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# Progression of $\beta$ -Lactam Resistance in *Staphylococcus aureus*

*Antresh Kumar and Manisha Kaushal*

## Abstract

*Staphylococcus aureus* is a notorious human pathogen that causes superficial and invasive infections both in nosocomial and community-acquired settings. The prevalence of staphylococcal infections became more challenging after emerging resistance against topical antibiotics. *S. aureus* evolved resistance to  $\beta$ -lactam antibiotics due to modification and expression of penicillin-binding proteins (PBP), inactivation of drug by  $\beta$ -lactamase synthesis, limiting uptake of drug by biofilm formation, and reducing uptake by expression of efflux pump. The wave of resistance was first observed in penicillin by  $\beta$ -lactamase production and PBPs modification. The second wave of resistance emerged to methicillin by appearing methicillin-resistant *S. aureus* (MRSA) strains. Cephalosporin has long been used as the last resort for preventing MRSA infections, but resistant strains appeared during treatment. In progression to control MRSA or related infections, carbapenems have been used but strains developed resistance. *S. aureus* is among the high-priority resistance organisms that need renewed efforts for the research and development of new antibiotics and innovative preventive approaches. However, a lot of toiling is involved in devising an effective treatment against drug resistant *S. aureus*. This chapter aim is to retrospectively determine the progression of resistance in *S. aureus*, against different  $\beta$ -lactam antibiotics and their challenges of medication.

**Keywords:** *Staphylococcus aureus*, Drug resistance,  $\beta$ -lactam antibiotics, Penicillin, Methicillin, Cephalosporin

## 1. Introduction

Infections caused by a variety of bacterial, fungal, viral, and other infectious microorganisms are considered to be the world's most leading problem. Infectious diseases are considered to be the world most leading cause of death, with almost 50,000 deaths per day [1]. Bacterial and fungal infections are the major cause of morbidity and mortality in both developed and developing countries [2]. *Staphylococcus aureus* is a gram-positive, coagulase-positive opportunistic bacterial pathogen, commonly found in the human nasal mucosa in the approximately 20–40% population [3, 4]. It causes a wide range of infections such as skin infections, including abscesses, impetigo, and necrotizing fasciitis; tissue infections, including osteomyelitis and endocarditis; and toxicities, including toxic shock syndrome, pneumonia, sepsis, and surgical site infections [5–7]. The superficial and invasive infections caused by *S. aureus* continue to raise serious health challenges globally as it notoriously exhibits resistance [8, 9].

These infections have rapidly developed resistance against most of the available antimicrobials, which pose serious threats [10–13]. Infections caused by *S. aureus* are associated with significantly higher mortality, because of the limitations of available antimicrobial therapies, difficulties in making a rapid and accurate diagnosis, and the development of multidrug resistance (MDR) [14]. The acute and chronic staphylococcal infections have now become more problematic after emerging multidrug resistance (MDR) against various frontline antibiotics [15, 16]. Antibiotics are small molecules that selectively inhibit the growth of a plethora of bacterial and other infections. These heterogeneous group molecules continue to be save many lives from different bacterial infections. Antibiotics are either naturally synthesized by microorganisms or chemically modified into exciting drugs.  $\beta$ -lactam antibiotics ( $\beta$ -LA) are considered to be the most successful and frequently used antibiotics against a number of bacterial infections. The underlying reason behind this is their wide spectrum activity, oral availability, excellent pharmacokinetics, lack of toxicity, and bactericidal action [17]. Due to the widespread and prolonged practice of  $\beta$ -LA emerged resistance to these resort and became an alarming and emerging problem to the public health. The microbial pathogens tend to adopt different resistance mechanism to skip the cytotoxic effect of  $\beta$ -LA. The progression in  $\beta$ -LA drug resistance to emerge multiple antibiotic-resistant microorganisms has made it difficult to manage many infectious diseases using common anti-infective drugs. In this chapter, we focus on emerging trends of drug resistance in *S. aureus* to the different  $\beta$ -LA.

