Chapter

Mechanistic Insights of Drug Resistance in *Staphylococcus aureus* with Special Reference to Newer Antibiotics

Atamjit Singh, Kirandeep Kaur, Pallvi Mohana, Avneet Kaur, Komalpreet Kaur, Shilpa Heer, Saroj Arora, Neena Bedi and Preet Mohinder Singh Bedi

Abstract

Staphylococcus aureus is the most ubiquitous microorganism in both environment as well as animals and exists as commensal and pathogenic bacterium. In past few years it has been emerged as a superbug causing serious burden on healthcare system. This bacterium has been found to be the most resistant one toward most of the antibiotics due to its rapid structural and genetic modifications. This chapter will shed light on various types of molecular mechanisms responsible for resistance of *Staphylococcus aureus* showcasing how it has been emerged as a superbug. Moreover, the recent approaches which include exploring of different drug targets keeping in view the structural and functional behavior of the *Staphylococcus aureus* has also been discussed.

Keywords: Antimicrobial resistance, *Staphylococcus aureus*, Superbug, Resistance Mechanism, Drug resistance, Bacterial resistance

1. Introduction

Staphylococcus aureus is a Gram-positive, catalase and coagulase positive strain of bacteria belongs to Micrococcaceae family. Staphylococcus spp. to which these bacteria belong is commonly found in nature and human flora. *Staphylococcus aureus* is generally isolated from community as well as hospital gained infections and have capability to cause superficial to life threatening infections [1–3]. However, the worst scenario in field of microbiology was observed in late 90's when resistance among several microbes including *Staphylococcus aureus* was reported for various antibiotics. *Staphylococcus aureus* was the most prominent threat among all other pathogens due to the rapid emergence of resistance in it. The inappropriate use of antimicrobials in clinical therapy and agriculture, extensive antimicrobial consumption and transfer of antimicrobial resistant genes due to increased anthropogenic activity are potential risk factors for development of antimicrobial resistance and considered as primary reasons responsible for the rapidly growing resistance

in *Staphylococcus aureus* [4–6]. Moreover, the intrinsic virulence of *Staphylococcus aureus*, its nature to adapt to the corresponding environment are some other factors which makes it the foremost challenge for microbiology scientists. Even though, many potential therapeutics have been synthesized/approved by USFDA for the treatment of *Staphylococcus* infections but unfortunately besides this the mortality rate of *Staphylococcu*s bacteraemia is 20-40% [7–9]. Furthermore, the clinical sample (blood samples) of patients with nosocomial infections/staphylococcus infections were investigated which confirmed the resistant strains of *Staphylococcus aureus* against various antibiotics that include first- and second-generation fluroquinolones, β-Lactam antibiotics, trimethoprim sulphamethoxazole and vancomycin etc. [7, 10, 11]. Surprisingly, the number of antibiotics emerging for treatment of this bacteria is directly proportionate to the rapidly evolving resistance mechanisms within *Staphylococcus aureus* to combat the therapeutic efficacy of these antibiotics. In year of 2002-2003 *Staphylococcus aureus* was found resistant to the highly efficient antibiotic vancomycin which left the physicians with no competent antibiotic for its treatment. Subsequently it urged the need to explore more drug targets and novel approaches for new antibiotics to treat staphylococcus infections. Conclusively, the rapid structural and genetic modifications of *Staphylococcus aureus* counterbalance the effect of even magnificent antibiotics. Therefore, various molecular mechanisms of *Staphylococcus aureus* have been deeply explored in the recent past to overcome the life-threatening implications of this resistant bacteria [12, 13]. This chapter enlightens the historical evolution of resistance in *Staphylococcus aureus*, molecular mechanism of resistance for various antibiotics and the modified approaches for its treatment.

2. Quorum sensing in *Staphylococcus aureus*

Quorum sensing is a well-known phenomenon used mainly by prokaryotes for communication among themselves [14]. Particularly in bacteria quorum sensing is monitored by a set of signaling molecules called autoinducers as density dependent variables. They are released by bacteria around their surrounding environment which up on reaching at particular concentration develop a well-coordinated response. Density of autoinducers is monitored by bacteria for tracking changes in cell number and to alter the gene expression pattern. This is also a factor that is responsible for resistance of bacteria against antibiotics [15, 16]. Quorum sensing in *Staphylococcus aureus* has been coordinated through modified oligopeptide

