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Review article

Investigating the Effectiveness of Novel Antimicrobial Combinations against Drug-Resistant Microorganisms

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ABSTRACT:
The supreme danger to the life of a human is the microorganism which is resistant to conventional drugs and causes several life-threatening diseases. The microbial resistance is mainly caused due to improper intake of medication or consumption of antibiotics for a long duration. There are certain microorganisms like bacteria and fungi that undergo mutation in their genetic materials after the rigorous use of antibiotics for the treatment of people. This leads to the emergence of resistance towards particular antibiotics. The development of multidrug resistance is a natural phenomenon but it can also occur due to improper hygiene, unhealthy intake of food, and using public toilets. This is a serious threat to the human race as the MDR of these microorganisms may lead to severe pandemic situations. Therefore to counter such problems associated with MDR, we decided to find a solution for this threat and a study should be made to find a proper drug for combating multidrug-resistant bacteria and other microorganisms.
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Keywords: Multidrug resistant, pathogenicity, antibiotic and bacteriostatic.

1. INTRODUCTION

The drug used to prevent the pathogenicity of microorganisms is called an antimicrobial agent. Examples – Antibiotics, antiseptics, and disinfectants. Antibiotics are substances that suppress the growth of microorganisms and eventually destroy them. Antibiotics are extracted from various species of microorganisms (bacteria, fungi, and actinomycetes) There are various microbial sources to obtain antibiotics, such as Bacteria species *Bacillus polymyxa* antibiotic polymyxin B is obtained and used for the treatment of urinary tract infection and *Bacillus subtilis* antibiotic bacitracin is produced used for the treatment of dermatitis and dysentery. Actinomycetes species *Streptomyces griseus* antibiotic streptomycin is obtained for the management of tuberculosis, *Streptomyces aureofaciens* antibiotic tetracycline is acquired and used in the treatment of cholera, tetanus,etc. *Streptomyces erythreus* antibiotic erythromycin is extracted and used to treat cholera and arthritis. Fungi such as *Cephalosporium acremonium* antibiotic cephalosporin is gained to treat meningitis, pneumonia, etc. *Penicillium notatum* antibiotic penicillin is acquired and used to medicate fever, pneumonia, and genital disease. Antibiotic griseofulvin is produced by *Penicillium griseofulvum* to manage skin infections. Antibiotics make it possible to cure diseases caused by bacteria such as pneumonia, tuberculosis, and meningitis. Some antibiotics are bacteriostatic in nature and some are bactericidal in nature. Bacteriostatic means inhibit the growth of microorganisms. Examples- are tetracycline, macrolides, clindamycin, trimethoprim/sulfamethoxazole, linezolid, and chloramphenicol. Bactericidal means antibiotics that kill the microorganism Example – Amoxicillin, gentamycin, ciprofloxacin, levofloxacin, metronidazole, etc. Antibiotics can be broad-spectrum antibiotics and narrow-spectrumantibiotics. Broad spectrum antibiotic is effective against both gram-positive and gram-negative bacteria. Examples- doxycycline, azithromycin, kanamycin, neomycin, and ampicillin. Narrow spectrum antibioticsare effective against either one of the bacteria, gram-positive bacteria or gram-negative bacteria. Examples- Penicillin-G, macrolides, and vancomycin. Antibiotics have different mechanisms of action from one to another. Beta-lactamantibiotics, vancomycin, and Fosfomycin inhibit cell wall synthesis. Aminoglycoside tetracycline Inhibits protein synthesis by attaching to the 30s ribosome site. Macrolides also inhibit protein synthesis but they attach to the 50s ribosome. Polymyxin and bacitracin alter the cell membrane. Quinolones inhibit DNA synthesis. Rifamycin and bacitracin inhibit RNA synthesis. Sulfonamide and trimethoprim act as antimetabolite and oxazolidines inhibit monoamine oxidase.

