found the active compound of essential oil. It inhibits synthesis of biofilm components i.e., polysaccharide intercellular adhesin (PIA) and extracellular DNA (eDNA).	
<i>T.schimper</i>	10□□l/disc	16 ± 0.4 mm	3.12 µl/ml	6.25 µl/ml	Essential oils when used in combination produced strong inhibitory effects and involvement of many antimicrobial mechanisms produced this synergism	
	20□□l/disc	21 ± 0.3				
<i>B. cuspidate</i>	10□□l/disc	19 ± 0.2	1.56 µl/ml	3.12 µl/ml		
	20□□l/disc	25 ± 0.1				
<i>B. ogadensis</i>	10□□l/disc	12 ± 0.1	3.12 µl/ml	6.25 µl/ml		
	20□□l/disc	17 ± 0.3				

¹: Minimum Inhibitory Concentration; ²: Minimum Bactericidal Concentration; ³: Not available

The antibacterial activities of plant-extracts and essential oils can be due to number of bioactive compounds present in different fractions of the extracts. Each antimicrobial phytochemical exerts a different and unique mechanism of action the details of few are given in (Table 5). Carvacrol is one such widely existing phytochemical that belongs to phenolic and polyphenolic class of secondary metabolites and has a hydrophobic nature. The hydroxyl group on its aromatic ring plays crucial role in its anti-infective property. H-bonding is involved in its interaction with Target bacterial DNA. Antibacterial potential of Carvacrol can be enhanced by low pH adjustments because reduced pH plays role in minimizing the dissociation of carvacrol and thereby augment its hydrophobicity, this increases the likelihood of carvacrol strong binding with hydrophobic regions of membrane's protein, and therefore better penetration of carvacrol can occur in membrane lipids and antibacterial effect is increased [91]. Another important phenolic structure having essential component is Eugenol which due to its OH group exerts its antibacterial effects [92].

Similarly, Thymol a monoterpene phenol, mostly present in oregano essential oil is also potent against MRSA infections. At values lower than MIC, thymol also prevents biofilm formation by MRSA [93]. In a recent research finding it is found that thymol cannot only prevent the formation but also the elimination of pre-formed mature MRSA biofilms by reducing the synthesis of polysaccharide intracellular adhesin (PIA) with concomitant release of extracellular DNA from MRSA cells. Also

synergistic treatment of thymol and vancomycin was found more remarkable than vancomycin monotherapy in mouse infection model for removal of MRSA biofilms [94]. Sesquiterpenes, a class of terpenoids are well established to potentiate the action of antibacterial action antibiotics against *S. aureus* strains [95].

Flavones are other ubiquitously present structures in plant-extracts, they exhibit phenol like structures with at least one carbonyl group. The addition of 3-hydroxyl group to this basic structure yields flavonol [96]. 3.13-6.25 µg/ml concentrations of tetra-hydroxyflavanones isolated from *Sophora exigua* and *Echinosophora korensi* are strong enough to inhibit the growth of clinically isolated MRSA strains [97]. Catechin, the strong antimicrobial compounds are also the reduced forms of flavonoids [98]. Catechins alone don't have exceptional innate potential to inhibit MRSA growth but can enhance the susceptibility of MRSA to β -lactam antibiotics in combinatorial approaches [99]. Substitution of catechin with other components is also useful strategy because 3-O-octanoyl catechin was found to be bactericidal against MRSA due to its increased membrane damaging potential as compared to Epicatechin gallate when used alone without any substitution with 3-O-acyl chains of variable lengths (C4-C18) [100]. Tannins are also found useful in inhibiting growth of clinically isolated and reference strain of MRS (AATCC 43300) [101]. A schematic illustration of the general antimicrobial mechanism of action of an essential oil on MRSA cell is shown in (Fig. 5).

