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A REVIEW ON THE CURRENT STATUS OF MULTI-DRUG RESISTANT *STAPHYLOCOCCUS AUREUS* AND ITS FUTURE PROSPECTS

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ABSTRACT: Infectious diseases are the most significant cause of fatalities worldwide. *Staphylococcus aureus* could be a common human infective microorganism that will trigger various infectious diseases, like soft tissue and skin infections, osteomyelitis, bacteremia, endocarditis, and fatal respiratory illnesses. In recent decades, because of the evolution of microorganisms and the abuse of antibiotics, the drug resistance of *S. aureus* has been stepped by step exaggerated, and the infection rate has risen worldwide. Accumulating proof has demonstrated that the resistance mechanisms of *S. aureus* are complicated, that is, resistant to several types of antibiotics. Multiple antibiotic-resistant *Staphylococcus aureus* is one of the common causes of severe nosocomial infections, and the gastrointestinal tract is an important source of its transmission. Productive treatment remains difficult and needs the analysis of each novel anti-microbial and connected aspect of care, like communicable disease consultation, diagnostic technique and supply source. This review focuses on developing resistance to currently used antibiotics and examines prospects for new antibiotics and the known use of drug combos.

INTRODUCTION: India carries one of the biggest burdens of drug-resistant pathogens worldwide. In 2008, NDM-1 reported that anti-microbial resistance had spread speedily to different countries. The Indian market is one of the biggest customers of antibiotics worldwide, and the global antibiotic trade is increasing speedily. Anti-microbial resistance arises once microbes develop a mechanism to escape the action of anti-microbial agents.

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Irrational and overuse of antibiotics is the main issue that contributes to anti-microbial resistance. In India, various actions are taken as well, including the setting up of a National Task Force on anti-microbial resistance containment (2010), the "Chennai Declaration" by an association of the Indian Medical Societies (2012), the setting up of an Indian Council of Medical Research national policy work network of laboratories, the "Red Line" campaign for educating the public and the National Action arranged on AMR 2017.

There is a requirement for group action AMR education in medical education [1, 2]. Multidrug-resistant (MDR) was outlined intrinsically due to their in vitro resistance to over one anti-microbial agent in three or additional anti-microbial classes. Antibiotic resistance is defined by the inability of a

drug or medication to kill a pathogen that was previously used to inhibit or kill an equivalent germ or pathogenic microbe (WHO, 2015). Anti-microbial resistance is widening globally, making it difficult to manage infectious diseases and therefore leading to mortality and morbidity of people [3].

Antibiotics are important agents in combating microorganism infections. However, currently, antibiotics have become less effective due to the emergence of drug-resistant microorganisms. It is imperative to research newer drugs that are active against drug-resistant microorganisms. Drugs derived from plants play a major role in interfering and treating human diseases. Microorganisms like bacteria have the genetic ability to transmit and acquire resistance to synthetic drugs that are used as therapeutic agents [4]. *Staphylococcus aureus (S. aureus)* is one of the main pathogens in hospital and community infections. It can cause many infectious diseases, such as mild skin and soft tissue infections, infective endocarditis, osteomyelitis, bacteremia and fatal pneumonia [5]. *Staphylococcus aureus* was first discovered in 1880 in Aberdeen, Scotland, by surgeon Alexander Ogston in patients with ulcerated sores. The ability of *S. aureus* to develop resistance to certain environmental conditions and a wide range of antibiotics and disinfectant agents. Bacteria have been implicated as a cause of long-term survival pathogens in the environment [6].

Staphylococci aureus is the most pathogenic member of the genus *Staphylococci* and the causative agent of many diseases, including superficial skin abscesses, food poisoning, and potentially fatal diseases as bacteremia, necrotic pneumonia in children and endocarditis [7]. In animals, it causes mastitis in cows, botryomycosis in horses, dermatitis in dogs, septicaemia and arthritis in poultry [8, 9]. The severity of the disease is due to the production of several putative virulence factors and possession of antibiotic resistance genes such as mecA, VanA, staphylococcal exotoxins and other factors that facilitate the initiation of the disease process, immune evasion and host tissue destruction [7, 10]. Antibiotic resistance development in *S. aureus* was first reported in the mid-1940-ties when a strain of *S. aureus* developed resistance against penicillin by producing a hydrolyzing enzyme called penicillinase [11].