1.1. Antimicrobial resistance (AMR):

Microbe'sobjectives are survival, replicate and spread under favorable conditions. Microbes adapt to surrounding over time. If something becomes an obstacle in their replication

or in spreading then they become immune to that thing and help them in their survival. Drug resistance is the default antimicrobial agent to kill or inhibit the growth of microorganisms. Antibiotic treatment has always threatened to become ineffective so pharmacists always seek a new and improved antibacterial agent. The chances of the ability of bacteria to acquire resistance to the current drug become less. Drug resistance is a natural process. In any case, a few components remain presently in question in the complex etiology of antibiotic resistance. One of the reasons for resistance is increased exposure to antibiotics to the microbes they acquire immunity against the drug and transfer the resistance mechanism to the next generation. Then drugs become ineffective, in another word it will be antibiotic overuse or abuse. Various reasons for resistance can be poor personal hygiene, bad health care environment, or sensitivity loss, Microbes are living-organism, and microbes are adaptive in nature. Microbe's main self-medication, inexact diagnosis, and improper antibiotic prescribing [1].

1.2. Natural antimicrobial resistance: Certain Anti-microbial agents (AMAs) are ineffective against some microbes. This occurs due to a lack of metabolic process, and the absence of a drug binding site. This resistance can be characteristic of a species or group of species. Natural resistance against the drug does not require any significant clinical problem. There are certain cases in which microbes are resistant to the drug like: Penicillin-G does not affect Gram-negative bacilli because their peptidoglycan layer is between the cell membrane so penicillin cannot inhibit the synthesis of the peptidoglycan layer. Aerobic bacteria are not affected by metronidazole since they do not generate these low intracellular oxidation-reduction potentials. Aminoglycosides are ineffective against anaerobic bacteria because anaerobic bacteria uptake across the bacterial cell wall is energy derived from aerobic metabolism.

1.3. Acquired antimicrobial resistance:

Organisms develop resistance due to the use of an AMA over a while. It is a major clinical problem. Resistant development depends on both microorganisms and drugs. Few microorganisms are infamous for quick obtaining of resistance like staphylococci, enterococci show resistance at low concentrations of antibiotics. Some micro-organism takes a certain period to develop resistance against drugs like Streptococcus pyrogen and spirochetes do not show any resistance against penicillin for more than 60 years of use despite its overuse.

1.4. Resistance can occur due to mutation or gene transfer:

Mutation is the sudden change of genes. It is stable and inheritable. Sensitive microbes contain a few mutant cells which require a high concentration of AMA for inhibition [2]. Mutation and resistance can be of two types single step and multistep. Single step mutation has a high degree of resistance and it arises rapidly. Example- Enterococci to streptomycin. Multistep involves several gene modifications. Sensitivity decreases gradually step by step. Examples- Erythromycin, tetracycline, and chloramphenicol. Gene transfer- Resistance-causing gene is transferred from one organism to another. It is also called horizontal transfer of resistance. Due to gene transfer,the rapid spread of resistance occurs and high-level resistance to several antibiotics. Gene transfer takes place through three processes conjugation, transduction, and transformation.

2. CLASSIFICATION OF ANTIMICROBIAL RESISTANCE

2.1. Drug uptake limitation: Gram-negative bacteria have less permeability to certain antibiotics so they become ineffective against gram-negative bacteria e.g.Vancomycin cannot penetrate through the outer membrane which is a prime representation of the natural resistance. Beta-lactam, tetracycline, and fluoroquinolones are highly affected by the permeability of the outer membrane. The reduction in porin expression causes the resistance of carbapenems in individuals from the Enterobacter ales order, Acinetobacter spp., and Pseudomonas spp. Like resistance to carbapenems in enterobacterial will arise in the absence of carbapenems enzyme activity, if porin production decrease due to mutation or mutated porin alleles is present.

2.2. Drug target modification:

Beta-lactam antibiotics like penicillin cephalosporin, and methicillin cefaclor have beta-lactamrings. The Beta-lactam ring is degenerated by the beta-lactamase enzyme. The Beta-lactam ring is the key part of the drug mechanism when microbes destroyed the beta-lactam ring by hydrolyzing it, the antibiotic become ineffective.