Figure 5. General Mechanism of anti-bacterial action of essential oils on MRSA

Table 5. Mechanism of action of some potent phytochemicals against MRSA

Potent bioactive phytochemicals	Mechanism of action	Ref.
Carvacrol	<ul style="list-style-type: none"> interacts with bacterial-plasma membrane to cause destabilization and expansion of membrane's structure thus fluidity and permeability of membrane is disturbed. Has ability binding with minor groove of <i>S.aureus</i> DNA 	[91]
Eugenol	<ul style="list-style-type: none"> Involved in Enzyme inhibition of target bacterium 	[92]
Thymol	<ul style="list-style-type: none"> Alters plasma-membrane permeability Inhibits protein synthesis and binary fission prevents biofilm formation 	[93]
Terpenoids	<ul style="list-style-type: none"> involved in inhibition of two crucial microbial processes: oxidative phosphorylation and oxygen uptake. 	[102]
Clerodane diterpene (CD)	<ul style="list-style-type: none"> involved in modulating the expression of efflux pump genes of MRSA also extends post-antibiotic effect in synergy or non-synergy with norfloxacin 	[103]
Flavonol	<ul style="list-style-type: none"> form complexes with target-bacterial-cell walls and other extracellular/soluble proteins. highly hydrophobic flavonoids are also associated with damage to microbial membranes 	[96]
Catechin	<ul style="list-style-type: none"> Catechin gallate can intercalate into phospholipid bilayers of target bacteria thereby, can alter the virulence and antibiotic resistance patterns in bacterial strain in combinatorial approaches can enhance the susceptibility of MRSA to β-lactam antibiotics. 	[98], [99]
Tannins	<ul style="list-style-type: none"> induce cell-wall disruption involved in release of intracellular-cytoplasmic constituents Suppress essential ribosomal pathways involved in transcription, protein-synthesis and DNA modification and repair processes. 	[101]
Alkaloids	<ul style="list-style-type: none"> Involved in pyruvate kinase inhibition modulation of efflux pumps intercalation with bacterial DNA inhibition of Quorum sensing-effects biofilm prevention. 	[104]

Despite having such strong antimicrobial potential, certain limitations impede practical utilization of essential oils in being acting as a major ingredient in any new therapeutic drug against MDR infections. Their isolation from plant organs is extremely laborious and energy intensive, their testing as potential antimicrobial agent requires their safe extraction and complete purification. Ascertaining their bioactive component being responsible for making them antimicrobial candidates is also a difficult task after initial anti-infective screening tests. Also, in comparison with synthetic additives, they pose high-cost concerns due

to their additional processing requirement prior to their testing of antimicrobial activity. Cost issues can be resolved by downsizing the total extraction volume of potential antimicrobial components [105]. However, the other major problem associated with anti-MRSA plants is their safety concerns, because some secondary metabolites of medicinal plants have also shown strong carcinogenic, mutagenic and toxic potential [106-108]. To address this issue, a critical evaluation and sequential screening of their antimicrobial, pharmacological, and toxicological aspects is required for ascertaining their safety

profile on immediate basis before their approval by regulatory authorities.

Bacteriocins and antimicrobial peptides

Bacteriocins are ribosomally synthesized small bacterial peptides that have Bacteriostatic and bactericidal potential against competing bacterial strains [109]. They are most valuable alternatives of conventional therapeutic antibiotics against clinical pathogens due to their high stability, non-toxicity, high potency even at very low concentrations, and due to their broad and spectrum of activity against competing strains [110]. It is investigated that bacteriocins are naturally produced in our GIT by certain species of lactic acid bacteria against infectious pathogens that gain entry through food. They are also emerging as potent anti-cancer, antifungal and antiviral substances. Bacteriocins from LAB (lactic acid bacteria) have attained GRAS status from FDA and Nisin is the only FDA approved commercially available bacteriocin used as food preservative in western countries [109]. Nisin exerts its strong antimicrobial effect by formation of pores in cell-membranes and subsequent efflux of essential metabolites from target cell [111]. The (Fig. 6) depicts the mechanism in which nisin is produced by producer bacteria. The genes involved in Nisin biosynthesis are present on 70 k.b conjugative transposon The *NisK* senses the existence of nisin in the external environment and auto-phosphorylates. The Pi is transferred to Response regulator gene (*NisR*), which triggers transcription of the *nisABTCIP* genes that encode structural, modification, transportation, Immunity and maturation proteins; *NisFEG* along with *NisI* confer Immunity and defend the producer-cell from toxicity of nisin (where P: promoter region, & P', P'' represent nisin-regulated promoters in operon cluster) [112]. The released Nisin then acts on target bacterial strains and inhibit their growth.

