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Emerging Trends in Antimicrobial Resistance and Novel Therapeutic Strategies

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Review Article

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ABSTRACT

Antimicrobial resistance (AMR) is a growing concern worldwide, as it can make many commonly used antibiotics ineffective against bacterial infections. AMR occurs due to the emergence of new and more resistant bacterial strains and the misuse and overuse of antibiotics. Therefore, it is crucial to find new ways to combat these pathogens. In this review, we will discuss the latest developments in AMR diagnostics, prevention, and treatment. We will explore the use of alternative antimicrobial agents, such as bacteriophages, peptides, and natural compounds, as well as the development of new drugs and vaccines. Additionally, we will investigate how genomics, proteomics, and nanotechnology can aid in discovering new antimicrobial agents and understanding the

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mechanisms of resistance. This review underscores the importance of finding new strategies to combat AMR and calls for global efforts to address this growing threat to public health. It will be a useful resource for clinicians and researchers working in infectious diseases and AMR.

Keywords: Antimicrobial resistance; novel therapeutic; strategies; infectious diseases.

1. INTRODUCTION

Antimicrobial chemotherapy has greatly improved human health by treating infectious diseases caused by microorganisms [1-6]. However, the overuse of antimicrobial agents has led to the emergence of drug-resistant bacteria, which remains a significant problem worldwide, including Japan [7-11]. With limited options for treatment and the decreasing number of new drugs being developed, the proper use of existing antimicrobial drugs and infection control efforts are crucial to preventing the spread of resistant bacteria [12-17]. This paper provides an overview of the history of antimicrobial agents, the emergence of resistant organisms, and practical strategies to prevent their spread.

2. EMERGENCE OF DRUG–RESISTANT BACTERIA

Antimicrobials are substances that can either kill microorganisms or stop their growth. They are classified based on the microorganisms they primarily act against, such as antibiotics for bacteria and antifungals for fungi [18-20]. They can also be categorized according to their function, as microbicides that kill microbes or bacteriostatic agents that only inhibit their growth. Antimicrobial medicines are used to treat infections (antimicrobial chemotherapy) or to prevent them (antimicrobial prophylaxis).

Disinfectants are non-selective antimicrobial agents that are used to kill a broad range of microbes on non-living surfaces to prevent the spread of illness. Antiseptics are applied to living tissues to reduce the risk of infection during surgery. Antibiotics can destroy microorganisms within the body and can be derived from living microorganisms or synthetic agents such as sulfonamides or fluoroquinolones. While the term "antibiotic" used to describe only antibacterial agents, it is now used to refer to all antimicrobials [21-25].

Antibacterial agents can be further divided into bactericidal agents that kill bacteria or bacteriostatic agents that slow down or stall bacterial growth [26-31]. However, recent advancements in antimicrobial technologies have resulted in solutions that go beyond simply inhibiting microbial growth. For example, certain types of porous media have been developed to kill microbes on contact.

3. GENERAL CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobial Agents can be classified basically into seven (7) categories;

1).Based on mechanism of action
2).Based on therapeutic use/ organisms affected
3).Based on spectrum of activity
4).Based on type of action
5).Anti-mycobacterial agents
6).Based on source
7).Based on Chemical structure

3.1 Based on Mechanism of Action

Cell Wall Synthesis inhibitors: Pathogenic bacteria have a cell wall that provides structural strength and maintains intracellular osmotic pressure. The synthesis of the cell wall involves three steps: first, monomers are produced in the cytoplasm from amino acids and sugars; second, Bactoperol transports the monomers across the cytoplasmic membrane where they are polymerized into linear peptidoglycan chains; and third, transpeptidase cross-links the chains into a three-dimensional matrix. Several drugs inhibit cell wall synthesis, such as vancomycin which targets monomer polymerization, and β-lactams (e.g. penicillins and cephalosporins) which block polymer cross-linking. β-lactam antibacterials also activate autolysins, which cause holes in the cell wall, disrupting its integrity. Autolysis and transpeptidase antagonism prevent bacterial self-maintenance, remodeling, repair and replication. Other drugs that inhibit cell wall synthesis include Cycloserine, Bacitracin, and Monobactam.