2.3. Drug inactivation:

Bacteria inactivate the drug by destroying the drug or by chemical alteration the drug. Chemical alteration of the drug prevents the binding of the drug to its binding site in the bacteria cell. It is achieved by transferring the adenyl, phosphoryl, and acetyl groups. It is the most effective way for the inactivation of drugs. Acetylation is the most effective mechanism against aminoglycoside, chloramphenicol, and fluoroquinolones.

2.4. Drug efflux: Tetracycline resistance is efflux-mediated resistance in this Tet efflux pump use proton exchange energy to expel tetracycline from the cell. The resistance of macrolide is another example of efflux resistance.

2.5. Combination therapy:

Combination therapy is an appealing strategy for increasing the life span of antimicrobials. It is given carefully to minimize the threat of evolution of resistance. In combination therapy, we give more than one drug to treat a disease or infection. Therapeutic activity is achieved by targeting the different mechanisms to destroy the diseased cell or microbes. Combination therapy is widely used to treat lethal diseases like tuberculosis, cancer, and heart disease [3].They are also used in anxiety. Combination therapy can

give a synergistic effect. The advantage and disadvantages of combination therapy is elaborated in Table 1.

Table 1: Advantage and disadvantages of combination therapy

Advantages of combination therapy	The disadvantage of combination therapy
Enhanced clinical outcomes. ● Potentiated antiviral activity. ● Reduced risk of respiratory complications. ● Reduced emergence of resistance. ● Reduced risk of individual drug.	● High cost of therapy. ● Increased risk of superinfection ● If an insufficient dose of no synergistic drug is used then the chance of resistance will be increased. ● Increased adverse effect reaction. The toxicity of one drug can be enhanced by other.

2.6. Combination of two bacteriostatic drugs:

Two bacteriostatic drugs are rarely synergistic. They are often addictive. When two bacteriostatic drugs are given in combination, they generally then become bactericidal in nature. For example, tetracycline, chloramphenicol, and erythromycin are static in nature and if they are given in combination with each other then they show an additive effect similarly Sulfonamide and trimethoprim both are bacteriostatic in nature but when they are given in combination then they are showing synergistic effects.

2.7. Combination of two bactericidal drugs: A combination of two bactericidal drugs is given then usually they show an additive effect, the combination of drugs is sometimes synergistic in nature. For example, Penicillin/ Amoxycillin + Streptomycin/ Gentamycin. This combination is used in subacute bacterial endocarditis conditions and it is bactericidal in nature. Ticarcillin + gentamycin uses to treat pseudomonas infection, especially in neutropenic patients. Ceftazidime+ ciprofloxacin is also used to treat pseudomonas infection in orthopedic prosthesis patients. Rifampin + isoniazid use to treat tuberculosis this combination shows a synergistic effect.

2.8. Combination of bacteriostatic and bactericidal drug:

If we give one drug bacteriostatic and one drug bactericidal then they can be synergistic or antagonistic. If the organism is highly sensitive to the bactericidal drug, then only the bacteriostatic drug will give a response so this will be bacteriostatic in nature. This is known as an apparent antagonist as the effect of a single drug is effective in the combination of two drugs. Penicillin + erythromycin in the infection of streptococci here also then show antagonist effect. Penicillin + tetracycline. Penicillin is highly sensitive to pneumococci bacteria, but in combination, if they are given in combination then they have less effect than a single dose of penicillin. Nalidixic acid + nitrofurantoin in the infection of E. coli combination show antagonism. When the organism is less sensitive to Bactericidal drug then the combination show synergism.e.g Penicillin + sulfonamide when acting against actinomycosis. This combination becomes bactericidal. Streptomycin + chloramphenicol combination uses against K. Pneumonia infection. It is also bactericidal in nature. Streptomycin + Tetracycline uses for brucellosis infection.