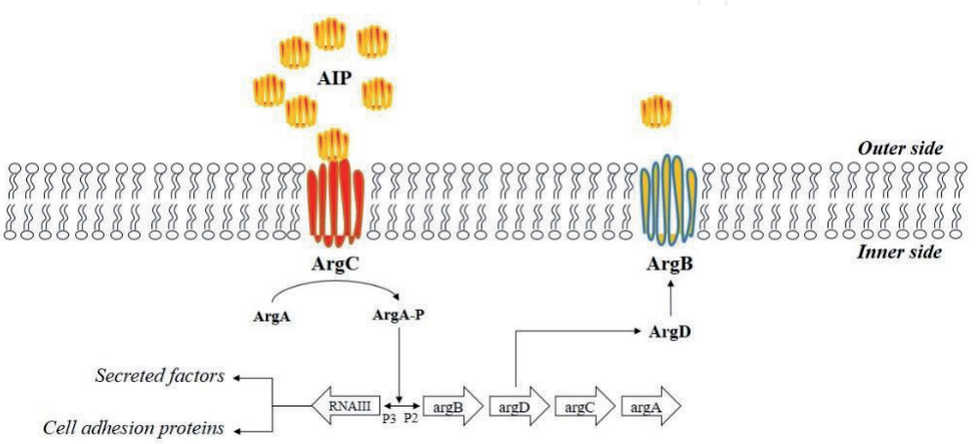

Figure 1.
Mechanistic insight of quorum sensing in Staphylococcus aureus.

known as autoinducing peptide (AID). In the pathophysiology of *Staphylococcus aureus* regarding quorum sensing, biphasic mechanism exist. At lower cell density, *Staphylococcus aureus* generally express protein factors i.e. Coagulase and fibronectin binding proteins A and B etc. which promote their attachment as well as colonization while at higher cellular density *Staphylococcus aureus* repress these traits and initiate secretion of toxins and proteases that needed for dissemination. The switching of this gene expression is controlled by Agr quorum sensing system that consist of autoinducing peptide (AID) encoded by agrD and two other sensor kinase-response regulators called AgrC and AgrA (**Figure 1**) [17–19].

3. Various resistance mechanisms of different classes of antibiotics in *Staphylococcus aureus*

3.1 Resistance to β-lactam antibiotics

In early 1940's introduction of penicillin improved the outcome cases due to *Staphylococcus* infections but soon penicillin resistance *Staphylococcus* were recognized in early 1942 [20] which among late 1960's reaches to 80% in both community and hospital-acquired staphylococcal isolates with well-established pattern of resistance [21]. Furthermore, blaZ gene is responsible for resistance in *Staphylococcus aureus*, that encodes for β-lactamase an enzyme which is synthesized when *Staphylococcus aureus* is exposed to β-lactam antibiotics by hydrolyzing the β-lactam ring, rendering the β-lactam inactive. blaZ is regulated by the two adjacent genes blaR1 and blaI. The gene blaR1 is anti-repressor and blaI is repressor [22]. For the synthesis of β-lactamase, the signaling pathway involves the sequential cleavage of these regulatory proteins such as blaR1 and blaI where on exposure to β-lactams, blaR1 which is a transmembrane sensor transducer cleaves itself [23, 24], cleaved protein acts as protease that directly or indirectly cleaves the repressor blaI and thus allowing the blaZ to synthesize enzyme [23]. Furthermore, Methicillin, the first semisynthetic penicillin which was resistance to penicillinase, introduced in 1961 and soon followed by the reporting of methicillin-resistance isolates [25]. The spread of Methicillin-resistant *Staphylococcus aureus* (MRSA) has been critical and the infections resulting from MRSA is worse than the infections outcome of methicillin ensitive strains [26]. MRSA isolates like the penicillin resistance strains too carried resistance genes for other antimicrobial agents [27]. For the resistance to methicillin, requires chromosomally localized mecA gene [28, 29], which is a part of large unique mobile genetic element, SCC mec found in all MRSA strains may contain additional genes for antimicrobial resistance [30, 31] is responsible for the synthesis of PBP2a/PBP2′ a 78-kDa protein which binds to penicillin (penicillin-binding protein 2a) [32–34]. Transpeptidation which is necessary for the cross-linkage of peptidoglycan chains is catalyzed by these membranes bound enzymes-PBPs, thought to have appeared and works similar as serine proteases. PBP2a blocks the binding of all β-lactams but allows transpeptidation and because of its low affinity it allows staphylococci to survive even in the high concentration exposure of β-lactam antibiotics. Isolates Resistance to methicillin shows resistance to all β-lactam agents, including cephalosporins [34–36]. In some MRSA strains its resistance mechanism by mecA via the mecI and mecR1 genes is regulated in the manner similar to the regulation of blaZ by the genes blaR1 and blaI when exposed to penicillin [37]. Fem genes (factor essential for resistance to methicillin resistance, also play a role in cross-linking the peptidoglycan strands and contribute in methicillin resistance [38]. Ceftaroline the fifth-generation cephalosporin according to the U.S. Food and Drug Administration (FDA) in 2010 has been considered

