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REVIEW ARTICLE Open Access

Beta–Lactam Drug Resistance Pattern in *Staphylococcus aureus* Isolates: A Review

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Abstract:
Methicillin Resistance *Staphylococcus aureus* (MRSA) is a serious human disease also considered as a chronological developing zoonotic pathogen of common health and in term of veterinary concern. Pyoginic endocariditis, otitis media, food poisoning, pyogenic infection of the soft tissues and the skin, suppurative pneumonia, and osteomyelitis all are prevalent infection of MRSA in people.
MRSA can induce botryomycosis and infected contamination in horses; severe mastitis and pyogenic infection in cattle and ewes with marked toxemia; pustular dermatitis in dogs and cats as well as food poisoning; greasy pig disease in pigs which also called exudative epidermatitis.
A number of multilevel random-effects models were fitted to estimate mean occurrence rates of antibiotic-resistant *S. aureus*, and subgroup analyses were performed to compare antibiotic resistance rates of *S. aureus* throughout the years and among the methods to determine the antimicrobial susceptibility.
This review provides a comprehensive illustration about MRSA including background, epidemiology, resistance, and others. On other hands, different types of antibiotics have been mentioned in which they have been utilized against *S. aureus* and their mechanism of action is explained as well. Therefore, this review is helpful by its simpleness and comprehensive contents.

Keywords: *Antibiotics; β-Lactamase; Methicillin; MRSA; Penicillinase; Staphylococcus aureus.*

1. Introduction

Staphylococcus aureus is an opportunistic pathogen and Gram-positive commensal bacteria [1]. Sir Alexander Ogston, a Scottish surgeon, was the first scientist to describe the Staphylococci, as the reason to cause several pyogenic infections (forming pus) in people. In 1882, the name of Staphylococcus were applied to this type of bacteria by himself while he discovered their shapes under the microscope, the name was derived from Greek (Staphyle: Grape bunch shape; coccus, means berry or grain) [2].

Staphylococcus aureus is one of the most infamous and ubiquitous bacterial pathogens, responsible for an unknown number of simple skin infections and hundreds of thousands to millions of more severe, invasive infections worldwide each year [3, 4].

It is a prominent cause of pneumonia and other respiratory tract infections, as well as surgical site, prosthetic joint, and cardiovascular infections and nosocomial bacteremia [5]. They can create a

diverse arsenal of poisons and demonstrate frequent, and occasionally multiple, antimicrobial resistance [6].

S. aureus has an amazing potential to build resistance quickly. Environmental variables, such as cell membrane rupture or DNA damage, can all have an impact on the rapid development of antibiotic resistance [7]. Antibiotic resistance is a developing issue, and treatment failures are connected with substantial human and medical costs. Antibiotic resistance develops through a variety of processes, including changed drug targets, enzymatic drug inactivation, enhanced antimicrobial component efflux, and altered drug accessibility [8].

Because of the release of penicillinase enzyme, the majority of S. aureus strains (94%) are notably resistant to penicillin and its derivatives [9, 10]. MRSA has been discovered as a strain of *S. aureus* that is resistant to methicillin. Methicillin resistance, as well as cefoxitin resistance, might be clinically diagnosed by PCR-based detection of the mecA gene. The penicillin-binding protein (PBP-2A) is responsible for this type of antimicrobial resistance, and the mecA gene mostly encodes for it [11, 12].

MRSA are aggressive zoonotic biovars of *Staphylococcus aureus* that meet particular requirements for cefoxitin and methicillin resistance. Different phenotypic and molecular characteristics might be used to identify methicillin-susceptible *S. aureus* (MSSA) from MRSA. MRSA is invariably multidrug resistant, not only to penicillin but also to a variety of other antibiotic classes such as macrolides, fluoroquinolones, aminoglycosides, tetracyclines, and lincosamides [9]. MRSA has the potential to cause serious infectious disorders in humans, such as pyogenic endocarditis, suppurative pneumonia, otitis media, osteomyelitis, pyogenic infections of the skin and soft tissues, and septic arthritis. The rise of multidrug-resistant virulent MRSA strains is a significant public health issue [13].