2.9. Prevent the emergence of resistance:

When any organism develops resistance against an antibiotic then another antibiotic is independent of the conferring mutation that causes mutation. When the combination of two resistant antibiotics is given then the combination becomes effective against the organism. The chances of developing resistance to antibiotics in bacteria also decrease when they are given in combination. Combination antibiotics are given in chronic diseases as antibiotic treatment will be for a prolonged time.

2.10. Broaden the spectrum of antibiotic:

Treatment of mixed infection means a person is infected by an aerobic and anaerobic infection like bronchiectasis, peritonitis, urinary tract infection, brain abscesses, and diabetic foot infection. During empirical therapy of initial treatment of severe infection. example combination of penicillin-G+ gentamycin. Topically used drugscome in combination example neomycin and polymyxin B.

2.11. Beta lactam antibiotics:

Beta-lactam antibiotics have 4- a membered lactam ring. The nitrogen atom is attached to beta carbon relative to the carbonyl group. This is ring is essential for antibiotic activity. If this ring is destroyed then the drug will become ineffective. Beta-lactamantibiotics exhibit their effect by the acylation of Penicillin-binding protein and inhibit the diacylation process. As a consequence of the beta-lactamase enzyme Beta-lactam.

2.12. Mechanism of beta-lactam antibiotics:

By covalently attaching to crucial penicillin-binding proteins (PBPs), enzymes involved in the last stages of peptidoglycan bridge across both Gram-positive as well as gram-negative bacteria, lactam antibiotics are bactericidal drugs that prevent the development of bacterial cell walls. Each bacterial species has a unique collection of PBPs, which can consist of three to eight enzymes for each species [36]. The mechanism is explained in the fig 1.

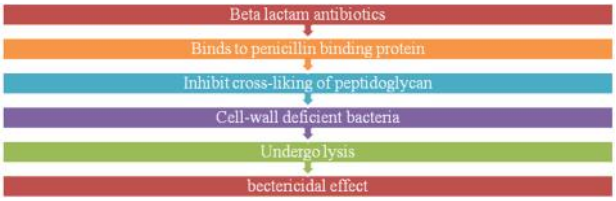

Fig 1: Mechanism of action of Beta lactam antibiotics.

2.13. The spectrum of beta-lactam antibiotic

Beta-lactam antibiotics contain different classes of antibiotics like penicillin, cephalosporin, carbapenem, and monobactams. Penicillin is of two type's narrow spectrum penicillin and broad-spectrum penicillin. Cephalosporins are broad-spectrum antibiotics. Monobactam and carbapenem are narrow-spectrum antibiotics [37].

2.14. Beta-lactam antibiotic in combination therapy:

Beta-lactamantibiotics are widely used in the treatment of various diseases. They act by interfering with the cell wall they bind with penicillin-binding protein (PBPs) membrane-bound enzyme. PBPs insert peptide glycan precursor in the nascent cell wall that inhibits the bacteria's growth. Beta-lactamantibiotics have 4 a membered lactam ring. The nitrogen atom is attached to beta carbon relative to the carbonyl group. This is ring is essential for antibiotic activity. If this ring is destroyed then the drug will become ineffective. Beta-lactam antibiotics exhibit their effect by the acylation of Penicillin-binding protein and inhibit the diacylation process. As a consequence of the beta-lactamase enzyme, the Beta-lactam ring undergoes both acylation and deacylation quickly. So, the effectiveness of beta-lactamantibiotics decreases. Effective retardation of beta-lactamase enzyme is required to stop deacylation of the acyl-enzyme intermediate, it requires sufficient time to suppress the activity enzyme or it can also form an enzyme-bound fragment an irreversible inactivate enzyme. Beta-lactam antibiotic resistance is of 2 types. Resistance has been shown in gram-positive and gram-negative bacteria by producing beta-lactamase enzymes. This enzyme is effective against all classes of beta-lactam antibiotics like penicillin, cephalosporin, carbapenems, and monobactams. Resistance was also shown by altering the target site PBPs as PBPs converted into PB2a.Beta-lactamase can be classified by two methods structural approach (Ambler) and functional approach (Bush-Jacoby-Medeiros). The different active site of Beta-lactamase enzyme is illustrated in table 2.