1. Drugs Resistant for Treatment: The high capability of *S. aureus* to improve resistance against most antibiotics has triggered issues in the cure of hospital infections. It has been documented that the majority of *S. aureus* traces had been resistant to distinct antibiotics **Fig. 1** as per Indian Council of Medical Research guidelines [12] and their mode of action in **Table 1.**

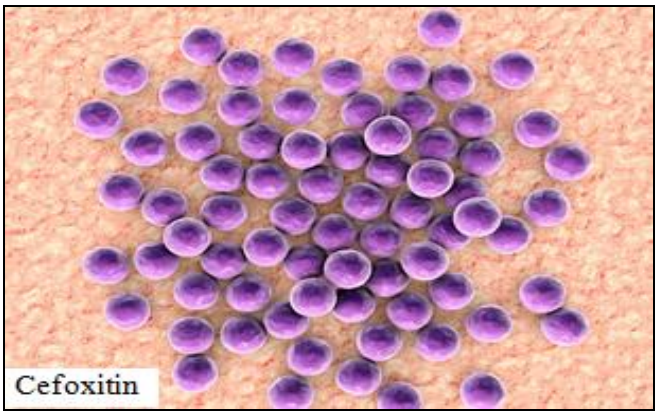

FIG. 1: PROMISING ANTIBACTERIAL AGENT AGAINST MULTI-DRUG RESISTANT (MDR) *S. AUREUS*

1.1 Cefoxitin: Cefoxitin could be a broad-spectrum, semi-synthetic cepha antibiotic for endovenous administration. It's derived from *cephamycin C* and it's made by *Streptomyces lactamdurans*. Cefoxitin could be a second-generation cephalosporin, its antibacterial drug activity [13]. It contains methoxy groups at the seven alpha positions has 2-thienylacetamido and carbamoyloxymethyl side-groups. Cefoxitin binds to penicillin-binding proteins (PBPs) situated on the inner membrane of the bacterial cell wall and inactivates the PBPs. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains essential for bacterial cell wall rigidity and strength. This leads to the weakening of the bacterial cell wall and causes cell lysis. It's resistant to beta-lactamase [14].

1.2 Ciprofloxacin: Ciprofloxacin could be a quinolone that's quinolin-4(1H)-one bearing cyclopropyl, acid, fluoro, and piperazin-1-yl substituents at positions 1, 3, 6 and 7, severally. Ciprofloxacin could be a synthetic broad-spectrum fluoroquinolone antibiotic.

Ciprofloxacin binds to and inhibits bacterial DNA gyrase, essential for DNA replication [15]. This agent is much more active against gram-negative bacteria than gram-positive bacteria. Ciprofloxacin could be a second-generation fluoroquinolone antibiotic that's widely utilised in the medical aid of mild-to-moderate urinary and respiratory tract infections caused by inclined organisms. Ciprofloxacin has been coupled with rare but convincing instances of liver injury, which will be severe and even fatal. It has a role as an anti-infective agent, a topoisomerase IV substance and medicinal drug, a DNA topoisomerase (ATP-hydrolysing) inhibitor, a DNA synthesis inhibitor, an anti-microbial agent, an environmental contaminant, and a xenobiotic. It's a quinolone antibiotic, a fluoroquinolone antibiotic, an N-aryl piperazine, a quinolone, an aminoquinoline, and a quinolinemonocarboxylic acid [16].

1.3 Clindamycin: Clindamycin is a semi-synthetic broad-spectrum antibiotic produced by chemical modification of the parent compound lincomycin. Clindamycin dissociates peptidyl-tRNA from the bacterial ribosome, thereby disrupting bacterial protein synthesis. Clindamycin is a broad-spectrum antibiotic used orally, topically, and parenterally for bacterial infections due to sensitive organisms. Clindamycin has been linked to rare instances of acute liver injury. Clindamycin is a lincosamide antibacterial. The physiologic effect of clindamycin is using decreased sebaceous gland activity. The chemical classification of clindamycin is lincosamides [17].

1.4 Erythromycin: Erythromycin is a broad-spectrum antibiotic that diffuses into bacteria through the cell membrane of bacteria and reversibly binds to the bacterial ribosomal subunit 50S and prevents protein synthesis. Erythromycin can also be bactericidal and bacteriostatic in action, depending on the concentration of the drug at the site of contamination [18]. Erythromycin is an oral macrolide antibiotic that has been in frequent use since the 1950s. Erythromycin has been linked to uncommon cases of acute liver damage, which can result in extreme harm and death. Erythromycin A is erythromycin that consists of erythronolide A, a cyclic ketone. At positions four and six, it has 2, 6-dideoxy- 3 -C-methyl - 3-O-methyl-alpha-L-ribo-hexopyranosyl and 3, 4, 6 – trideoxy - 3-(dimethylamino) – beta – D – xylo - hexopyranosyl residues attached.

