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REVIEW ARTICLE **OPEN ACCESS**

A Review on Multiple Drug Resistance of *Staphylococcus aureus* and Future Assessment

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ABSTRACT

The continuing spread of drug-resistant S.aureus in the world is an increasing problem. Staphylococcus aureus is an opportunistic infectious organism. It leads to an array of infections, hazardous to human health. S.sureus is resistant to most of the discovered antibiotics; beginning from penicillin & up to linezolid & daptomycin. It acquires resistance due to genetic modification and a mutation. This review highlights increasing antibiotic resistance strains and the future outlook.

Keyword: *Spread, durg, human helth, antibiotics*

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INTRODUCTION:

Staphylococcus aureus is naturally present on human skin and the nasopharynx.It can cause a wide range of infections, from minor skin infections to post-surgical wound infections. It was the first time identified, in the 1880s, by scientists Ogston from purulent fluids of legs abscess [1-5]. It was clinically isolated in 1960 at a hospital. Transmission of *S.aureus* is due to direct contact, also through skin-to-skin contact with an infected person, although contact with contaminated objects and surfaces also lead to infection. Infective endocarditis, bacteremia, bone infection and soft tissue, and some skin disease are caused due to *S.aureus.*[8].*S.aureus* acquired resistance to many antibiotics discovered after the pre-antibiotic era,like penicillin, methicillin, vancomycin, trimethoprim, erythromycin, clindamycin, etc. Due to the high mutation rate, rapid changes occur in the genetic constitution of *S.aureus.* Within a very short period of time, mutated strains were discovered. For example, HA-MRSA, CA-MRSA, ST93,etc. In this review article, we discussed different variants of the *S.aureus* strain and provided probable situations for diseases caused due to *Staphylococcus aureus* in near future [7, 8]

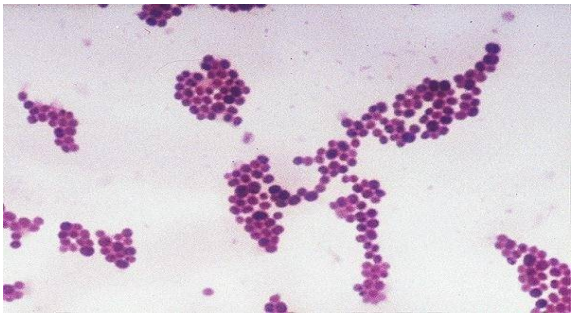

Fig 1.Gram-positive nature of *Staphylococcus aureus*[14].

Infections caused by *S.aureus* antibiotic-resistant strains have reached an epidemic extent worldwide. In the pre-antibiotic era, i.e. before the discovery of penicillin in 1928$_{S,}$ 70-80% of people affected due to *S.*aureus(Fig.2)[3]