Activity of bacteriocins against MRSA has been tested by various researches with fruitful results [110, 113, 114] In finding

by Karska-Wysocka *et al.*, 2010, 99% elimination of the MRSA cells was obtained on direct interaction with LAB after 24 hours at 37°C incubation [115]. Due to their strain specific inhibitory activities Aureocin A53 and epidermin from *Staph. aureus* and *Staph. epidermidis* respectively also shown potential effects against MRSA [116].

Also, another effective strategy would be utilization of antimicrobial peptides (Host defense peptides) that are small cationic peptides and have ability to combat infections either by directly killing the pathogens or by modulating host's defense responses. They are present in almost all life forms against infectious agents [117]. Electrostatic interactions between positively charged AMPs and negatively charged bacterial surface are leading the factors of their antimicrobial activities, they can either physically disrupt the integrity of host's plasma-membrane or can translocate the membrane for interacting with intracellular targets [118]. Hydrophobic nature of these peptides allows penetration through anionic lipid membrane. These compounds have gained importance and are being used against antibiotic resistance [119]. Omiganan Pentahydrochloride (MBI 226) is 12 amino-acid cationic peptide was found effective against MRSA at MIC of ≤ 64 mg/ml [120]. Similarly, another peptide Chitosan in its aminoderivatized form showed promising results in synergy with β -lactams against MRSA strains with Fractional inhibitory concentration (FIC) indices of 0.252-0.508 with a significant reduction in MIC of β -lactams [121]. Another peptide L12 derived from enterocin, of *E. faecium* was also found effective against MRSA infections [122]. Despite their strong anti-MRSA potential, for both, AMP's and Bacteriocins, thorough insights are required to answer questions related to their poor solubility and stability, high production and purification costs. Their inactivity by degradation of intestinal proteases also makes them less effective in-vivo [111].

Low in-vivo metabolic stability due to tissue-proteases also limits clinical use of AMP's. A deep understanding of both AMP's and bacteriocin's biology and biochemistry is required for formulation of

innovative approaches and drug-delivery systems for improving the aspects of safety, stability, and antimicrobial-effectiveness at low concentrations.

Figure 6. Presumed Model of Lantibiotic Nisin Biosynthesis [112]

Phage therapy

To combat against the global threat of antibiotic resistant strains particularly MRSA, another effective strategy is utilization of bacteriophages. These bacterium eating viruses have huge therapeutic potential because bacteriophages can only interact with and kill their specific bacterial hosts. In Lysogenic states they incorporate their genomic DNA into bacterial genome and exist as prophage and through multiple crucial mechanisms prophage controls bacterial-pathogenicity and behavior [123,124]. Lytic phages have high potential to disrupt host's metabolism thus cause rapid lysis of target bacterial cells. They are highly specific towards their target bacterial species or even strains [125]. Felix d'Herelle, is known as the first microbiologist who observed bacteriophage phenomenon in 1910 in Mexico [126]. In 1917 he started administration of phages in different patients via ingestion phenomenon and found them efficacious against different bacterial diseases [127]. Since then, numerous researches have been conducted against their anti-infective potential for known resistant and susceptible bacterial-strains. Bacteriophages are far better than antibiotic strategy of controlling infectious diseases because they do not induce secondary infections produced as a result of antibiotic-associated dysbiosis of normal flora, directly concentrate and replicate at the site of infection for immediate lysing of pathogenic bacteria instead of distributing throughout the body like antibiotics. They are not known to cause any side effects during or after their administration while antibiotics can pose concerns of allergies, secondary infections and resistance in pathogenic bacteria. Also, if under some circumstances, target bacteria attain resistance against phage, it will remain susceptible to other phages having identical target-range [128]. Additional benefits of bacteriophages over other antimicrobial agents include their auto-replication ability

and eco-friendly status [123]. They are also more effective in terms of cost-effectiveness over antibiotics. However, their combination with antibiotic may prove a valuable approach for therapeutics of infectious diseases [129]. Owing to these facts and rapid emergence of MRSA strains worldwide, bacteriophage effectiveness has also been evaluated against MRSA strains from different sources and promising results have been procured. The (Table 6) represents some promising studies to control MRSA infections via bacteriophage therapy.