superior among other comparator drugs for the treatment of complicated skin and soft tissue infections as well as pneumonia [39]. β -lactam antibiotics bind to other PBPs, named PBP1, −2, −3, and − 4 but in the presence of PBP2a they are unable to bind effectively to their PBP targets. Ceftaroline on other hand is active against MRSA strains because of its high binding affinity for PBP2a as comparison to other β -lactam [40]. Binding of PBPs by ceftaroline block these enzymes to catalyze the transpeptidase function that is important for the synthesis of staphylococcal cell wall [41]. Ceftaroline is generally considered safe and successfully used to treat wide infections alone and in combination with other active drugs often with daptomycin [42]. Several studied over MRSA clinal strains showed these were susceptible to ceftaroline in wide range such as >98.4% in North America [43], >83.3% in Latin America [44], >83% in Europe [45], 78.8% in Asia/South Pacific countries [46] the variation in resistance among MRSA may be due to the variation in geographical distribution of strains around the world [47, 48]. MRSA strains carry mobile genetic element known as SCCmec, which carries mecA gene [40]. Ceftaroline resistance is usually due to the nonsense mutations in mecA, resulting in amino acid sequence change in PBP2a hence a target protein mutation [49]. Glu447Lys mutation in mecA in presence of ceftaroline on SF8300 USA300 MRSA strain yields low level resistance isolates whereas COL common laboratory strain showed high ceftaroline resistance due to mutations in pbp2, pbp4 and gdpP not due to mecA [50]. There are strains developing resistance with no change in mecA [51].

3.2 Resistance to vancomycin

Vancomycin, a lipopeptide antibiotic approved by Food and Drug Administration of the United States in 1958 found in recent years that the MRSA isolates are resist to it [52]. Vancomycin works by binding to bacterial cell envelopes and inhibiting their cell wall synthesis instead of targeting protein like other antibiotics [53]. It binds to C-terminal D-Ala–D-Ala residue of the pentapeptide to inhibit the cross-bridge formation between pentapeptide and pentaglycine preventing cell wall synthesis [54]. MRSA strains shows different ranges of resistance against vancomycin according to their MIC and are named accordingly such as MRSA showing complete resistance to vancomycin is termed vancomycin-resistant *Staphylococcus aureus* (VRSA), showing medium resistance is termed as vancomycin intermediate-resistant *Staphylococcus aureus* (VISA) and least resistance as VSSA [55].

Failure in vancomycin treatment of MRSA results due to formation of intermediate-resistant isolates namely hetero resistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) and vancomycin intermediate *Staphylococcus aureus* (VISA) [56] which includes features such as cell wall thickening, reduced autolytic activit and reduced growth rates [57]. Several studies found that the mutation in genes VraS(S329L), MsrR(E146K), GraR(N197S), RpoB(H481Y), Fdh2(A297V) and Sle1(67aa) were also responsible for vancomycin resistance in VISA strain Mu50 [58]. Other genes involving in high- and low-level resistance to vancomycin includes vanA, vanB, vanD, vanF, vanI, vanM, encodes for D-Ala:D-Lac ligases whereas vanC, vanE, vanG, vanL, and vanNgenes encoding D-Ala:D-Ser ligases (**Figure 2**) [59, 60].

3.3 Resistance to lipopeptide based antibiotic daptomycin

The only approved and available lipopeptide in the US in the year 2003 with in vitro bactericidal activity and an alternative to vancomycin for various MRSA infections, is daptomycin [61]. However, during the treatment, the emergence of non-susceptible MRSA strains for daptomycin has been reported [62, 63]. Even