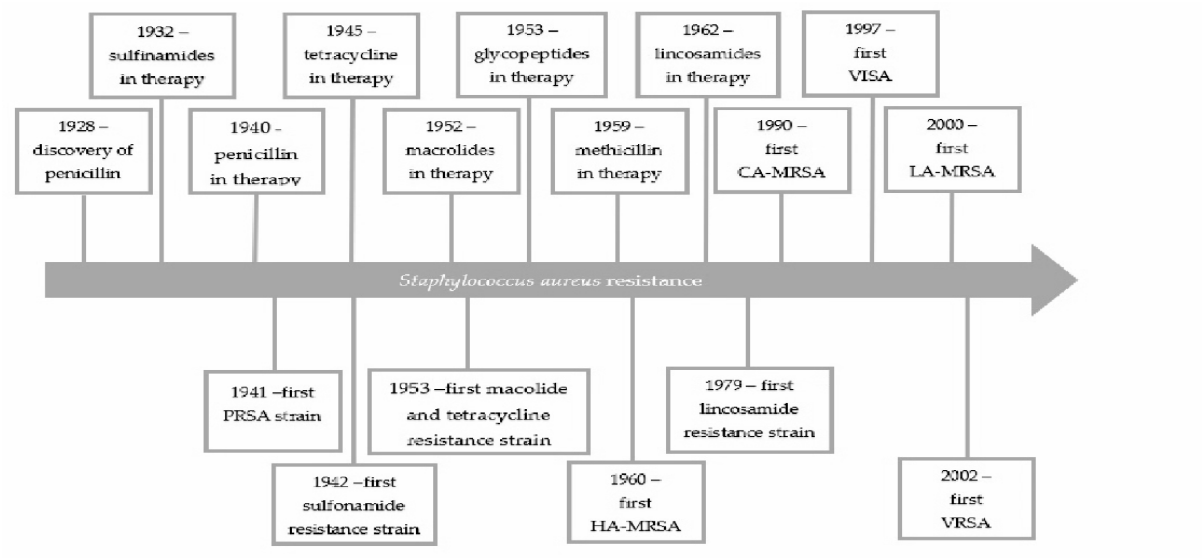

Fig.2: Discovery and resistance of antibiotics [4].

Penicillin:

The 1st resistance strain of penicillin was isolated from a hospital and the subsequent population in 1942(fig.2). The *S.auerus* resistant strain is mediated by a blaZ gene coding β-lactamase enzyme.It is an extracellular enzyme,produced during exposure to β-lactam(fig .4)[3].

Methicillin:

In 1961(fig .2) *S.aureus* became resistant to Methicillin.It is a β lactam antibiotic, involved in the synthesis of peptidoglycan. The mecA gene produces PBP2a with a low affinity for β-lactam ring [6].However, the main mechanism is, Due to the expression of unknown PBP, and PBP2a genes. *S.aureus* acquires resistance to many beta-lactam antibiotics like methicillin. But it performsthe function of host PBP2.[12].

Tetracycline:

In 1953(fig.2), *S.aureus* became resistant to tetracycline. There are two main mechanisms of tetracycline resistance in *S. aureus* active secretion, by expression of tetK and tetL genes located in the plasmid and ribosomal protection by elongation factor by gene encoding tetM or tet O(fig.4)[2].

Vancomycin:

In 1997(Fig.2), the first details of vancomycin transitional-resistant *S. aureus* are isolated two forms of vancomycin-resistant *S.aureus* strains are identified. Alterations in peptidoglycan, a cell wall component biosynthesis may result in decreased sensitivity to vancomycin. VISA strains are notable for an excess amount of synthesized peptidoglycan.Cross-linking of peptidoglycan strands is also reduced, exposing more D-Ala-D-Ala residue(Fig.3)[3].

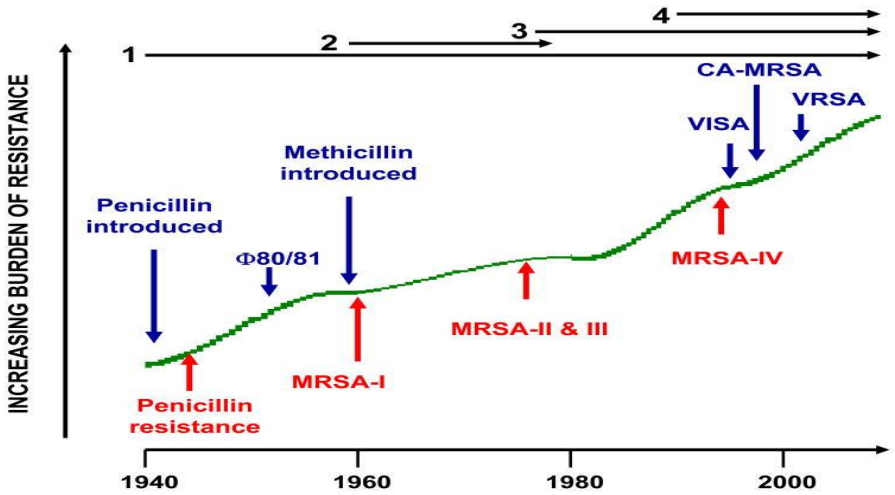

Fig 3. The increasing burden of resistance[1].