1.5 Gentamicin: Gentamicin is a broad-spectrum aminoglycoside antibiotic obtained from *Micromonos porapurpurea* and related species. Gentamicin is a complex of antibiotics consisting of four major classes: C1, C1a, C2, and C2a and several minor components. Gentamicin binds irreversibly to the 30S ribosomal subunit of bacteria, causing interference with the translational initiation complex and mRNA misreading. These effects inhibit protein synthesis (genetic translation) and result in bactericidal activity. Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi, and viruses, typically used for moderate to severe gram-negative infections. It may cause ear and kidney damage [20].

1.6 Linezolid: Linezolid is an organofluorine compound composed of 1,3-oxazolidin-2-one with an N-3-fluoro-4-(morpholin-4-yl) phenyl group at position 5 and an acetamidomethyl group. It is an oxazolidinone, a member of the morpholine family, an organofluorine compound, and an acetamide member. Linezolid is a derivative of synthetic oxazolidinone; Linezolid selectively inhibits bacterial protein synthesis and affects blood pressure through monoamine oxidase inhibition [21]. It is effective against Gram-positive organisms, including coagulase-negative *Staphylococci*, *methicillin*-resistant *Staphylococcus aureus* strains, penicillin-resistant *Streptococcus pneumonia*, and vancomycin-resistant *Enterococci strains.* It is used against problematic or serious infections caused by resistant *staphylococcal or enterococcal organisms*. Prolonged therapy with linezolid has been linked to rare instances of lactic acidosis and liver injury, probably due to hepatic mitochondrial toxicity. Linezolid is a synthetic antibacterial agent. It has a role as an antibacterial drug and a protein synthesis inhibitor that inhibits protein synthesis by binding to a site on 23S ribosomal RNA of the 50S subunit and prevents further formation of a functional 70S initiation complex [22].

1.7 Mupirocin: Mupirocin, formerly termed pseudomonic acid A, is a novel antibacterial agent with a unique chemical structure and mode of action compared to other antibiotic agents.

Produced by fermentation using the organism *Pseudomonas fluorescens*, mupirocin is a naturally-occurring antibiotic that displays broad-spectrum activity against many gram-positive bacteria and certain gram-negative bacteria *in vitro.* Mupirocin is a natural crotonic acid derivative extracted from Pseudomonas fluorescens [23]. It has a role as a bacterial metabolite, an antibacterial drug and a protein synthesis inhibitor with excellent activity against gram-positive *staphylococci* and *streptococci*. It is primarily used for the treatment of primary and secondary skin disorders, nasal infections and wound healing. Mupirocin inhibits bacterial protein synthesis by specific, reversible binding to bacterial isoleucyl tRNA synthase.

It is a monocarboxylic acid, a member of the oxanes, an epoxide, secondary alcohol, a triol and an alpha, beta-unsaturated carboxylic ester. It primarily works by inhibiting bacterial protein synthesis. Due to its unique mode of inhibiting the activity of bacterial isoleucyl-tRNA synthetase, mupirocin does not demonstrate cross-resistance with other classes of anti-microbial agents, giving it a therapeutic advantage. Due to extensive systemic metabolism, it is available in topical formulations only and is used in the treatment of impetigo caused by *Staphylococcus aureus* and *Streptococcus pyogenes* and traumatic skin lesions due to secondary skin infections caused by *S. aureus* and *S. pyogenes* [24]. There is also some clinical evidence that suggests the potential role of mupirocin in eradicating nasal carriage of *Staphylococci* when administered intra-nasally. Mupirocin is commonly marketed under the brand name Bactroban.

1.8 Penicillin: Penicillin G and V are first-generation penicillins widely used to treat infections due to susceptible organisms and have been linked rarely and only weakly with idiosyncratic liver injury. Drugs in the penicillin class work by indirectly bursting bacterial cell walls. They act directly on peptidoglycans, which play an essential structural role in bacterial cells [25]. Peptidoglycans create a mesh-like structure around the plasma membrane of bacterial cells, which increases the strength of the cell walls and prevents external fluids and particles from entering the cell. When a bacterium multiplies, small holes open up in its cell walls as the cells divide. Newly-produced peptidoglycans then fill these holes to reconstruct the walls. Penicillins block the protein struts that link the peptidoglycans together. This prevents the bacterium from closing the holes in its cell walls. As the water concentration of the surrounding fluid is higher than that inside the bacterium, water rushes through the holes into the cell, and the bacterium bursts [26].