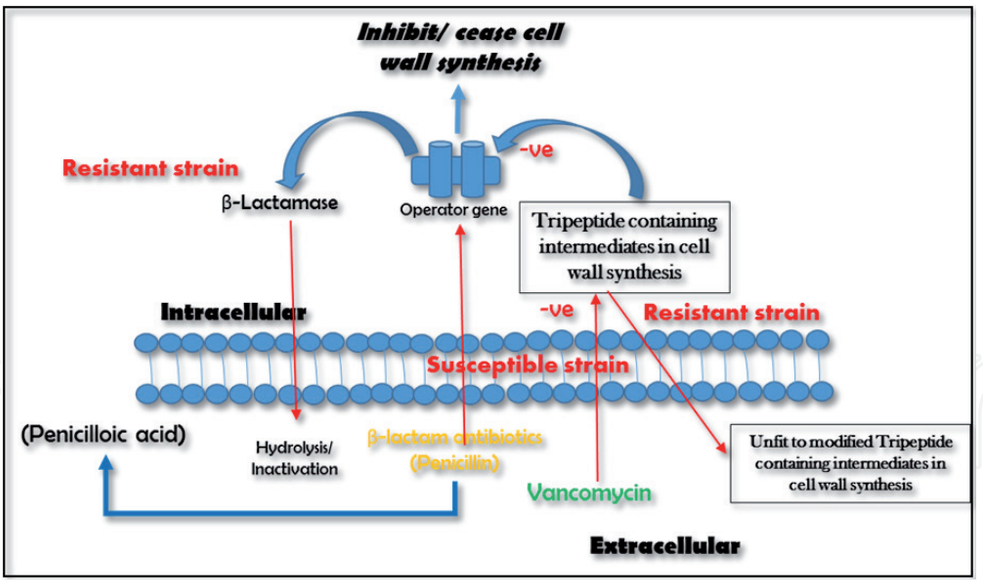

Figure 2.
Molecular mechanism of Staphylococcus aureus *resistance toward penicillin and vancomycin.*

before the approval of drug, Silverman et al. observed daptomycin non-susceptible mutants and identified number of changes such as increase in membrane fluidity, increase in net positive charge over the surface, decrease in susceptibility to daptomycin-induced depolarization and low in surface binding of daptomycin in the cytoplasmic membrane of non-susceptible strains [64, 65]. Though the basis for reduction in susceptibility to daptomycin in MRSA strains has not been fully clarified [66]. The transfer and addition of positively charged lysine molecules to phosphatidyl glycerol in the cell membrane associated with the activity of enzyme lysyl-phosphatidyl glycerol synthetase is encoded by mprF gene [67], Mutation in mprF gene causes an increase of lysyl-phosphatidyl glycerol in the outer layer of the cell membrane, leading to an increased positive charge resulting in reduced susceptibility to daptomycin [68]. mprF mutations are the most common type of mutation in MRSA strains with reduced susceptibility to daptomycin (**Figure 3**) [69]. Several more genes are also identified which are associated with the reduced susceptibility to daptomycin such as dsp1 or asp23. The inactivation of these genes leads to reduced daptomycin susceptibility and the overexpression of single or both of the genes leads increase in susceptibility [70] whereas expression of dltA gene contributes to the staphylococcal net positive surface charge [71]. Kanesaka et al. using transmission electron microscopy, found that the some of the strains which were exposed to daptomycin which shows resistance developed an increase in the thickness of their cell wall and their thickness decreases on revert to daptomycin susceptible [72].

3.4 Resistance to aminoglycosides

Aminoglycosides works by mistranslation and changing the conformation of tRNA during bacterial protein synthesis by binding to A-site present on 16S rRNA of the 30S ribosome. Some even acts by inhibiting initiation /or elongation phase thereby blocking bacterial protein synthesis [73]. Most common mechanism of resistance to aminoglycosides especially in *Staphylococcus aureus* includes Aminoglycoside modifying enzymes which works by acetylating, phosphorylating, or adenylating amino or hydroxyl groups therefore inactivating aminoglycosides. Hundreds of aminoglycosides modifying enzymes are known encoded by genes which are commonly found on plasmids and transposons [74]. On clinical practising with some

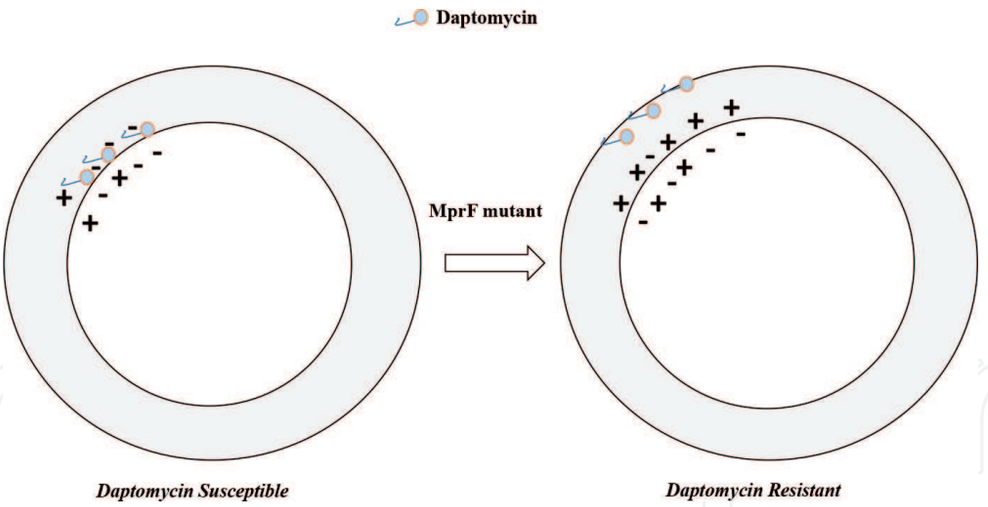

Figure 3.
Molecular mechanism of Staphylococcus aureus *resistance toward daptomycin via mprF.*