Aminoglycoside:

Aminoglycosides like gentamicin,plazomicin, and streptomycin, were introduced in 1944 whereas resistance is developed in1950s.Resistance in staphylococci is due to three events such as chromosomal

mutation, which changes the binding site of ribosomes; leads to the production of low-level cross-resistance; and enzymic modification(fig.4)[12].

Macrolide:

Since 1953(fig*.2)S.aureus* has become resistant to macrolides like erythromycin. In *staphylococcus aureus,* the msr A gene and erm genes are responsible for an efflux mechanism that encodes enzymes that are not possible to change and they are constitutively resistant to Macrolide antibiotics. The mechanism required for resistance is a modification of ribosomes in bacteria, Inactivation of enzymes and macrolide play a role in the process in which bacteria transport compounds outside the cell which are potentially toxic, or it is the protection of ribosomes by ABC F proteins.These mechanisms are also seen in Lincosamide-Streptogramin B (fig.4)[4].

Mupirocin:

In the United Kingdom, in 1987, a Mupirocin-resistant strain of *S. aureus* was reported. There are two types of Mupirocin resistance. The first is high-level mupirocin resistance, and the second one is low-level mupirocin resistance. mupirocin interdicts the protein synthesis of bacteria by interfering with the activity of isoleucyl-tRNA synthetase [10].

Quinolone:

It is Gram-negative antibiotic used as an anti-staphylococcal agent identified in the 1980s. Quinolone-resistant strains are emergent from MRSA strains. Resistance is developed due to chromosomal mutation in antibiotics. Spontaneously, a mutation occurred in a target site like gyrase required for supercoiling whereas topoisomerase iv for concatenated DNA separation. Amino acid changes during translation of mRNA transcribed for the synthesis of both target sites, gyrase (gyrA subunit) and topoisomerase iv (parC or grlAssubunit) which reduces quinolone affinity[3].

Sulfamethoxazole (SMZ) and Trimethoprim (TMP):

Sulfamethoxazole (Gantanol),is a type of sulfonamide it acquired resistance in 1942(fig.2). Sulfonamide's main functions are related to the specific cell process mostly, p-aminobenzoic acid metabolism. The sulfamethoxazole resistance gene is sulA which synthesis a gene product Dihydropteroate synthase. Mode of resistance is developed due to the Overproduction of p-aminobenzoic acid enzymes(fig.4). Whereas TMP is involved in the inhibition of dihydrofolate reductase (DHFR), which has catalytic activity in the formation of tetrahydrofolate from dihydrofolate[11].

Oxazolidinones:

The Resistance gene is rrn. The gene product is the 23S rRNA Mechanism of resistance towards mutations in domain V of the 23S hi rRNA component of the 50S ribosome. Interferes with ribosomal binding[13].

Quinupristion dalfopristion linezolid:

It is a combination of two antibiotics. The resistant gene in staph aureus is ermA, ermB, ermC,and the gene product is Ribosomal methylases. The mechanism of *S. aureus* for this antibiotic is to reduce binding to the 23S ribosomal subunit. Whereas for dalfopristin the resistant genes are vat, vatB. And the gene product is acetyltransferases. The mechanism for dalfopristin is an enzymatic modification of dalfopristin. Nowadays, Quinupristin-dalfopristin is the antibiotic used for the treatment of *S.aureus,* but recent studies showed that Quinupristin -dalfopristin is becoming Susceptible to *S. aureus* [12].