3.1.1 Inhibitors of DNA synthesis or integrity

However, some bacteria lack a cell wall, while others possess unique structures that resist the

effects of cell wall inhibitors. To prepare for cell division, bacteria must replicate their double-stranded DNA. This process requires bacterial DNA gyrase, a topoisomerase type II, to unwind and separate the DNA strands before reassembly. Additionally, bacteria must synthesize folate, which begins with the formation of dihydropteroic acid from pteridine and para-aminobenzoic acid (PAPA), catalyzed by dihydropteroate synthase. Dihydropteroic acid and glutamate condense to form dihydrofolate (DHF), which is reduced by dihydrofolate reductase (DHFR) to tetrahydrofolate (THF). THF is an essential cofactor in the synthesis of DNA, RNA, and protein. Drugs that inhibit DNA synthesis or integrity include fluoroquinolones, Metronidazole, Antimetabolites (Sulfamethoxazole, Trimethoprim), among others.

Inhibitors of Transcription; Bacteria require proteins for their survival and reproduction, just like mammalian cells. The process of protein synthesis begins with transcription, which involves the formation of a single-stranded RNA molecule from a DNA template, catalyzed by RNA polymerase [32-37]. The newly synthesized RNA then undergoes translation, which involves the use of messenger RNA (mRNA) to inform ribosomes about which proteins to synthesize, transfer RNA (tRNA) to transport specific amino acids to the ribosomes, and ribosomal RNA (rRNA) to ensure that the correct amino acid is used. Protein synthesis is initiated when the mRNA attaches to the 30S ribosomal subunit and tRNA linked formyl methionine (fMet). Inhibitors of transcription or translation can target different components of the protein synthesis process, including binding with the 50S or 30S RNA units, inhibiting elongation factors, and using drugs such as Chloramphenicol, Tetracyclines, Clindamycin, Macrolides, Aminoglycosides, and Spectinomycin.

Cell Membrane Synthesis Inhibitors; Bacteria rely on their cell membrane for survival as it acts as a protective barrier and is involved in various essential functions. Some bioactive molecules and antibacterial peptides can target the bacterial cell membrane and demonstrate potential as antibacterial agents. However, traditional drug screening efforts have not focused on targeting the bacterial cell membrane due to concerns about damaging mammalian cell membranes. Recent successful medical applications of antibiotics such as daptomycin, telavancin, oritavancin, and dalbavancin have shown that antibacterial drugs targeting cell membranes can be specific to bacteria. This specificity is achieved by binding to the negatively charged phospholipids and zwitterionic phosphatidylethanolamine that are abundant in bacterial cell membranes, using compounds with a positive charge. For instance, daptomycin can form an amphiphilic structure in the presence of calcium ions, which provides a surface with a false positive charge, thereby increasing its affinity for negative ions [38-41]. Furthermore, the binding to peptidoglycan precursors and bacterial membrane proteins also contributes to the specificity of drugs such as daptomycin and lipoglycopeptides. Other examples of drugs that target the bacterial cell membrane include Amphoterecin B, Polymyxin, Nystatin, and Meconazole.

3.2 Based on Therapeutic Use/ Organisms Affected

Antibacterial drugs include Penicillin, Chloramphenicol, tetracyclines, and Aminoglycosides. Antifungal drugs consist of AmphotericinB, Griseofulvin, and ketoconazole. Antiviral drugs are Acyclovir, Idoxuridine, Vidarabine, Zidovudine, and Ribavirin. Antiprotozoal drugs are Metronidazole, Quinapyramine, and Diminazine. Anthelmintic drugs include Albendazole, Levamisole, Niclosamide, and praziquantel. Lastly, Ectoparasiticides consist of Cypermethrin, Lindane, Amitraz, and Ethion.

3.3 Based on Spectrum of Activity

Those with broad spectrum of activities include; Tetracyclines, Chloramphenicol, Gentamycind and Ampicillin.

Those with Narrow spectrum of activities include; penicillin G, Streptomycin, Erythromycin, Vencomycin etc.

3.4 Based on Type of Action

Antibiotics can be categorized into two types based on their action: bacteriostatic and bactericidal. Antibiotics that are bacteriostatic include erythromycin, sulfonamide, trimethoprim, clindamycin, and chloramphenicol. On the other hand, antibiotics that are bactericidal include penicillin G, streptomycin, vancomycin, bacitracin, potentiated sulfonamides, and cephalexin.

3.5 Antimycobacterial Agents

These include Isoniazide, Paraamino salisyclic acid.

3.6 Based on Source

The following antibiotics are based on different sources:

Fungi-derived antibiotics include Penicillin G, Cephalexin, and Griseofulvin.