aminoglycosides such as gentamicin, tobramycin, and amikacin these three among Aminoglycoside modifying enzymes such as ANT(4=) nucleotide transferase, bidomain AAC(6=)le-APH(2=)la acetyltransferase and phosphotransferase, and APH(3=)IIIa phosphotransferase which are common in MRSA isolates with varied appearance, shows resistance [75]. Plazomicin, a synthetic aminoglycoside showed in vitro activity against 55 MRSA isolates that expressed one or more aminoglycoside-modifying enzymes [76] and has no protection against other resistance mechanism such as 16 s rRNA methyltransferases that modifies the aminoglycoside target site but these enzymes are not reported in S. aureus (**Figure 4**) [77].

3.5 Resistance to oxazolidinones

Oxazolidinones, the synthetic antibiotics blocks the formation of functional 70S initiation complex thereby preventing bacterial protein synthesis. Linezolid and tedizolid types of drugs from Oxazolidinones works interrupting transitional RNA positioning by binding to the bacterial 23S rRNA at the ribosomal peptide-transferase center. Even with the similarity in both of the structure tedizolid still

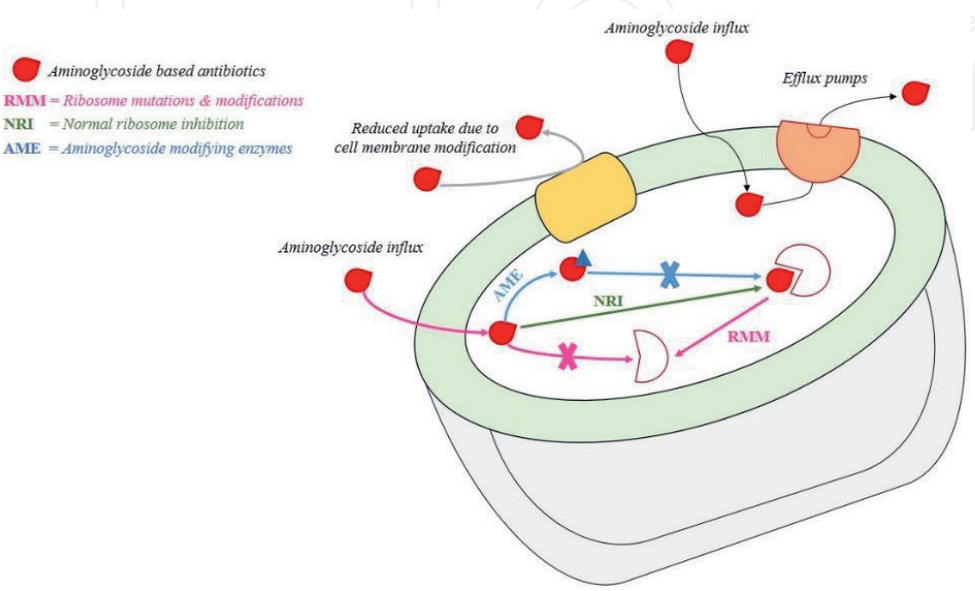

Figure 4.
Molecular mechanism of Staphylococcus aureus *resistance toward aminoglycosides.*

shows increased and better interactions at the binding site with increased potency [78]. All these resistance mechanisms make alteration to oxazolidinone binding site, most common are the point mutations occurring in the genes encoding for 23S rRNA mostly in the central loop of domain V [79]. S. aureus has four to seven copies of 23S rRNA gene collection of which determines the effect and degree of linezolid resistance [80, 81]. This kind of mutation, G2576T, in all five copies of its 23S rRNA gene has been found in the first clinical isolates of linezolid-resistant MRSA [82] are most common. Mutations in the genes which are encoding for L3 and L4 similar to mutation in 23S rRNA, induces a change in the linezolid binding site shows linezolid resistance. Studies showed structural rearrangement of the linezolid binding site due to deletion of one amino acid in L3 causing change in the position of several of the 23S rRNA bases as targeted by point mutations. Gene cfr (chloramphenicol-florfenicol resistance) linked with various mobile genetic elements also shows resistance to linezolid and other antibiotics by change in the drug binding site at the ribosomal peptide-transferase center by encoding a rRNA methyltransferase that causes change in position A2503 [83–85]. Several bacterial species port the cfr gene, a reservoir for drug resistance. MRSA isolates with cfr genes are more likely have additional antibiotic resistance genes as compared to non-cfr gene isolates. Another gene, optrA found commonly symbiosis with cfr gene in MRSA isolates also shows resistance to oxazolidinones [84]. Acts as an ATP-binding cassette transporter, which mediate the influx and efflux of drugs. Another optrA structurally similar gene poxtA first identified in MRSA isolates, shows in vitro resistance to oxazolones [86–89].