Table 2: Active site of Beta-lactmase enzyme

Class	Active site	Example
A	Serine(non-metal) site / Serine beta lactamase	Penicillinase, TEM, SHV, IMI, GES etc.
B	Metal site (Zn++)/Metallo beta lactamase	VIM, IMP, NDP, GIM
C	Serine(non-metal) site / Serine beta lactamase	AmpC
D	Serine(non-metal) site / Serine beta lactamase	OXA, OXA-48, OXA-23

2.15. Ceftolozane-tazobactam:

A new cephalosporin called ceftolozane was created to have greater stability against the class C Pseudomonas-derived cephalosporins (PDC, also referred to as Pseudomonas AmpC). Tazobactam, the beta-lactamase inhibitor partner, is a sulfone-based inhibitor having weak inhibitory efficacy against class A carbapenems and class D oxacillinases. Tazobactam is also available in the combination with penicillin and piperacillin. Ceftolozane-tazobactam looks to be more economical than piperacillin-tazobactam since it results in longer quality-adjusted life years. The effectiveness of ceftolozane-tazobactam against P. aeruginosa, even multi-drug resistant (MDR) strains, may be proven by the 90– 98% of recent isolates that tested sensitive. Additionally, ceftolozane-tazobactam is a promising carbapenem-sparing therapeutic approach for Enterobacteriaceae that produce ESBLs. Serine carbapenemase-producing Enterobacteriaceae are typically resistant to the combination.

2.16. Ceftazidime-avibactam:

In combination with metronidazole, ceftazidime-avibactam has been authorized by the FDA for the treatment of cUTIs, including acute pyelonephritis and cIAIs in patients under 3 months of age (Table 1) [39]. Another clinical evidence supporting the treatment of HABP/VABP (hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) included later added for older individuals than 18. Ceftazidime-avibactam is extremely effective against Enterobacteriaceae bearing blaKPC and blaOXA-48. Similar percentages of isolates tested susceptible (96.8%) as with ceftolozanetazobactam (99%) indicate that this combination has an action against P. aeruginosa. The spectrum of activity of ceftazidime-avibactam is attributable to avibactam's ability to inhibit class A, C, and some D βlactamases, including KPC and OXA-48 carbapenemases. Resistance to ceftazidime-avibactam was discovered both during treatment and during in vitro testing. It may be said that avibactam outperforms the previous generation -lactamase inhibitors like clavulanic acid 14 and tazobactam and considerably enhances the effectiveness of ceftazidime 6 against bacterial infections generating class A, C, and certain class D -lactamases. However, the ceftazidime avibactam combination shows a narrower range of MICs for P. aeruginosa strains and low action for Acinetobacter spp. and MBL-producer bacteria.

2.17. Vabomere (Meropenem-vaborbactam):

Meropenem-vaborbactam had positive in vitro activity in clinical studies, demonstrating the combination's safety, tolerability, and effectiveness. Meropenem-vaborbactam and its comparator medication combination (piperacillin-tazobactam) were assessed for the treatment of complex urinary tract infections in a randomized clinical study. Patients tolerated meropenem-vaborbactam well, and it wasshown to be non-inferior to the comparative treatment. In 2017, the FDA authorized the drug combination of vaborbactam and meropenem (Vabomere) for the treatment of severe urinary tract infections.

2.18. Aminoglycoside:

Aminoglycosides are actinomycete-derived natural or semisynthetic antibiotics. A number of them have been licensed for use in humans. They were among the first antibiotics to be introduced for frequent clinical use. Natural or semi-synthetic antibiotics generated from actinomycetes are known as aminoglycosides. They were among the earliest antibiotics to be made available for regular therapeutic use.