Antibiotics produced by Actinomycetes include Erythromycin, Chloramphenicol, Streptomycin, and Tetracyclines.

Bacteria-derived antibiotics include Polymyxin B, Colistin, and Bacitracin.

Synthetic antibiotics include Sulfonamide, Trimethoprim, Quinolones, Nitrofurans, and Nitroimidazole.

3.7 Based on Chemical Structure

The given antibiotics can be categorized based on their chemical structures. Some of the categories are sulfonamide group which includes drugs like trimethoprim, diaminopyramidine group consisting of drugs such as sulphadimidine, quinolones which include drugs like nalidixic acid, beta-lactam antibiotics such as ampicillin, aminoglycosides consisting of drugs like streptomycin and gentamicin, tetracycline group including drugs such as doxycycline, macrolides which include drugs like azithromycin, polypeptide antibiotics such as bacitracin, nitrofuran derivatives including drugs such as nitrofurantoin and nitroimidazoles consisting of drugs like metronidazole [42-44]. There are also polyene antibiotics including drugs such as amphotericin B and imidazole derivatives such as ketoconazole and clotrimazole.

4. ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) occurs when bacteria, fungi, viruses, and parasites change over time and no longer respond to medications or medicines, making infections difficult to treat and increasing the risk of disease spread, severe illness, and death. This happens because these microorganisms evolve mechanisms that protect them from the effects of antimicrobial drugs used to treat the infections they cause. The more the antimicrobial agents are used, the more the possibility for the microorganisms to become resistant, making the medicines ineffective, and infections persist in the body.

AMR is a natural process, but improper usage of antimicrobial drugs and management of infections caused by microorganisms accelerates it. The resistance is usually acquired by the microbes, and every class of microbe can evolve resistance. Antibiotic resistance is a major and urgent problem as antibiotics are the cornerstone of modern medicine, and most medicinal procedures in human and animal health rely on them.

Antimicrobial agents used for the treatment of bacterial infections are often categorized according to their principal mechanism of action, which includes interference with cell wall synthesis, inhibition of protein synthesis, interference with nucleic acid synthesis, inhibition of a metabolic pathway, inhibition of membrane function, and inhibition of ATP synthase. Bacteria that become resistant to antibiotics are considered extensively drug-resistant or totally drug-resistant, and are sometimes referred to as superbugs. AMR threatens the effective prevention and treatment of an increasing range of infections, including blood poisoning, pneumonia, diarrhea, gonorrhea, tuberculosis, HIV/AIDS, and malaria.

5. WHY ANTIMICROBIAL RESISTANCE IS A GLOBAL CONCERN

Antimicrobial resistance is a serious global public health threat, as it leads to the emergence and spread of bacteria that cannot be treated by existing antibiotics. The COVID-19 pandemic has caused a rise in superbug infections, wiping out progress made against deadly pathogens. While we need new antibiotics, it's also crucial to change our behavior towards antibiotics to prevent new antibiotics from eventually becoming ineffective [45,46]. Antibiotic resistance leads to increased medical costs, longer hospital stays, and a higher rate of death, with profound costs to health systems and national economies. Global deaths attributable to antimicrobial resistance in 2019 numbered 4.95 million, including 1.27 million deaths associated with bacterial antimicrobial resistance, and one in five of those who died were children under five years old. In 2018, the World Health Organisation considered antibiotic resistance to be one of the biggest

threats to global health, food security, and development.

Antimicrobial resistance has significant impacts on patients, including increased morbidity and mortality rates. When compared to non-resistant bacteria, resistant bacteria increase the likelihood of patients developing severe health issues by two-fold and the risk of death by three-fold [47,48]. These negative outcomes are even more severe in cases where the infection is more resistant and the patient is more vulnerable. By 2050, mortality rates due to antimicrobial resistance are projected to exceed those of major global causes of death.