## 2. $\beta$ -Lactam antibiotics ( $\beta$ -LA)

The landmark discovery the beta-lactam penicillin has been developed with the remarkable weapon to control bacterial infections during the Second World War [18]. It was naturally synthesized from *Penicillium chrysogenum* (also known as *Penicillium notatum*). Penicillin G was the first  $\beta$ -lactam antibiotic ( $\beta$ -LA) discovered in 1944, which began the era of antibiotics against a wide range of infectious microorganisms [19]. The development of penicillin led to search its different derivatives (amoxicillin and methicillin) for the betterment of their efficacy, bio-availability, solubility, stability, and other pharmacokinetic properties and to evade steadily emerging problem of multidrug resistance (MDR). Structurally, penicillin is composed of a thiazolidine ring attached to a side chain of a four-membered beta-lactam ring. All penicillins are derivatives of 6-aminopenicillanic acid, which sometimes differ in their side-chain structure. Many  $\beta$ -LA have lactam ring as an integral part of a molecule such as cephalosporins, monobactams, cephamycins, and the carbapenems (imipenem and meropenem). These  $\beta$ -LA antibiotics came into the light to rescue mankind from different Gram –ve and Gram +ve bacterial infections including *S. aureus*.  $\beta$ -LA are the most available and over 34  $\beta$ -LA approved by the FDA, which together constitute ~50% of all antibiotic prescriptions worldwide. Now,  $\beta$ -LA share the annual consumption of over \$15 billion, which contribute almost 65% of the total antibiotics [20].

The  $\beta$ -LA primarily target the cell wall of a bacterial pathogen. Peptidoglycan or murien present in the cell wall provides the mechanical strength to the bacterial cell membrane, which is composed of an alternating unit of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) residues, joined together by  $\beta$ -1  $\rightarrow$  4 linkage. The NAM is further linked with a pentapeptide stem, which is composed of L-Ala-D-Glu- L-Lys-D-Ala-D-Ala. The order and type of amino acids are almost similar in Gram –ve and Gram +ve bacterial with some slight variations. The last D-Ala is lost during maturation and glycan assembly is cross-linked to form a bridge

with the carboxyl group of D-Ala at position 4 and the amino group of the amino acid at position 3. Mechanistically,  $\beta$ -LA acts upon a 4-membered “beta-lactam” ring, which shows a resemblance to D-Ala-D-Ala sequence of the cell wall [21]. The primary function of PBP is in the elongation of the cell wall, which is composed of two distinct components termed as PBP1–4. The radioactive analysis revealed that penicillin specifically interacts with PBP protein *via* covalent interactions [22]. The tight binding of  $\beta$ -LA to the transpeptidase domain of PBP (penicillin-binding protein) thereby inhibits the peptidoglycan synthesis by acylating transpeptidase, involved in crosslinking peptide to form peptidoglycan [23].