Irrespective of the fact that large number of publications are present about phage therapy but very limited ones are known to reveal the pharmacokinetics and toxicology of therapeutic phages, the detailed and critical information is required for their successful implementation in clinical settings. Findings of some researchers suggest that bacteriophages can get entry into bloodstream of laboratory animals within 2-4 hours and their persistence within internal organs can be found within 10 hours of administration. They can sustain within in human bodies for relatively extensive period i.e., till up to several days [127].

Other technical and financial issues regarding their production at large scale involves serious attention because they need to be produced within their bacterial hosts, and pathogenic bacterial hosts involvement requires high safety protocols for working members in the production plant and nearby community. Another important challenge is implementation of maximum precautionary measures (for not producing a virulent and pathogenic gene transferring phage) while propagating therapeutic phages within their host bacteria, because some phages can carry host's pathogenicity inducing genes to other previously non-virulent bacteria. Although chances of such events to occur are very rare but cannot be overlooked. Alternative strategy for coping up with the issue is generation of avirulent, non-

pathogenic and genetically well-characterized producer bacteria, but again preparation of such bacterial hosts is highly cost-intensive and requires prolonged periods of investigation and throughput [134]. MRSA associated skin and mucous membrane infections might not require application of whole therapeutic phage rather administration of its active lytic enzyme that induces host's cell-lysis is sufficient. A pictorial representation of bacteriophage's mode of action on host bacterial cell by lytic cell-cycle and by its endolysin (lytic enzyme) is shown (Fig. 7). Viability of this approach is proved by experimental findings of Loeffler *et al.*, 2001 who observed rapid killing of *Streptococcus pneumoniae* via pneumococcal bacteriophage lytic enzyme (Pal) that was basically a cell-wall hydrolase [135].

Nanoparticles

Besides being used in delivering anti-MRSA agents, nanoparticles can themselves be used against MRSA strains. For this, various materials have been investigated to design nanoparticles against MRSA. As like the naturally occurring peptides that can cross the lipid membrane and meld into the target species thereby disrupting the structure of the membrane, the cationic nanoparticles exhibit antimicrobial activity due to similar attributes. This mechanism of interaction between positively charged nanoparticle and negatively charged bacteria has been shown in (Fig. 8) where the high charge density on the nanoparticle might be due to amines or alkylated ammonium groups that protrude from the outer-surface and develops interaction with the negatively charged bacterial membrane [136].

The antimicrobial properties of chitosan (that is both biodegradable and biocompatible) nanoparticles have also been investigated. They exhibit quaternary ammonium groups on their surfaces and formed by ionic gelation. Through assays, it is revealed they are active against MRSA biofilms. This ability is due to the cationic

charges on the external surface of nanoparticles which develop interaction with the negatively charged bacterial cell surface, thereby weakening the membrane [137]. Similarly, nanoparticles with metallic nature have also been examined with silver being the most studied one [137]. This is because it can be taken up by the bacterial species and cross their cell-walls [138]. In addition to this, silver ions can interact with the thiol group present on cysteine amino-acid [139]. As Ag ions exhibit strong affinity for Phosphorous ions present in the DNA, they can affect DNA replication [138]. The size of the Ag⁺ nanoparticle affects the anti-MRSA activity and cytotoxicity toward the human cells. A small size of 10 nm is very active with no cytotoxicity whereas 100nm is lethal for both bacteria and eukaryotes. Silver nanoparticles are less toxic compared with ionic silver against eukaryotic cells. Highly charged silver ion e.g. Ag (+3) contains stronger antibacterial properties compared with Ag (+1) [140].