3.6 Resistance to quinolones with a focus on novel antibiotic delafloxacin

The fluoroquinolones (FQ) were first introduced into clinical practice in the year 1962 along with the development of Nalidixic acid. Fluoroquinolones (FQ) are class of fully synthetic antibiotics which are active against a broad range of gram positive and gram-negative bacteria and have a pivotal role in multidrug resistance therapy in Mycobacterial infection (Tuberculosis and non-tuberculosis). To treat acute bacterial skin and skin structure infections (ABSSSIs) with both enteral and intravenous preparations FDA approved non zwitter ionic FQ delafloxacin in 2017 [90]. Due slower MICs against S. aureus than other FQs delafloxacin has a higher barrier to resistance, it can serve as ant staphylococcal drug as monotherapy. Delafloxacin is found to be effective against multiple like Streptococcus pneumoniae, anaerobic bacteria Legionella, *Chlamydia pneumoniae*, *Neisseria gonorrhoeae*, Mycoplasma spp., in addition to *Staphylococcus aureus*. Its activity against the enterococci is variable [91]. Delafloxacin shows a property of "dual-targeting" in which it can form complexes with DNA and topoisomerase IV or DNA gyrase. Double strand break can be produced by the inhibiting the one or both the enzymes which results in the death of bacterial cell as they lack enzymes that can repair double strand break in DNA. Delafloxacin shows more potency against Gram positive bacteria as it shows anionic behavior at neutral pH due to the substitution of the R7 position (3-hydroxy-1-azetidinyl) [90, 92]. An anionic behavior of delafloxacin makes diffusion and accumulation of drug within the bacteria more readily as it is retained in bacterial cell for longer duration at neutral intracellular pH [93]. These characteristics makes antibiotics more effective in acidic environments [94]. Depending upon the ambient pH it shows activity against biofilm related infections and intracellular infections [91]. Estimated concentration of Delafloxacin selecting resistant mutant is 8 to 32 times lesser than for other Fluoroquinolones. This difference is due to the drugs dual targeting mechanism of action. Point mutations are method by which resistance is shown by bacteria, resistance occurs due to point mutations in target enzyme or by the action of efflux pump. Point mutation in ParC

subunit of topoisomerase IV results in resistance in case of *Staphylococcus aureus*. Delfatoxin resistance occurs due to various mutations in the target regions of topoisomerase IV [92–95]. Resistance to the FQs, including delafloxacin, often involves point mutations in the target enzymes or the action of efflux pumps in bacterial cells. In S. aureus, resistance is usually mediated by point mutations in the ParC subunit of topoisomerase IV. Delafloxacin often retains potency against S. aureus resistant to other FQ drugs due to target gene mutations or modifications. This relative resistance seems related to the structure of delafloxacin (perhaps due to C-7 and C-8 substitutions); delafloxacin resistance occurs only with several mutations in the target regions of topoisomerase IV. NorA, NorB, NorC, MdeA, QacA, and QacB includes a resistant phenotype of Common S. aureus efflux pumps active against Fluoroquinolones. The antiseptic chlorhexidine gluconate is also removed from cells by the plasmid-encoded efflux pumps QacA and QacB, sometimes called antiseptic resistance genes and their acquisition in a S. aureus population is co-selected by use of chlorhexidine or FQs. Delafloxacin is not as active substrate for typical *Staphylococcus aureus* efflux pumps compared to other drugs in the class [96–99].