1.9 Teicoplanin: Teicoplanin is a glycopeptide antibiotic complex isolated from the bacterium Actinoplanes teichomyceticus. Teicoplanin inhibits peptidoglycan polymerization, resulting in inhibition of bacterial cell wall synthesis and cell death. Lipoglycopeptide antibiotic from Actinoplanes teichomyceticus is active against gram-positive bacteria. It consists of five major components, each with a different fatty acid moiety [27].

1.10 Tetracycline: Tetracycline is a broad-spectrum naphthacene antibiotic produced semi synthetically from chlortetracycline, an antibiotic isolated from the bacterium *Streptomyces aureofaciens*. In bacteria, tetracycline binds to the 30S ribosomal subunit, interfering with aminoacyl-tRNA binding to the mRNA-ribosome complex, thereby inhibiting protein synthesis. Tetracycline is a broad-spectrum polyketide antibiotic produced by the Streptomyces genus of actinobacteria [28]. It has a role as an anti-microbial agent, an antibacterial drug, an antiprotozoal drug, a protein synthesis inhibitor, and an Escherichia coli metabolite. It is a tertiary alpha-hydroxy ketone and a member of the tetracycline family. It is the conjugate acid of tetracycline (1-) and a tetracycline zwitterion. Tetracycline is a broad-spectrum polyketide antibiotic produced by the Streptomyces genus of Actinobacteria. It exerts a bacteriostatic effect on bacteria by binding reversibly to the bacterial 30S ribosomal subunit and blocking incoming aminoacyl tRNA from binding to the ribosome acceptor site. It also binds to the bacterial 50S ribosomal subunit and may alter the cytoplasmic membrane, causing intracellular components to leak from bacterial cells [29].

1.11 Trimethoprim Sulfamethox Azole: Sulfamethoxazole with trimethoprim is a fixed antibiotic combination that is widely used for mild-

to-moderate bacterial infections and as prophylaxis against opportunistic infections. Like other sulfonamide-containing medications, this combination has been linked to rare instances of clinically apparent acute liver injury. A drug combination with broad-spectrum antibacterial activity against both gram-positive and gram-negative organisms. It is effective in the treatment of many infections, including *Pneumocystis pneumonia* in AIDS [30].

1.12 Vancomycin: Vancomycin is a complex glycopeptide that derives from a vancomycin aglycone. It has a role as an anti-microbial agent, bactericidal activity, and bacteriostatic effect against most organisms. It inhibits a specific step in synthesizing the peptidoglycan layer in the Gram-positive bacteria *Staphylococcus aureus* and *Clostridium difficile*. Vancomycin is a branched tricyclic glycosylated peptide with enterococci [31]. At a site different from penicillins and cephalosporins, vancomycin binds tightly to the D-alanyl-D-alanine portion of cell wall precursors, thereby interfering with bacterial cell wall synthesis. This leads to the activation of bacterial autolysis that destroys the cell wall by lysis. Vancomycin may also alter the permeability of bacterial cytoplasmic membranes and may selectively inhibit RNA synthesis [32].

TABLE 1: ANTIBIOTICS RESISTANT AGAINST *S. AUREUS*

S. no.	Antibiotic	Formula	Mode of action
1	Cefoxitin	$C_{16}H_{17}N_3O_7S_2$	Inhibition of bacterial cell wall synthesis
2	Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	Inhibits DNA replication by inhibiting bacterial DNA topoisomerase and DNA-gyrase
3	Clindamycin	$C_{18}H_{33}C_lN_2O_5S$	Disrupts protein synthesis by interfering with the transpeptidation reaction
4	Erythromycin	$C_{37}H_{67}NO_{13}$	Inhibition of protein synthesis by binding to the 23S ribosomal RNA molecule in the 50S subunit of ribosomes
5	Gentamicin	$C_{21}H_{43}N_5O_7$	Inhibition of bacterial protein synthesis by binding to 30S ribosomes
6	Linezolid	$C_{16}H_{20}FN_3O_4$	Disrupts bacterial growth by inhibiting the initiation process of protein synthesis
7	Mupirocin	$C_{26}H_{44}O_9$	Reversibly inhibiting isoleucyl-transfer RNA, thereby inhibiting bacterial protein and RNA synthesis
8	Penicillin	$C_{16}H_{18}N_2O_4S$	Acts by inhibiting the transpeptidase enzyme
9	Teicoplanin	$C_{88}H_{97}C_{l2}N_9O_{33}$	antibacterial activity by binding to the d-alanyl-d-alanine moiety and sequestration of the lipid II substrate
10	Tetracycline	$C_{22}H_{24}N_2O8$	inhibit protein synthesis through reversible binding to bacterial 30 S ribosomal subunits
11	Trimethoprim sulfamethoxazole	$C_{24}H_{29}N_7O_6S$	halts the production of tetrahydrofolate to its active form of folate
12	Vancomycin	$C_{66}H_{75}C_{l2}N_9O_24$	Inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminal of the growing peptide chain during cell wall synthesis