### 3. $\beta$ -Lactam resistance in *S. aureus*

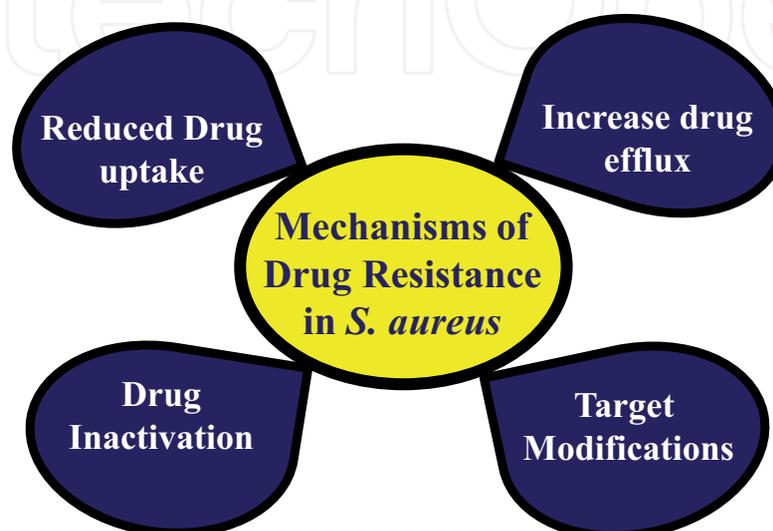
According to the European Centre for Diseases Control (ECDC), antimicrobial resistance is the single biggest threat facing the world in the area of infectious diseases. With the progression of antibiotics discoveries and their prophylactic usages have emerged drug resistance to single or multiple drugs. Antibiotic resistance is a natural selection process when microorganisms are treated with different antibiotics, and microorganisms tend to escape this selection pressure with greater competency to survive and thus show antibiotics resistance. In contrast, bacteria with a susceptible nature are killed with exposed antibiotics. Emerging resistance to  $\beta$ -LA is a serious health concern that causes a major hurdle in the treatment of bacterial infections. The condition of drug resistance is primarily developed by increasing and indiscriminate usage of antibiotics in clinical ailments, unregulated sales of antibiotics, a long course of medication, and poor public health infrastructure. According to a hospital survey, over 80% of clinical samples of *S. aureus* were established resistance to the frontline antibiotics including methicillin [24, 25]. It has been reported that 70% of nosocomial bacterial pathogens have emerged resistance to more than one antibiotic during medication of chronic infections. In contrast, an alarming increase in resistance of community-acquired bacteria has also been observed with significant high rate both in acute and chronic bacterial infections. The emergence of drug-resistant strains of Gram-positive (*Staphylococcus*, *Enterococcus*, *Streptococcus sp*) and Gram-negative (*Pseudomonas*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, *Salmonella sp*) bacteria is the more serious in the present therapeutic scenario. *S. aureus* clearly represents one of the most challenging pathogenic bacteria. Resistance in *S. aureus* strains has been continuously increasing; thus, the ability of these pathogens to spread in both hospital and community settings increased. Bacteria remarkably developed resistant to antimicrobial drugs in several ways. Upon antibiotics treatment, bacteria tend to overcome the selection pressure of the drug by morphological and genetic alterations or drug inactivation. Alterations of membrane integrity and transfer of resistance genes from one strain to another are the common examples of  $\beta$ -LA-mediated resistance in *S. aureus*.  $\beta$ -LA, Penicillin was initially succeeded in the treatment of *S. aureus* infections but widespread and prolonged uses of penicillin were no longer be effective and resistance has been emerged soon after in the 1950s [19]. Antibiotic resistance can be a typical feature of a bacterial species (intrinsic resistance) or acquired by the individual organism that is naturally susceptible (acquired resistance). The acquired resistance is the consequence of chromosomal mutations or acquisition of resistance genes by horizontal gene transfer [26]. Resistance to multiple  $\beta$ -LA can be acquired by individual strains, resulting in multidrug-resistant phenotypes. The high prevalence of drug resistance is primarily adopted by unregulated sales of antibiotics without prescription, a long course of medication, indiscriminate usage of drugs, and poor health infrastructure. The mobility and mortality caused by drug resistance in public

health are difficult to evaluate. In 2013, Center for Disease Control and Prevention (CDC) reported more than 11,000 deaths in the USA had a methicillin-resistant *S. aureus* (MRSA)-related infection (CDC 2013). This represents almost 50% of all causalities caused by antibiotic-resistant bacteria. As per WHO report, the MRSA remains among the high-priority multidrug-resistant organisms that need renewed efforts for the research and development of new antibiotics and innovative preventive approaches.

#### 4. Mechanism of $\beta$ -lactam resistance in *S. aureus*

Different mechanisms of drug resistance in bacterial pathogens are the major hurdle in their treatment. With emerging resistance, it became a serious concern to look into drug resistance mechanism, which can help us to prescribe a specific medication to effectively overcome the problem of resistance.