MRSA is the leading cause of hospital-acquired infections (HA-MRSA) and community-acquired infections (CA-MRSA), therefore it is more than just a nosocomial bacteria. The morbidity of CA-MRSA infections has increased globally. CA-MRSA is genetically distinct from HA-MRSA in that it has a small kind of SCCmec and produces Panton-Valentine leukocidin and cytotoxin often [14].

The aim of this review is to mention the resistance of *Staphylococcus aureus* against several antibiotics, although there are several research articles mentioning this phenomenon, but herein we are summarizing the updated information about their resistance against the antibiotics in one source.

2. Epidemiology

The widespread commensal bacteria *Staphylococcus aureus* is found on the skin, in the throat, and nares of a wide range of animal species, including humans. *S. aureus* may spread from person to person (directly or by the use of spores), and it can also be disseminated zoonotically through close contact with animals or their products, such as raw foods. Additionally, it may be kept in the environment by using dung, water, or air [15, 16].

In high-income nations, the incidence of *Staphylococcus aureus,* a frequent cause of community-acquired (CA) and healthcare-associated (HA) bloodstream infections, is 20–30 cases per 100,000 people per year [17].

The persistence of methicillin-resistant *S. aureus* (MRSA) over the past several decades in both human and animal species has increased the risk of contracting a resistant infection that makes treatment more challenging and expensive. *S. aureus* is frequently resistant to one or more classes of antibiotics [18].

In the United Kingdom, seventeen pandemic MRSA strains have been identified, however EMRSA-15 and EMRSA-16 are the most common. Infections with MRSA in humans are mostly caused by the EMRSA-16 clone in both Europe and America [19].

Epidemiological information on the prevalent clones that cause the majority of outbreaks in Africa is scant. As stated by [20].

The CA-MRSA clones ST88-IV, ST5-IV, and ST239-III are the most common ones of African ancestry. A clone called ST88-IV has been seen in both community infections and hospitals. According to the description of the European lineage (EMRSA-16), it came from sub-Saharan Africa [21] as well as in community and hospital acquired illnesses in Algeria [22].

The MRSA lineage that predominates in pigs and other food animals is CC398. Other lineages of human origin include CC1, CC5, CC8, CC22, CC30, and CC45. The strain CC398 (ST398) poses a risk of interspecies transmission, which can be aided by frequent contact, contaminating environments, and a person's immunity. According to host specification, reservoir, and source of transmission, three main settings were identified [23].

3. Beta Lactam Groups

3.1 Beta Lactams

Beta-lactam drugs are one of the most well-known and widely used antibacterial groups. Molds, notably Penicillium chrysogenum, provided the first beta-lactams for human treatment [24]. While a Greek peasant lady purportedly healed injured soldiers using mold scraped off cheese in the sixteenth century BC; soldiers in Sri Lanka used poultices made from moldy oilcakes to wounds in the second century BC, according to the Ebers papyrus from Egypt, which dates from approximately 1550 BC and prescribes treating infected wounds with "spoiled wheat grain" [25]. Molds were used for medicinal purposes until the eighteenth century, with little thought given to how the molds were exerting their impact.

From a molecular standpoint, these medications share a similar feature: a four-member ring containing three carbon atoms (one of them is carbonyl group) and one nitrogen atom (Figure 1), these compounds can be divided into the following classes:

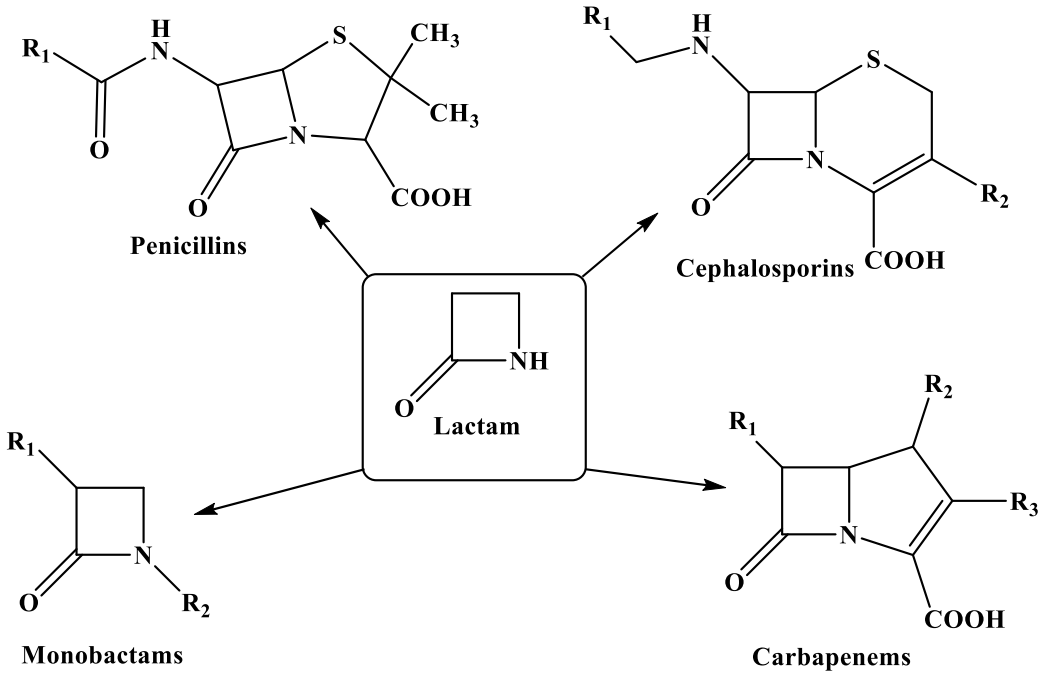

Figure 1: Chemical structure of beta lactams

3.1.1 Penicillins:

This type of antibiotics contain nuclei of lactam and thiazolidine ring (6-amino penicillanic acid) with different substituents attached to the ringside (most of them ends with suffix -cillin). This category includes natural penicillins, β – lactamase resistance agents, ureidopenicillins, carboxypenicillins, and aminopenicilins.

Over the years, several forms of penicillins were developed to combat different bacterial strains and enhance their effectiveness. Some frequently encountered penicillin variants are as follows:

1. Penicillin G (benzylpenicillin): One of the first and most widely used penicillins, primarily effective against Gram-positive bacteria.
2. Penicillin V: Similar to Penicillin G but administered orally, this antibiotic is often used to treat infections such as strep throat.
3. Amoxicillin: A broad-spectrum penicillin that is effective against both Gram-positive and Gram-negative bacteria and is frequently used to treat respiratory and urinary tract infections.
4. Ampicillin: A broad-spectrum antibiotic that is used to treat a variety of illnesses, including respiratory and urinary tract infections.
5. Piperacillin: A broad-spectrum penicillin that is routinely used in hospitals to treat more serious infections.

One of the difficulties with penicillins is the emergence of antibiotic resistance. Bacteria can develop penicillin resistance by production of enzymes called beta-lactamases, which break down the antibiotic. To overcome this, combination therapy with beta-lactamase inhibitors such as clavulanic acid are used to boost penicillin efficiency [26-29].

3.1.2 Cephalosporins:

Cephalosporins are a type of beta-lactam antibiotic with a broad spectrum of action.

Dr. Giuseppe Brotzu discovered them in the 1940s and isolated them from the fungus Acremonium (formerly known as Cephalosporium). Because of their efficiency against a wide range of bacterial strains, cephalosporins have proven to be valuable therapeutic agents in the fight against bacterial infections [30].

7 – aminocephalosporanic acid is involved in the backbone structure, and the ring of 3,6-dihydro-2*H*-1,3-thiazine as a side chain substitute. Although this terminology is not universally used, cephalosporins are generally split into five classes or generations.

Cephalosporins, like penicillins, work by blocking the synthesis of the bacterial cell wall. The bacterial cell wall is essential for maintaining the structural integrity of the microorganisms, and its damage results in bacterial lysis and death. Cephalosporins inhibit the trans-peptidase enzymes that cross-link the peptidoglycan strands, a vital step in the formation of bacterial cell walls [31, 32].

Cephalosporins are classified into generations depending on their antibacterial characteristics and activity spectrum. First-generation cephalosporins primarily target Gram-positive bacteria, whereas subsequent generations offer a broader spectrum of activity that includes a growing number of Gram-negative bacteria [33].