2.19. Spectrum of aminoglycoside:

In both Gram-positive and Gram-negative species, aminoglycosides are effective. The Enterobacteriaceae

family, which includes *Escherichia coli*, *Klebsiella pneumonia* and *K. oxytoca*, *Enterobacter cloacae* and E. *aerogenes*, *Providencia spp*., *Proteus spp*., *Morganella spp*., and *Serratia spp*., is particularly sensitive to aminoglycosides [4]. Additionally, aminoglycosides are effective against the pathogens that cause the plague and tularemia, respectively, *Yersinia pestis* and *Francisella tularensis* [5]. The class is also effective against P. aeruginosa, and to a lesser extent, *Acinetobacter baumannii*, as well as methicillin- and vancomycin-resistant isolates of Staphylococcus aureus. Many Mycobacteria spp. are also susceptible to aminoglycosides including Mycobacterium tuberculosis, M. fortuitum, M. chelonae, and M. avium [6][7]. Aminoglycoside absorption into cells requires active electron transport, hence the class is essentially inactive against anaerobic bacteria [8]. Additionally, aminoglycosides are ineffective against the majority of Burkholderia species, Stenotrophomona species, Streptococcus species, and Enterococcus species [9].

2.20. Mechanism of action

Aminoglycosides attach with a high affinity to the A-site on the 30S ribosome's 16S ribosomal RNA to prevent the production of new proteins [10].By causing codon misreading when the aminoacyl transfer RNA is delivered, this interaction causes the antibiotic to encourage mistranslation. Due to this, erroneous amino acids can combine into polypeptides during the process of protein synthesis, which can then be released to harm the cell membrane and other tissues [11].The three unique steps of aminoglycoside entrance into bacterial cells are as follows: the first step enhances bacterial membrane permeability; the second stage depends on energy, and the final step is also energy-dependent [12]. Once aminoglycoside molecules enter the cytoplasm, protein synthesis is inhibited and proteins are translated incorrectly. These incorrectly translated proteins enter the cytoplasmic membrane, disrupt it, and make it easier for aminoglycosides to enter later [13]. As a result, the cytoplasm quickly absorbs extra aminoglycoside molecules, protein synthesis is inhibited more severely, translation errors occur more often, and accelerated cell death [14][15]. Mechanism of action of Aminoglycosides is explained in fig 2.

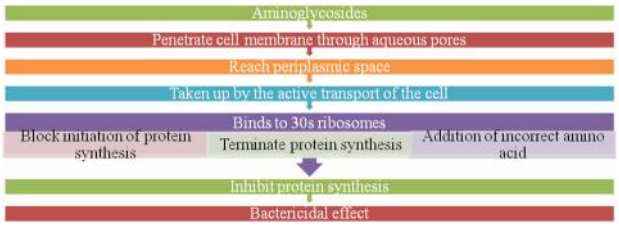

Fig 2: Mechanism of actions of Aminoglycosides

2.21. Aminoglycoside resistance

Aminoglycoside resistance takes many different forms including enzymatic modification, target site modification via an enzyme, or chromosomal mutation and efflux. Each of these mechanisms has varying effects on different members of the class and often multiple mechanisms are involved in any given resistant isolate. Resistance to aminoglycosides via target site mutations has not been observed because nearly all prokaryotes, except for Mycobacterium spp [16] and Borrelia spp [17] encode multiple copies of r-RNA. **Combination Therapy:**The use of reduced dosages of each of the combined medications may also be permitted by combination treatment. Mycobacterium TB infection treatment was the first instance of the clinical application of antimicrobial combination therapy that was effective. whereby combined treatment reduced the pace at which rifampin resistance developed. Later, the same strategy was used for the control of artificially caused by a Staphylococcus species, valve endocarditis.

2.22. Combination of beta-lactam and aminoglycoside

A B-lactam and an aminoglycoside combination can be used to either lower the risk of treatment failure or the possibility that resistant strains would evolve, according to data from many trials. However, to reduce the probability of antimicrobial drug resistance, many practitioners abuse combination treatment.