Several biochemical mechanisms are responsible for  $\beta$ -LA resistance, including enzymatic ( $\beta$ -lactamase) production inactivation of the drug (drug inactivation), modifications of drug target in penicillin-binding protein (PBPs) (target modifications), limiting uptake of drug by biofilm formation (reduced drug uptake), and active efflux of the drug (drug efflux) as shown in **Figure 1** [27, 28]. Bacterial pathogens resist the inhibitory action of antibiotics primarily due to the presence of an enzyme that inactivates the antibiotic or modified antibiotic target by mutation or by the post-translational mechanism, which reduces binding of the antibiotic to the target or bypass of the function dependent on the antibiotic target by an alternative enzyme that is not inhibited by the antibiotic. Moreover, overexpression of drug efflux pumps rendered to reduce uptake of the antibiotic inside the cell, by pumping out the antibiotics from the cell. In contrast, encapsulation of biofilm over the cell boundary reduces the cell permeability to resist antibiotics entry into the cell. The expression of chromosomal  $\beta$ -lactamase can be induced by either producing the plasmid-encoded penicillinase ( $\beta$ -lactamase) enzyme that hydrolyzes  $\beta$ -lactam ring or expression of PBP2a, and a penicillin-binding protein (PBP) encoded by gene *mecA* spread through horizontal gene transfer with low affinity to  $\beta$ -lactam antibiotics is primarily responsible for penicillin resistance [17]. The penicillin-binding cascade induces the *blaZ*-encoded penicillinase in *S. aureus*, which is transcriptionally regulated by regulatory genes *blaI* and *blaR1* [26, 29].



**Figure 1.**  
 $\beta$ -Lactam resistance mechanism of *S. aureus*.

## 5. Methicillin resistance in *S. aureus*

Methicillin was introduced in clinical practice for the effective treatment of penicillin-resistant *S. aureus* infections [30]. After 2 years, the second wave of resistance against methicillin came into the light and the first report on methicillin resistance *S. aureus* (MRSA) strain was published by MP Jevons in 1961 [31]. Statistically, incidences of methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant *S. aureus* (VRSA) infections have increased up to 54% in both hospital-acquired (HA) and community-acquired (CA) [32]. These antimicrobial-resistant infections cause a significant economic burden on public health. The economic burden of antibiotic resistance in Europe was estimated at almost 1.5 billion euros. However, USA spent more than 55 billion dollars each year on the treatment of antibiotic-resistant infections [9]. It was found that acquisition of methicillin resistance in *S. aureus* was primarily contributed by the integration of a *mecA* gene encoded for low-affinity penicillin-binding protein 2a or 2' (PBP2a or PBP2') into the staphylococcal chromosomal cassette (SSC*mec*) element of methicillin-sensitive *S. aureus* (MRSA) [33]. The expression of *mecA* in MRSA is induced by the interaction of methicillin and other antibiotics to the regulatory network. MecIR a regulatory protein, homologous to the BlaIR proteins, controls the expression of *mecA*. It is under the control of MecIR regulatory proteins that are homologous to the BlaIR proteins that regulate BlaZ expression [34, 35]. The SSC*mec* is located specifically with an unknown gene (orfX) of the staphylococcal chromosomal. The function of the unknown gene is mediated by two recombinases termed as *ccrA* and *ccrB* that help in the site-specific integration or excision of DNA elements from the staphylococcal chromosomal [36, 37]. The insertion sequence, transposon (Tn554) or erythromycin- and spectinomycin-encoded resistance genes, and tobramycin and kanamycin resistance-encoded pUB110 plasmid can be additionally jumped in the SSC*mec* region. Typing of SSC*mec* elements is fundamental for the molecular epidemiology of MRSA and categorized majorly into five types, that is, type I-V [38]. The SSC*mec*-type I-III elements are present in hospital-acquired MRSA strains, which are typically resistant to non- $\beta$ -lactam antibiotics. In contrast, SSC*mec*-type IV-V are only resistance to methicillin, which are primarily present in community-acquired MRSA (CA-MRSA). Different studies revealed that multiple insertions of SSC*mec* elements in the staphylococcal chromosome of MSSA strains yield a MRSA lineage. The *mecC* gene, homolog to *mecA* gene, exhibits 68.7% nucleotide identity is identified in *S. aureus*, *Staphylococcus sciuri*, and *Staphylococcus xylosus* strains [39]. The recent studies revealed that *mecC* carrying *S. aureus* contributes in methicillin resistance in the human population by up to 2.8% of MRSA strains [40–42], while no report was found on *mecB*-carrying *S. aureus* resistance to methicillin. In many MRSA strains, the expression of *mecA* is also affected either by the synthesis of truncated MecIR regulatory proteins or by repression by  $\beta$ -lactamase regulators BlaI and BlaR. The Mec and Bla regulatory proteins can alter the functional behavior and expression of PBP2a-encoded gene in MRSA strains. In a short period, MRSA strains have been identified all around the globe particularly Asia, USA, and Europe [43]. In spite of the rapidly spreading of methicillin resistance, MRSA exhibited broad-spectrum drug resistance against methicillin, penicillins, cephalosporins, and carbapenems. The MRSA cases were increased in hospitals and other healthcare facilities (hospital-acquired), and in communities (community-acquired infections). People with immediate surgeries or stay in healthcare facilities are at MRSA higher risk. Infection also spreads if a medical device has been put in their body or when they come close to contact with MRSA-infected patient. MRSA spreads in communities through uncovered or draining wounds mostly associated with crowded living, sharing personal items,