3.7 Resistance to new class of antibiotics: pleuromutilins

In 1951 a compound Pleuromutilin a class of antibacterial which is isolated from a fungus called Pleurotomariids. Pleuromutilin and its natural molecule found to be effective against Gram-positive bacteria. For veterinary use Tiamulin used in livestock for the treatment of gastrointestinal and respiratory disease. Valnemulin is a second veterinary systemic Pleuromutilin antimicrobial approves and widely use in Asia and Europe. For systemic human use lefamulin was synthesized in 2006, lefamulin is novel pleuromutilin drug effective against most MRSA strains [100]. In phase 2 lefamulin was non inferior to intravenous Vancomycin. Pleuromutilin interferes with the process of protein synthesis by inhibiting the 50s subunit of the ribosome binding at site called peptidyl transfer centre [101, 102]. They specifically target the inhibition of initiation of translation. The extensive use of tiamulin and valenemulin for decades in livestock leads to MRSA strains and their mechanism of resistance to pleuromutilin are well studied. One of the resistance mechanisms involves alteration of target site on the ribosome which may require three or more mutations to develop resistant phenotype [103–105]. Resistant clones may be formed when *Staphylococcus aureus* acquire new genes by horizontal gene transfer including transferable cfr gene methylation a specific site on 23S rRNA. This methylation by cfr gene product results in resistance to several class of antibiotics including pleuromutilin, linezolid, streptogramin, phenicol, and lincosamides. In *S. aureus* is the family of at least four vga genes with variants, including vga(A)v, vga(A), vga(C), and vga(E), as well as lsa(E), all result in ribosomal protection results in cause of pleuromutilin resistance in S. aureus. Plasmid or transposons can carry strains vga(A) may become transmissible among strains. In ST398 livestock-associated MRSA strains found vga(c) strain also be carried on plasmid. The spread of mobile genetic elements among animal and human S. aureus strains raises concern for the emergence of widespread pleuromutilin resistance among human strains if drugs in this class are widely used [106, 107].

3.8 Resistance to mupirocin

Mupirocin was used as a decolonizing agent. It is widely used in CA-MRSA epidemic United States in 1990. But it was discovered in in 1970. Resistance to mupirocin by MRSA developed [10, 108]. Mupirocin resistance is developed due to ileS-2 gene [109]. The mupA and mupB genes responsible for resistance to mupirocin these genes encode novel isoleucyl-tRNA synthetases and can be carried out by

plasmids [110]. The threes aspect of REDUCE-MRSA study was cluster-randomized trial that evaluate screening, isolation, and decolonization with chlorhexidine and mupirocin in intensive care unit patients [111]. Mupirocin is best suitable option for MRSA nasal decolonization but shows some side effects. Development of novel decolonization agent should be our propriety. We can also develop agents that can act synergistically with mupirocin as recently described [112, 113].

3.9 Resistance to lipoglycopeptides

Dalbavancin, oritavancin, and telavancin, the semisynthetic derivatives of glycopeptides are the three lipoglycopeptides available in the US. Glycopeptides usually inhibits bacterial cell wall synthesis by binding to D-alanyl-D-alanine (D-Ala-D-Ala) terminal of growing peptidoglycan chains [114]. Due to their distinctiveness in structural modifications of each drugs heptapeptide core, lipoglycopeptides are more powerful than vancomycin which contains lipid side chain that helps in holding the drug to cell membrane providing stability and an increase in concentration of local drug. In case of oritavancin and telavancin their interaction with the cell wall promotes another mechanism of action as concentration-dependent depolarization of cell membrane leading to increase in permeability. Because of the structure of oritavancin it allows several other mechanisms of action which includes binding to the secondary site in peptidoglycan chains, pentaglycyl bridging segment of lipid II, transpeptidation inhibition and RNA synthesis inhibition [115, 116]. A survey study conducted from 2010 to 2014 in US and Europe showed 99.9% isolates of S. aureus susceptible to oritavancin and 98% isolates susceptible to dalbavancin in global survey during 2002 to 2012 [117] with rare Lipoglycopeptide resistance among S. aureus. Recently for dalbavancin, Resistance in some clinical isolates has been reported. On structural analysis showed an increase in the thickening of cell wall and abnormal cell wall construction in dalbavancin non-susceptible isolates [118, 119].

4. Evolution of *Staphylococcus aureus* as superbug

Alexander Flaming accidently discovered penicillin as fungal contaminant also having bactericidal effect against Staphylococcus aureus which in turn led to bulk production of this antibiotic [120]. Consequently, death rate due to bacterial pneumonia and meningitis fell down during World War II. Penicillin was discovered to act by breaking peptidoglycan assembly within bacterial cell wall followed by cell death due to osmotic fragility [121]. In early 1940's death rate of Staphylococcal infections was approximately 80%. However, resistance *Staphylococcus aureus* strains were observed after overuse of penicillin which got predominant in 1945 [122–124]. The major cause of this resistance was the eventual formation of plasmid encoded-lactamase which found to have ability of hydrolysing active moiety i.e. lactam ring of penicillin [124, 125]. The ability of plasmid encoded-lactamase to readily transfer which rises the penicillin against bacterial resistance rate up to 90-95%. Moreover, in 1950 a resistant clone of *Staphylococcus aureus* called phage 80/81 was responsible for the outbreak pandemic of skin infections, sepsis of skin and pneumonia. Initially it was concerned inside the premises of hospital but eventually it outspread within the public outside [126]. Australia, America and Canada were the majorly effected countries during this epidemic which lasted for almost 10 years until a methicillin came into market [127]. It was purposely designed in 1959 for the lactamase resistance strains of staphylococci and their treatment but surprisingly it worked efficiently for only one year because later on the methicillin resistance strain of Staphylococcus aureus was first observed in 1961 in United