2.23. Aminoglycoside + penicillin-G or ampicillin (synergistic effect)

Lack of penetration into the bacterial cell renders aminoglycosides ineffective against enterococci when used alone. However, synergism is shown when ampicillin or penicillin G is coupled with either streptomycin or gentamicin. This is because penicillin damages the bacterial cell wall, allowing the aminoglycoside to be taken up by the bacterium. The aminoglycosides can work bactericidal once they have been absorbed. In this sort of synergy, the presence of the cell-wall active agent along with the aminoglycoside kills the targeted organism (Enterococcus spp.), although neither medication is bactericidal active when taken alone [18].

2.24. Aminoglycoside + Vancomycin or penicillinase-resistant penicillin (synergistic effect)

Treatment of severe S. aureus infections such as endocarditis and bacteremia can benefit from the combination of aminoglycosides with penicillinase-resistant penicillin or vancomycin. This has been demonstrated experimentally for isolates of S. aureus that are penicillin-susceptible and resistant [40]. When an aminoglycoside is present, a sort of synergy, the staphylococci are destroyed significantly more quickly than when the S. aureus is exposed solely to penicillinase-resistant penicillin or vancomycin [19].

2.25. Cefotaxime or imipenem + aminoglycoside (synergistic effect)

B-lactams (cefotaxime or imipenem) and aminoglycosides (gentamicin, netilmicin, or amikacin) were recently combined to test their effectiveness against Streptococcus pneumoniae isolate with high levels of penicillin, streptomycin, and/or kanamycin resistance. In vitro testing revealed synergistic efficacy for all tested combinations. The

process is assumed to be similar to that of enterococci, where the b-lactam causes cell wall disruption and increases aminoglycoside absorption. This implies that the combination of a b-lactam and an aminoglycoside may be effective for treating penicillin-resistant pneumococcal infections that do not affect the central nervous system [20].

2.26. Aminoglycoside + carbenicillin (antagonist effect)

If carbenicillin and aminoglycosides are combined in the same intravenous container and left to stand. In this case, the aminoglycoside will be inactivated by the b-lactam, at least in vitro [21].

2.27. Aminoglycoside + Tetracycline or macrolides (antagonist effect)

Tetracycline and chloramphenicol are examples of bacteriostatic medications that only restrict bacterial development and the activity of aminoglycosides. Consequently, mixtures of either of these two medications should be taken with an aminoglycoside. Used cautiously in the management of severe illnesses like endocarditis or meningitis [22].

2.28. Sulfonamide:

Prontosil was not intended to be a prodrug since reductive enzymes quickly discovered that it released an active ingredient, para-amino phenyl sulfonamide. Sulfonamides, a class of extensively used antibacterial, were discovered as a result.Sulfonamides are the first medications that could be administered systemically to treat bacterial infections were sulfonamides, which had a selective impact on bacteria. Sulfonamides are broad-spectrumantibiotics [23]. Organo-sulfur compounds with the -SO2NH2 and/or -SO2NH- group are known as sulfonamide structures, and they are characterized by the presence of the sulfanilamide group and unique 6- or 5membered heterocyclic rings. Sulfamethazine, Sulfadiazine, Sulfamethoxazole, Sulfasalazine, sulfisoxazole, sulfamerazine, sulfadimethoxine, sulfafurazole, and sulphanilamide are SN-derived medications that have been produced up to this point [24].

2.29. Mechanism of action of sulfonamide

The dihydropteroate synthase (DHPS), an enzyme that transforms PABA as a substrate into dihydrofolic acid, is competitively inhibited by the sulfonamides, which are structural analogs of para-aminobenzoic acid (PABA) (folic acid). Sequentially, a different enzyme called dihydrofolate reductase transforms dihydrofolate into tetrahydrofolate (folic acid). Trimethoprim, a dihydrofolate pyrimidine, inhibits dihydrofolate reductase, which is a step further down the process for the manufacture of folic acid. A sulfonamide that has been "potentiated" by the addition of a diaminopyrimidine, such as trimethoprim, ormethoprim, methoprim, or pyrimethamine, is referred to as such. Any of these dihydrofolate reductase inhibitors can be added to a sulfonamide to sequentially block the enzymes, ultimately leading to the synergistic inhibition of purine bases, the building blocks of nucleic acids, which interferes with protein synthesis and a cell's capacity to divide. When a diaminopyrimidine is introduced, observe the successive inhibition of the enzymes dihydropteroate synthase and dihydrofolate reductase [29]. The mechanism of actions of sulfonamides is explained in fig 3.