3.1.3 Carbapenems:

Their characteristic structure is a linked carbapenem to the β-lactam ring, in which helps the drug to obtain resistance versus mot β-lactamases. Nevertheless, gram positive bacteria can form carbapenemase, which is a serious problem for the drugs and antibiotic due to the resistance.

Carbapenems are a type of broad-spectrum antibiotic that is well-known for its robust effectiveness against a wide range of bacteria, including many multidrug-resistant species. They belong to the beta-lactam class of antibiotics, which also includes penicillins and cephalosporins. Carbapenems were introduced in the 1980s and have since become crucial antibiotics in clinical practice due to their potency against difficult and potentially fatal bacterial infections [34].

Carbapenems are distinguished from other beta-lactam antibiotics by their extraordinary resistance to beta-lactamases, which are enzymes produced by bacteria to breakdown beta-lactam antibiotics. Also, they are less vulnerable to these enzymes, making them extremely efficient against bacteria resistant to other beta-lactam antibiotics [35].

Also are frequently considered medications of last choice for serious infections caused by multidrug-resistant bacteria due to their broad spectrum of activity and resistance to beta-lactamases. They are widely used to treat difficult intra-abdominal infections, nosocomial (hospital-acquired) pneumonia, urinary tract infections, and immunocompromised individuals' illnesses.

To avoid the formation of carbapenem-resistant bacteria, the clinical use of carbapenems must be carefully regulated. Overuse or misuse of these powerful antibiotics can result in the establishment and spread of carbapenem-resistant organisms, posing a serious public health risk [36, 37].

3.1.4 Monobactams:

The beta-lactam ring is not bonded to another ring and stands alone. Aztreonam, the first monobactam developed and clinically used, was released in the 1980s. Aztreonam has demonstrated exceptional activity against Gram-negative bacteria, including several types resistant to conventional beta-lactam antibiotics. It is especially efficient against aerobic Gram-negative bacteria including Pseudomonas

aeruginosa and several Enterobacteriaceae. Monobactams, like other beta-lactam antibiotics, work by blocking the formation of bacterial cell walls [27, 38].

One of the major benefits of monobactams, notably aztreonam, is their little impact on Gram-positive and anaerobic bacteria. Because of their affinity for Gram-negative bacteria, they are an important therapeutic option for infections caused by these organisms, particularly in people who are allergic to conventional beta-lactam antibiotics [39].

The establishment and spread of antibiotic resistance, as with all antibiotics, is cause for concern. While monobactam resistance is less widespread than resistance to other beta-lactam antibiotics, it is critical to use these antibiotics sparingly in order to maintain their efficacy [40, 41].

3.2 Mechanism of Action of Beta Lactam Antibiotics

Antibiotic resistance is a developing issue, and treatment failures are connected with substantial human and medical costs. Antibiotic resistance develops through a variety of processes, including changed drug targets, enzymatic drug inactivation, enhanced antimicrobial component efflux, and altered drug accessibility. β-lactam drugs (which considered as most common antibiotics), they are playing an important role as a bactericide due to inhibiting the bacteria to synthesize the cell wall [42].

The basic function of these antibiotics are interrupting the polymerization of peptides in which the peptidoglycan constituents of cell wall of bacteria have been linked to each other, this process also called transpeptidation. Although the complete illustration of the mechanism still is not interpreted particularly, but the most preferred method is binding of the beta lactam antibiotic to inert target part inside the bacterial surface cell membrane, this targeted part called PBPs (Penicillin Binding Proteins) [43, 44].

PBPs are consisting of three enzymes (endopeptidase, trans peptidase, and carboxy peptidase), these enzymes are participating in the final steps of gathering the cell wall of bacteria and its reshaping while growing and cell division.