Kingdom [128]. The major cause of acquired resistance was mecA gene at specific site of chromosome. mecA gene was reported to encode an alternative penicillin binding protein gene called PBR2a and PBR2 which possessed very little binding affinity against penicillin, methicillin, nafcillin and cephem derivatives [129]. However, this resistance was found to be different from penicillin acquired resistance as it included broad spectrum antibiotics i.e. almost entire class of lactams except ceftaroline and ceftobiprole [130]. Adding on, a genetic element was found to be the prime carrier of mecA gene and was responsible for the broad-spectrum resistance as well as outbreak of its infections in 1980 [131]. Few countries that had major impact were Ireland, United States and United Kingdom. Despite the fact that it was first observed in 1961 it was highly appeared in 1980 and responsible for pandemic. MRSA was major risk for people having low immunity therefore death rate was approximately 15 times and bacteraemia was observed to be 24-fold than earlier [132]. MRSA outspread in Europe in early 1970's was confirmed to be caused by one of the MRSA clones called 83 phages; an archaic clone which eventually became demolished and replaced by another five lineage clones of MRSA by 1980's. The foremost MRSA infection case was observed in Sydney in 1965 followed by sporadic nosocomial MRSA infections in Melbourne, Sydney and other cities of Australia [133, 134]. Western Australia was rather reported to be free from these infections until late 1980's when gentamicin susceptible Non-Multidrug Resistant (MDR) MRSA was observed first which later on outspread very fast [135, 136]. However, the quickest outbreak of MRSA was observed in Boston, United States of America in 1968 [137]. Number of cases increased drastically from 2.4–29% from 1968 to 1975 which rose to 56.1% till 2003 [138, 139]. Moreover, high rate of MRSA infections was observed in other parts across the world also [140–147]. In japan MRSA infections invaded in academic hospitals in 1980 which later become community spread in 1990 [148]. Number of MRSA infected patients were comparatively lower than observed in America however mild increase was observed in frequency of MRSA patients from 3.8% - 9.6% in 1990-1994. But when only the outpatients were considered the MRSA infection rate was observed to be drastically rose from 4.5-35% in 1994 [149, 150]. The first clinical isolate of MRSA known to carry PVL gene in CA-MRSA era was observed in 2003. Furthermore, according to the data given by National Infectious disease register in 10-fold increase in MRSA infectious cases i.e. 120-1458 has been found in 2004. Meanwhile the countries like Norway, Sweden, Denmark and Netherland were found to be free from these infections due to strict surveillance. In the period of six years (2000-2006), Eastern Australia and Queensland were reported to have an increase of 75-315 patients per million. MRSA strains prevalent in these countries were majorly non-MDR strains which have susceptibility to ciprofloxacin and resistant at least to one of the β-lactams. It was a period of high emergence of non-MDR strains of MRSA. In 2011, surveillance studies were carried out in Asian countries to find out the patients with MRSA infections [151–154]. Data revealed HA-MRSA prevalence was highest in Sri Lanka (86.5%) followed by Vietnam (74.1%), South Korea (65%), Thailand (57%) and Hong Kong (56.8%). However, the rate of infections in Indians and Philippines was quite low i.e. 22.6 and 38.1% approximately. Infected patients and staff were the major reason for the outbreak of MRSA across the countries and continents. With time and resistance MRSA had been found to be emerged, declined and modified accordingly. When initially observed, the MRSA strains were confined only to the hospitals and health care centres which later on becomes a pandemic via community spread. Moreover, livestock was also found to be affected by MRSA infections. According to last research report vancomycin was an antibiotic susceptible to MRSA however later on some investigations demonstrated Vancomycin Intermediate resistance *Staphylococcus aureus* (VISA) and Vancomycin Resistant *Staphylococcus*

aureus (VRSA) in some clinical strains. If this trend gets continued to be followed further then MRSA will undoubtedly become completely resistant strain which is a serious topic of concern in field of infectious diseases [155–158].

5. Conclusion

The rapid evolution of resistance in *Staphylococcus aureus* toward almost every antibiotic makes it a most challenging threat for human health as well as for the microbiology scientists. This bacteraemia has been reported to possess resistance mechanisms on the exposure of antibiotics only. Staphylococcus aureus quickly develop the defense/survival mechanism for even the new antibiotics which probably due to their fast structural and genetical alterations. Keeping this in view, several novel compounds are in pipeline to combat the resistant strains of *Staphylococcus aureus*. Moreover, identification of additional drug targets, better stewardship and combination therapies are also in process for the treatment of resistant strains of *Staphylococcus aureus*.

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Conflict of interest

The authors declare no conflict of interest.

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