Copper-oxide nanoparticles, on the other hand, are required at higher concentrations to kill bacteria. The mechanism of action is different from silver nanoparticles, as the release of copper-ions leads to a change in pH and charge which disrupts the membrane and affects the function of intracellular molecules like enzymes. Zinc oxide nanoparticles cause cell lysis by damaging the membrane lipids and proteins. Different metallic nano-particles can be used as surface coating materials for medical devices. Copper nano-particles provide anti-MRSA coating as well [137]. However, the size of nanoparticle can also pose toxicity concerns as compared to micrometer particle of the same size [141]. The need of the hour is to know the interaction of MeO-NPs with human-cells and organs, such as their ability to cross the blood-brain barrier and the blood-testicular barrier [142]. Also, MeO-NPs interaction with ABC transporters can also bring new insight into their mechanism of action [143].

Table 6. Some novel bacteriophages against MRSA infections

Bacteriophage Collection-site	Findings	Results	Ref.
Hospital sewage	Bacteriophage-titer: 1×10^9 PFU/ml latent period: 20 min Burst size: 190 PFU/infected cell	The isolated phage was effective against 27 out of 30 MRSA strains isolated from hospitalized burnt patients	[130]
LizAnk Bacteriophage isolated from clinically isolated MRSA strains during performance of infectivity studies on 13 lysogenic phages against MRSA strains	Time taken by phage to kill 10^7 CFU/ml of MRSA: 8 hours	The isolated phage was potent antibacterial agent against 6 clinically isolated strains of MRSA and exhibited no cytotoxicity against mammalian cell	[131]
10 lytic bacteriophages were collected from raw sewage water	Only 2 bacteriophages Φ NUSA-1 and Φ NUSA-10 showed remarkably broad host-range against >80% of MRSA and MSSA tested.	Wide host range of isolated bacteriophages including both MSSA and MRSA supports hypothesis that bacteriophages employ inhibitory mechanisms clearly distinct from bactericidal mechanism of antibiotics. Also sewage water is a valuable source for clinically potent staphyphages	[132]
Sewage sample of Ruijin Hospital	burst size: 13 PFU/ml infected cell Phage's stability temperature: 40°C pH: between 6 and 9 80% adsorption on MRSA surface occurred: in 4 mins Latent period: 12min Growth period: 9min	phage VB_SauS_SH-St 15644 lysed 12 clinically isolated MRSA strains out of 37 isolates invitro and subcutaneous injection into MRSA infected mice showed its potential against MRSA skin infections	[133]

Figure 7. Mechanism of Lytic cell-cycle and Endolysins mediated cell-lysis of MRSA by Bacteriophage

Figure 8. Pictorial representation of positively charged nanoparticle interaction with negatively charged MRSA cell [137]

Other alternative strategies

Graphene-oxide (GO), is an excellent antibacterial agent, due to its membrane penetrating ability. Also, due to its large surface-area and ultra-high drug loading capability, it is being seen as a potential candidate to be used in conjugation with another strong antibacterial compound, curcumin, against MRSA infections.

Curcumin alone is effective at 125-150 μ g/ml concentration, which is inopportunately highly lethal for eukaryotic cells. And Graphene-oxide (GO) although found effective against MRSA infections (at MIC>60 μ g/ml) needs improvement in its biocompatibility, stability and toxicity concerns. This issue is resolved by a composite based on Curcumin-loaded graphene sheets (GOCU) which has recently