2. Novel Drugs Approved for Treatment of Resistant: There is an urgent need for the development of novel antibiotics targeting *S. aureus*. Fortunately, a number of new agents active against MRSA (Methicillin-resistant *Staphylococcus aureus*) and other Gram-positive pathogens have been developed and introduced into clinics. Linezolid, daptomycin, and tigecycline are three novel antibacterial classes used to treat MRSA (Methicillin-resistant Staphylococcus aureus) infections [33].

2.1 Linezolid: Linezolid is a novel drug recently launched to treat infections due to MRSA (Methicillin-resistant *Staphylococcus aureus*) and other drug-resistant Gram-positive bacteria. Linezolid, a completely synthetic oxazolidinone, inhibits the initiation of protein synthesis at the 50S ribosome. Although linezolid blocks protein synthesis like many other antibiotics such as macrolides, aminoglycosides, tetracyclines, streptogramines, chloramphenicol and lincosamides, the mode of action of linezolid is unique as the drug inhibits protein synthesis at a very early phase [34].

The binding of linezolid to the 50S subunit of the ribosome prevents assembly of the ribosome and thereby, forms a functional initiation complex consisting of a ribosome, tRNA and mRNA. Cross-

resistance to currently used antibiotics has not been observed [35].

2.2 Daptomycin: Daptomycin is a semi-synthetic cyclic lipopeptide antibiotic isolated from the bacterium *Streptomyces roseosporus* with broad-spectrum antibiotic activity against Gram-positive bacteria. Daptomycin has a unique mode of action that kills bacteria concentration-dependent by binding preferentially to Gram-positive bacterial membranes [36]. Insertion into the membrane causes rapid membrane depolarization and bacterial cell death due to disrupting critical metabolic functions, such as protein, DNA and RNA synthesis. *In-vitro* studies demonstrated that daptomycin had bactericidal activity equal to or greater than vancomycin, linezolid and quinupristin-dalfopristin [37]. Daptotomycin can be used as an alternative to vancomycin in managing MRSA (Methicillin-resistant *Staphylococcus aureus*) bacteremia[37].

2.3 Tigecycline: Tigecycline is a semi-synthetic derivative of minocycline with a glycylamido moiety attached at position nine of the D-ring of the base molecule. It is the first clinically available drug in the class of glycylcyclines. The drug exhibits a broad spectrum of activity against most Gram-positive and Gram-negative pathogens [38]. Tigecycline inhibits protein synthesis in a broad range of bacteria by binding to the 30S ribosomal subunit with five times higher affinity than tetracycline, blocking entry of amino-acyl tRNA molecules into the A site the ribosome. This prevents amino acid residues from elongating peptide chains, inhibiting protein synthesis and bacterial growth across a broad spectrum of pathogens. It is approved for the treatment of skin and soft tissue infections and intra-abdominal infections. It is currently being tested to treat hospital- and community-acquired pneumonia.

CONCLUSION: Therefore, patients and the public increasingly view rates of hospital-acquired multidrug-resistant (MDR) *Staphylococcus aureus* as indicators of the quality of patient care. Detection and eradication of MRSA are becoming public health priorities worldwide due to difficulty in therapeutic dosage monitoring and a lack of evidence on the efficacy of combination therapy. Moreover, in recent years, pharmaceutical organizations have curtailed antibiotic production. Daptomycin, tigecycline, and linezolid are the only three progressive drugs to remedy Methicillin-resistant *Staphylococcus aureus* infections produced in the last 20 years. At present, although the availability of linezolid, daptomycin and tigecycline has improved options for the treatment of Methicillin-resistant *Staphylococcus aureus* infections, the use of these antibacterials should be carefully monitored to avoid the future spread of resistance. To update existing guidelines, new trials are needed to compare these new drugs for the treatment of severe infections due to MDR *Staphylococcus aureus*. Nevertheless, major efforts should be focused on improving specific guidelines for hospital antibiotic use and infection control measures to reduce the nosocomial spread of multidrug-resistant MDR *Staphylococcus aureus* strains.

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