Beta-lactam antibiotics have many attractions for several PBPs, depending on their bounds having dissimilar influences on bacteria [44]. Stopping the activity of some Penicillin Binding Proteins such as PBP 1A, 1BS, 2 and 3 are causing death to the bacterial cell. On the contrary, some other PB proteins like PBP4, PBP5 and 6 are not necessary for the bacterial viability, this makes their inactivation via β-lactam drugs baleful to the specific bacteria. There are some other reasons that involved in the lysis of bacterial cell. When the beta lactam compounds are binding to the bacteria they are inactivating the endogenous inhibitors the autolysins of bacteria [45]. The autolysins are able to cause cleavage of covalent bonds in the cell wall of bacteria and causing the lysis of bacteria lysis. The growth of a particular bacteria or other microorganisms can be inhibited by beta lactam molecules but not being killed this phenomenon called bacterial tolerance [46, 47].

3.3 Methicillin

Methicillin, commonly known as Staphcillin, is a semisynthetic penicillin-related antibiotic (Figure 2) that used to be effective against staphylococci (staph) resistant to penicillin because they manufacture the enzyme penicillinase. Methicillin is no longer widely used, having been mainly replaced by Vancomycin. Staph bacteria have developed resistance to a variety of medicines during the last 50 years, including the routinely used penicillin-related drugs, such as methicillin. Methicillin-resistant *Staphylococcus aureus*, or MRSA, is the name given to these antibiotic-resistant bacteria [48].

Beecham invented the antibiotic methicillin in 1959. It was historically used to cure certain infections caused by sensitive gram-positive bacteria, particularly penicillinase-producing species like *Staphylococcus aureus*, which would be resistant to most penicillins otherwise [49].

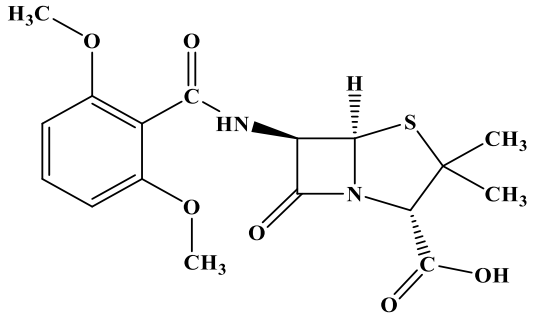

Figure 2: Chemical Structure of Methicillin

3.4 Beta Lactamase

This enzyme inactivates the beta-lactam antibiotics (penicillin) by cleavage of the β-lactam ring [50]. *S. aureus* facilitated the production of penicillinase and in which introduced the resistance to penicillin, encoded and prearranged by blaZ.

There are four types of penicillinase are available and described in *S. aureus* defined in terms of A–D [51].

The mode of action of penicillin involves inhibition of the formation of the normal cross-linkages in the cell of the bacteria wall and particularly in (peptidoglycan layer). Penicillin forms an inactive complex with transpeptidase a key enzyme in cell-wall synthesis, so that the peptide cross-linkages do not form [52].

Microbiologists innovated a scheme that is used for the classification, based on the utilization of biochemical properties and the molecular structure of the enzyme as well as nucleotide sequence of the defined gene to replace the beta lactamases with other functional groups [53].

β-Lactams such as penicillin are the most widely used antibiotics, and β-lactamases are the greatest source of resistance to penicillins. β-lactamase is produced by the Staphylococci that have blaZ genes [54-56]. The MIC of penicillin has the formal sensitivity range equal and greater than 0.12 mg/L, but the CLSI is recommending the additional tests to get the high performance. The phenotypic procedures were applied for the detection of penicillinase, i.e. penicillin disk diffusion, nitrocefin test, starch-iodine method, and cloverleaf assay, versus PCR assay for blaZ [57].

3.4.1 β-lactamase Hyperproduction

The most common mechanism of MRSA is PBP2a, beside this mechanism, many studies have reported the isolation of disputed strains of oxacillin resistant *S. aureus* in the society. Tehse strains have been characterized by MIC oxacillin close to breakpoint differentiating between methicillin resistance strain and methicillin susceptible, while the MIC of oxacillin for most of strain of MRSA are remarkably high. The major mechanism to interpret this phenotype is β – lactamase hyper production.