recent stays in healthcare facilities, etc. In 2017, CDC reported that more than a 0.3 million cases and over 10,000 deaths from MRSA-related infections are estimated in-hospital patients with more than 1.7 billion healthcare burdens in the United States. This figure represents mere a 50% of all the mortalities caused by antibiotic-resistant bacteria. The prevalence of MRSA infections in India has been reported to increase from 29% in 2009 to 47% in 2014 [35].

## 6. Cephalosporin resistance in *S. aureus*

Similar to penicillin or other  $\beta$ -lactams, cephalosporins also target to bind penicillin-binding proteins (PBPs) to inhibit peptidoglycan formation in bacteria. These are effectively used in the treatment of superficial (skin and soft tissue) infections, and nosocomial and community-acquired pneumonia. Different strains of *S. aureus* strains have evolved resistance to cephalosporins, which evolved by reducing the binding affinity of cephalosporins to transpeptidase of PBPs, and also,  $\beta$ -lactamases are produced by bacteria having encoded plasmid for inactivation of therapeutics effect of cephalosporins. The plasmid-mediated  $\beta$ -lactamase resistance is corroborated by the amount and activity of the enzyme produced in bacteria.

Recent studies revealed that the prevalence of cephalosporins resistance in *S. aureus* is comparable to the  $\beta$ -lactamase-resistant penicillin, which accounts for 30–35% [44, 45]. Ceftaroline is the fifth-generation antibiotics, approved by the FDA in 2010, which has a broad-spectrum activity against a plethora of bacterial pathogens. Ceftaroline is active against methicillin-resistant *S. aureus* (MRSA) and has been successfully used for the treatment of different invasive bacterial infections with low adverse effects. This potent third-generation drug was found resistance in MRSA-ST293 strain in different geographical regions. Ceftaroline had the higher affinity to PBP but nonsense or missense mutations in the *mecA* gene alter the amino acid sequence of PBP protein, which causes alteration in the ceftaroline binding to PBPs. In addition, alteration of the promoter sequence of PBP4 by mutation increases PBP4 production that leads to resistance to ceftaroline [46].