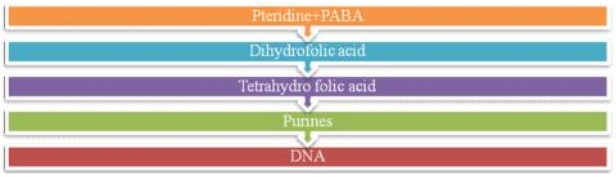

Fig 3: Mechanism of actions of sulfonamides

3. MICROBIAL RESISTANCE

Chromosomes and plasmids both have a role in sulfonamide resistance. The most frequent form of resistance appears to be altered enzymes with decreased affinities for the substrate. For instance, chromosomally mediated resistance in staphylococci entails a change in the genes that code for dihydropteroate synthase (DHPS). Despite the near structural similarity between the inhibitor and substrate, these mutant DHPS enzymes display considerable insensitivity to sulfonamides while maintaining normal binding to the p-aminobenzoic acid substrate. Four mobile sulfonamide resistance genes, designated Sul1, Sul2, Sul3, and most recently Sul4, have been found to date in addition to chromosomally mediated resistance. Each of these genes codes for a modified enzyme with a lower affinity. Genes producing alternative dihydrofolate reductase, which results in high-level resistance to trimethoprim, are responsible for another plasmid-borne resistance. Some enterococcal sulfonamide resistance mechanisms may have been transferred to staphylococci.

Overproduction of PABA can also overcome competitive inhibition of dihydropteroate synthase since sulfonamides work competitively. Low-level resistance could potentially be attributed to alternative folic acid production routes. Sulfonamides frequently exhibit cross-resistance, and typically, resistance to one sulfonamide signals resistance to others. Ampicillin and tetracycline resistance are frequently associated with plasmid-mediated sulfonamideresistance in intestinal gram-negative bacteria. Sulfonamides are naturally resistant to organisms like enterococci that may absorb folic acid from their surroundings. Most Pseudomonas, Klebsiella, and Proteus strains are extremely resistant, as are the majority of Rickettsia, Mycoplasma, and Chlamydia strains [30].

3.1. Trimethoprim and sulfonamide resistance

Trimethoprim is a potent and affordable antibacterial medication that can be used alone or in conjunction with a sulfonamide. Nevertheless, during the past several years, against a backdrop of significant sulfonamide resistance, trimethoprim resistance has dramatically increased [31].The combination of sulfonamide and trimethoprim shows a synergistic effect in in-vitro studies [32].Sulfonamide and trimethoprim resistance eliminatesthe synergistic effect [33].

3.2. Trimethoprim-Sulfamethoxazole combination.

Trimethoprim and sulfamethoxazole act as an alternative therapy in the treatment of methicillin-resistant staphylococci infection as trimethoprim and sulphametoxazole were effective against methicillin-resistant staphylococci but now this strain developed resistance against this combination [34].Trimethoprim and sulfamethoxazole combination is also alternative therapy for MSSA and MRSA infections [35].

4. CONCLUSION

From our extensive study we want to conclude that pathogenic microbes develop resistance with regular use of antibiotics. Although there are number of antibiotics combinations available to combat multidrug resistant microbes but after continuous uses of these combinations the microbes find away to develop resistance against these combinations. So special effort should be made to develop novel combination therapy either the modern medicines or natural drugs to permanently kill or prevent the growth of these multidrug resistant microbes.

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