been found as an effective strategy against MRSA infections even at MIC of 1 µg/ml with a significant reduction in cytotoxicity associated with GO [144]. Another potential strategy is the utilization of a pre-emptive approach i.e., vaccination against *S.aureus* strains, immunotheapeutics have gained renewed interest in the recent years in both human and veterinary medicines [145]. Against PBP2a protein of MRSA, researches have formulated a DNA vaccine that contains *mecA* region and antibodies were found to be produced against the specific portion of PBP2a protein that confers resistance to whole MRSA, this vaccination was unaffected on normal microflora but significantly reduced bacterial number in kidneys of infected mice [146]. But due to certain limitations not even a single vaccine against *S.aureus* (that showed promising results in murine models) has made its way in successful prevention against MRSA in human trials. Due to multiple virulence factors possessed by *S.aureus*, a vaccine against any one of them might not give significant results in clinical trials so, current trials are particularly focusing on the use of a purified mixture of multiple antigenic preparations. However, utilization of live attenuated D-alanine auxotroph strain of *S. aureus* provides significantly promising results [147].

Lipidated α /Sulfonyl- α -AA heterogeneous peptides have been discovered as a new class of lipid containing peptides. These lipidated and sulphonated peptides mimic host Defense Peptides (HDPs). They are effective against Gram-positive bacteria and the development of resistance in target bacterium is very difficult due to their unique mechanism of action. Moreover, they have been found to be less toxic for humans. Their lipidation, hydrophobicity, and cationic nature are crucial factors in the induction of membrane disruption in target bacteria [148]. However, concerned drawbacks with these synthetic peptides and others include their high cost, stability, and time of synthesis [149].

Strategies for the prevention of transmission

All medical care staff taking care of MRSA infected or colonized individuals should utilize contact safety measures to restrict spread between patients [150]. This implies putting the MRSA infected patient into a solitary or private room and wearing outfits and gloves when entering the patient's room and eliminating them prior to leaving [150]. Strict contact precautions should be taken throughout an infected person's admission to the hospital and with any person who has recovered from MRSA infection [150]. The hospital should have a management system that can alert the healthcare staff about the readmission or transfer of MRSA-infected patients so that appropriate measures can be taken on the arrival of such patients [150]. Hand hygiene campaigns in hospitals have greatly reduced MRSA infections [151].

Since MRSA can contaminate the air, the rooms of MRSA patients need to be sterilized and disinfect properly. All the furniture including overbed tables, floors, sinks, handrails, and healthcare equipment should be properly disinfected [150]. Decontamination with radiations using Xenon-UV light can also be done and the presence of MRSA and other pathogens can be eliminated up to 99% [152]. In the design of the building of a healthcare facility, there should be the use of copper alloys to reduce the environmental burden and transmission of pathogens [153]. Intensive care units with a high number of MRSA patients should have an active surveillance program to spot asymptomatic carriers of MRSA [150].

Surveillance along with the prophylactic treatment approach is an effective way to decrease the cases of surgical site infections. These protocols may include intranasal antibiotics such as mupirocin with an antibacterial body wash or preoperative antibiotics. Surveillance is the key, however, to forestall abuse and misuse of antibiotics [154].

Conclusion

Staphylococcus aureus is the cause of multiple types of infections and, unfortunately, *Staphylococcus aureus* has attained the ability to develop resistance against many drugs and it is known as methicillin-resistant *S. aureus* (MRSA). MRSA has remarkably evolved and disseminated widely in 60 years since it was first identified.

Its huge prevalence in hospital settings poses a huge risk for susceptible individuals in getting nosocomial infections. Increasing drug resistance ability is making them more aggressive and difficult to assassinate by existing antimicrobial approaches (e.g. antibiotics). So MRSA, being the high priority multi-drug-resistant bacteria, requires intensive efforts for research and development of novel preventive approaches, novel genomic driven approaches for drug development must also be explored. Along with that there is the necessity to adapt fast molecular and immunochromatographic diagnostic techniques that can reduce delays in diagnosis and treatment. These factors alone cannot contribute in mitigation of MRSA associated challenges rather, the need for vigilance and effective preventive measures must also be implemented to facilitate the control of this highly successful pathogen.

Authors' contributions

Conceived and designed the experiments: SM Faheem & S Riaz, Performed the experiments: SM Faheem & S Riaz, Analyzed the data: UF Gohar, contributed materials/ analysis/ tools: UF Gohar, Wrote the paper: SM Faheem & S Riaz.

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