## 7. Carbapenem-resistance

The  $\beta$ -lactam antibiotic carbapenems are the last resort, potent, broad-spectrum antibiotic against Gram +ve and Gram -ve bacterial pathogens. They contain a carbapenem structure linked together with a beta-lactam ring, which primarily targets to bind with PBPs of the cell wall. Due to high potency, low adverse effect appeals to prefer the use of carbapenems. Prolonged and widespread uses of the drug have developed carbapenems resistance, which is contributed by a different mechanism. The resistance that arises to carbapenems is due to  $\beta$ -lactamase gene transfer/production, mutational alteration in PBPs, and expression of efflux pump systems [47, 48]. The carbapenem resistance is mainly contributed by  $\beta$ -lactamase production.

## 8. Future perspective

Emerging resistance in *S. aureus* is a serious human health problem, which continuously increasing mortality and morbidity rates in both nosocomial and acquired infections. The constant evolution of resistance to topical antibiotics

including the continuing appearance of new resistance mechanisms and complexity in multidrug-resistant phenotypes are appealing to find new diagnostic tools and therapeutic strategies to get rid of this problem. However, a lot of toiling has continued to devise a workable treatment against staphylococcal infections particularly for the elimination of MRSA and VRSA pathogens. Emerging MDR in *S. aureus* has evolved major challenges in research and need to expend research to the next level to understand the progression of drug resistance pathways and infections pattern of *S. aureus*. The new search of therapeutics targets and bioactive molecules and their judicious use may be proven significantly to prevent the problem of drug resistance [2, 49]. Reducing the outer membrane permeability of bacterial cells can circumvent the problem of drug resistance. Iron conjugated with the antibiotic method may help to selectively interact to the outer membrane to active transport of antibiotic inside the cell [50]. Another possible approach has been targeted to inhibit quorum sensing that is primarily related to the virulence factors release and associated with the microbial pathogenesis. Chemically, virulence factors are toxic to the host cells that disrupt immune response, along with host cell disruption and cell adhesion. SarA and agr are two main quorum sensing mechanisms of *S. aureus*, which can be targeted to block the quorum sensing for controlling *S. aureus* infections. In addition, bacteriophage therapy is one of the potential methods for controlling the drug resistance in *S. aureus* infection. Phage therapy has many advantages over chemotherapy, for example, very specific, no side effect, environmental friendly, no allergenic effects, and harmless to the eukaryotic host [51]. Phage has been used to eliminate MRSA infections but is still immature in clinical application [51]. The phage-based treatment of resistant *S. aureus* will further be helpful to select the gene responsible for its control. These strategies will pave a way to develop a vaccine in future against the *S. aureus*.

## 9. Conclusion

It is very clear that bacterium including *Staphylococcus aureus* shows extraordinary adaptability to cope with antibiotic effect and emerge drug resistance against antibiotics. The phenomenon of drug resistance was first observed when  $\beta$ -lactam antibiotics became ineffective after indiscriminate uses and plasmid-responsive  $\beta$ -lactamase (penicillinase) synthesis. The second wave of resistance against methicillin has been primarily contributed by the stable integration of a *mecA* gene-encoded penicillin-binding protein and penicillin-binding protein 2a or 2' (PBP2a or PBP2') into the staphylococcal chromosomal cassette (SCC<sub>mec</sub>) element. Cephalosporins have been proven as an effective drug preventing MRSA infections but failed. In progression to antibiotics, carbapenems have been used for preventing *S. aureus* infections, but multidrug resistance (MDR) strains developed. The common cause of bacterial resistance involves horizontal gene transfer, target alteration by point mutations, and expression of efflux pump, which made a variety of antibiotics ineffective and induces persistent infections in both hospital and community settings. Moreover, the prolonged and widespread use of different antibiotics, lack of awareness, and insanitation, primarily contribute in rapidly developing multiple drug resistance (MDR) in developing countries that causes a major financial burden in the treatment of infectious diseases. Though a lot of toiling is involved in devising an effective treatment against staphylococcal infections particularly for the elimination of MRSA and VRSA, the new search of bioactive molecules and their judicious use may be proven significantly to prevent the problem of drug resistance.

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