Isolates of *S. aureus* can be classified according to their susceptibility to penicillin G where MIC is equal and less than 0.12 mg/L, resistance to penicillin and susceptibility to methicillin with their MIC values ≥ 0.25 mg/L, and ≤ 8 mg/L respectively, by implementation of certain criteria National Committee for Clinical Laboratory Standards, oxacillin was not effective in the annihilation of (a)

BORSA with oxacillin MIC ≥ 4 µg/mL or (b) beta lactamase hyper production BORSA where MIC is ≤ 2 µg/mL. Further examination into dosing of beta lactam strategies versus various BORSA strains is necessary to prevent possible failure of therapy. All strains of BORSA resulted positive for the S. *aureus* of specific gene femA and the results were negative for MRSA specific gene mecA [58, 59].

3.5 Methicillin Resistance *Staphylococcus aureus*

Common problem is the strains of methicillin resistance *Staphylococcus aureus* MRSA which carry multiple resistance to a variety of antibiotics and antibacterial agents, such as cephalosporins, methicillin, tetracycline, gentamicin, quinolones, and erythromycin. Some strain attained resistance to all main groups excluding the vancomycin. Maximum number of these isolates were collected in hospital, where they involve approximately 40 % of *S. aureus* infections. An even greater cause for concern are reports of vancomycin resistance. Infectious disease specialists are monitoring this new trend and introducing drug replacements such as synercid [60].

The gene femA generated and encoded as a factor that is necessary for resisting the methicillin which is abundantly available in all isolates of *S. aureus*. 48-kDa protein is the product of gene femA, has been associated in metabolism of cell wall, as well as in the growth of most cultures [61].

Three well known mechanisms are available for the *S. aureus* to resist the methicillin hyper production of beta lactamase; normal penicillin binding proteins modification; and the existence of attained PBP2a.

The most common mechanism is the acquisition of a gene of a new transpeptidase, which has reduced affinity for β-lactam antibiotics, but it's still able to carry out its enzymatic function of cross-linking peptidoglycan [62].

The resistance gene mec A codes for a unique penicillin-binding protein and is transmitted chromosomally. In contrast, PBP2a is not the inherent set part of *S. aureus* PBPs, but unique, acquired, and inducible protein which has the molecular mass nearly 76 kDa, and only is produces by MRS.

The intermediated PBPs isolates are including the resistance mechanism against all types of beta lactams, such as penicillins, carbapenems, beta lactam/beta lactamase inhibitor collection and cephalosporins.

Song and his colleagues in 1987 found the first *mecA* sequence, later this gene is defined to be carried on a mobile genetic element, the SCC mec. Additionally, carrying mecA gene, SCC involving regular gene; IS431mec inserting sequence; also recombining gene ccr, which the responsibility to excise and integrate the SCC mec. Variable combinations of mec complex gene categories and ccr complex gene have been defined, four types of SCC mec, labeled SCC mec types I – IV. Nowadays, type V SCC mec also has been examined and explained which have been collected in Australia by the isolates of CA-MRSA strain. Community-Acquired Methicillin-Resistant *Staphylococcus aureus* isolates can be distinguished from Hospital-Acquired or Hospital associated Methicillin-Resistant *Staphylococcus aureus* isolates via some distinguishable characteristics, for instance antibacterial susceptibility, pulsed field gel electrophoresis, multilocus sequencing type, and staphylococcal chromosomal cassette mec typing [63, 64].

4. Conclusion

Although there are several antibiotics available nowadays, but in the other hand, bacteria are trying to resist the activities of the drugs and medications, for this reason some drugs are no longer used to cure the diseases and infections happened by bacteria.

The availability of different structure of medicine and their derivatives to cure the patients are quit important to synthesize the new generation of the treating illnesses and protection from bacteria.

Additionally, further experiments are required to increase the reliability and efficiency of the antibiotics to accompany with increasing the rate of resistance of microorganisms, the process should be following the process of inhibiting the activity of resistance especially MRSA and trying to discover a new method to follow the activity of new forms of pathogenic organisms.

New chemicals should be involved in the preparing of antibiotic derivatives in order to be more sufficient against the MRSA.

5. Author's Contribution:

We confirm that the manuscript has been read and approved by all named authors. We also confirm that each author has the same contribution to the paper. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

6. Conflict of Interest:

There is no conflict of interest for this paper.

7. Acknowledgment:

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