Daptomycin:

One type of antibiotic generated from the fermentation of *Streptomyces roseosporus* is daptomycin, a cyclic lipopeptide. The way that daptomycin destroys bacteria relies on the concentration; it secures preferentially to membranes of Gram-positive bacteria and inserts itself into the membrane. Due to the interference of crucial metabolic processes such as RNA synthesis, DNA, and protein, bacterial cells experience depolarization and ultimately die(fig.4).This antibiotic is used mostly till now but recently daptomycin is becoming non-susceptible[4-9].

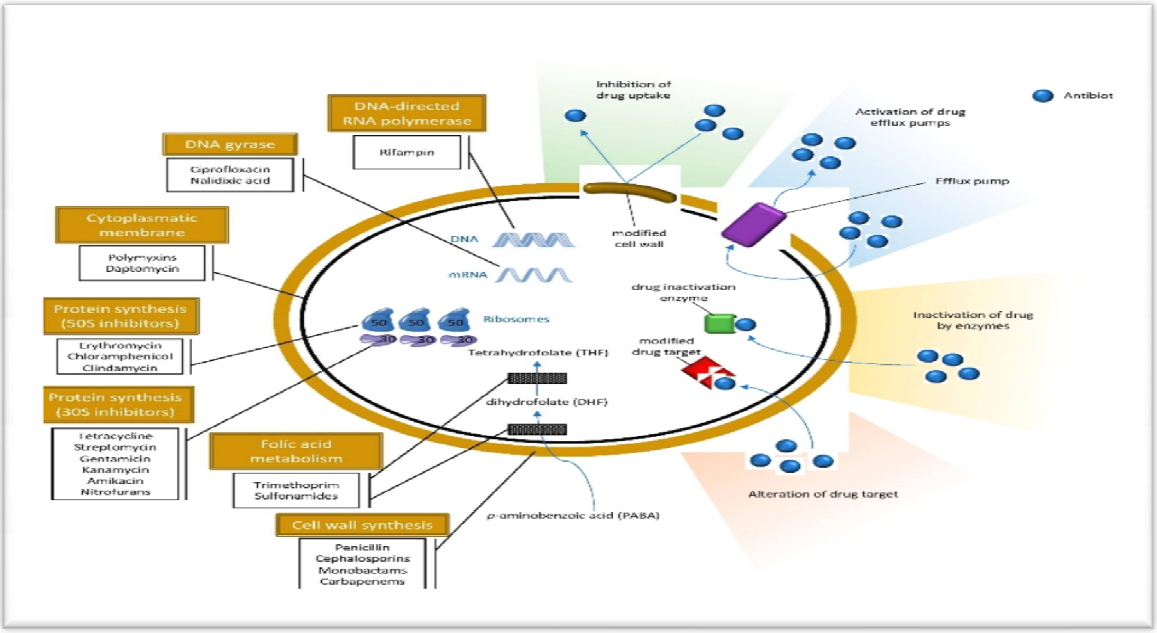

Fig.4. Schematic representation of target site and its mechanism of antibiotics resistance [11].

FUTURE ASSESSMENT

Multiple drug resistance of *Staphylococcus aureus* hasled to many issues. The advent of the antibiotic era, the overuse and inappropriate use of antibiotics have led to the rapid emergence of multidrug-resistant pathogens, which increases the number of people suffering from diseases caused due to *staphylococcus*, Increase in death rate, healthcare costs, and hospitalization.Multi-drug resistance (MDR) is a global concern that has a dire impact on healthcare. Microorganisms are becoming resistant to antibiotic treatment due to continuous exposure to antibiotic treatment. Although MDR is thought to be a relatively natural process among bacteria, its prevalence is rising for a variety of causes, including the use of unspecified antimicrobial medications, filthy sanitary settings, and subpar medical facilities. Bacteriophage Therapy may be used in therapeutic settings to treat patients successfully and stop or slows the emergence of bacterial resistance. In this review, we concluded that the speed of *S.aureus* to get resistance is very fast, therefore it is very difficult to treat the infection. Hence, it is very important to find novel drugs against *S.aureus* as soon as possible.

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