Table 1. Abducted from "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

Place	Deaths per 100,000 attributable to AMR
North Africa and Middle East	11.2
Southeast and East Asia, and Oceania	11.7
Latin America and Caribbean	14.4
Central and Eastern Europe and Central Asia	17.6
South Asia	21.5
Sub-Saharan Africa	23.7

Table 2. Adapted from Antimicrobial resistance: tackling a crisis for the health and wealth of nations, 2019

Cancer	8.2 Million
Cholera	100,000–120,000
Diabetes	1.5 Million
Diarrheal-disease	1.4 Million
Measles	130,000
Road Traffic Accidents	1.2 Million
Tetanus	60,000
Antimicrobial Resistance	10 Million

6. ORIGINS OF ANTIMICROBIAL RESISTANCE

Antibiotic resistance can be described in different ways, such as innate or acquired, and phenotypic or genotypic. Phenotypic resistance refers to changes in physical or biochemical properties of bacterial cells in response to environmental stress, such as exposure to antibiotics. This is also known as adaptive resistance, and it can be reversed when the stress is removed. Examples of phenotypic resistance include generic factors like biofilm growth, which can make bacteria more resistant to antibiotics and biocides due to their slower growth rate, and specific factors like E. coli's greater resistance to aminoglycosides under anaerobic conditions. Another major example of phenotypic resistance is the induced synthesis of B-lactamases in response to the presence of B-lactam antibiotics, which is not a genetic change but rather a protective mechanism that bacteria can switch on and off as needed to conserve energy.

6.1 Resistance Arising by Mutation

The frequency of mutants arising in bacteria is affected by the size of the population and its reproduction rate. Mutations are a realistic and significant source of antibiotic resistance, particularly in infections that require prolonged treatment. Some bacterial species are more susceptible to mutation-induced resistance than others, and some antibiotics are more vulnerable to resistance development by this means than others. The mutation rate is influenced by the antibiotic concentration and environmental conditions. Resistance by enterococci to vancomycin and aminoglycosides is a recent example of mutation-induced resistance [49-52]. However, the use of multiple antibiotics is often recommended for the treatment of infections that require prolonged therapy. This is because the chance of a single cell becoming resistant to both antibiotics simultaneously is the product of their mutation rates, not the sum.

6.2 Resistance Arising by Receipt of New Genetic Information

Bacteria can acquire new genes in three ways. One way is called transformation, which occurs when a bacterial cell picks up DNA released by a dead cell and incorporates it into its own chromosome. This process is only observed in a few bacterial species, such as Streptococcus, Neisseria, Helicobacter, and Acinetobacter, and only under certain environmental or nutritional conditions. Bacteria that can naturally perform this process are known as competent. While this mechanism is less common than other ways for bacteria to acquire resistance, it can be very effective in some bacterial-antibiotic combinations, such as in the development of resistance to benzyl penicillin or amoxicillin (and ampicillin) in Streptococcus pneumoniae and gonococci.

Transduction: When a bacteriophage infects a bacterial cell, it may enter a dormant state within the host and integrate its nucleic acid into the host's genetic material. This state can end if the cell is exposed to a particular stimulus, causing the phage to replicate and kill the host cell. The resulting phage particles can then infect new hosts, potentially carrying bits of the original host's genetic material, including antibiotic resistance genes. This process, known as transduction, is specific to certain species and cannot transmit resistance between dissimilar bacteria. Transduction is most notable for transferring B-lactamase genes between strains of Staphylococcus aureus, but it can also transfer genes responsible for producing toxins and other virulence factors.

Conjugation: Plasmids are small, self-replicating DNA molecules found in bacteria that carry non-essential genes, such as those responsible for antibiotic resistance, toxin production, and fimbriae formation. Conjugation, a mechanism of horizontal gene transfer, allows for the transfer of plasmids from one bacterium to another. During conjugation, the donor bacterium uses a sex pilus to attach to the recipient bacterium, and a copy of the plasmid is transferred to the recipient. This process can occur between different strains of the same species or even between different genera of bacteria, making it a powerful means of gene transfer.

Transposons, also known as "jumping genes," are mobile genetic elements that can move within a cell's DNA and can promote the transfer of genes between bacteria. Unlike plasmids, the genes required for conjugation are located on the chromosome of the cell. Antibiotic resistance genes can be transferred between plasmids and chromosomes within cells by transposons, and plasmids may carry genes that confer resistance to multiple antibiotics at once. These plasmids can be lost if the relevant antibiotic is not present, which is why antibiotic cycling strategies are used as part of stewardship programs to limit the spread of antibiotic resistance.

The mechanisms of antibiotic resistance at cellular level: These includes;

Enzyme inactivation and modification,
Modification of the antibiotics target site
Overproduction of the target, Replacement of the target site
Efflux and reduced permeability.

6.2.1 Enzyme inactivation

One of the earliest mechanisms of antibiotic resistance was found in Staphylococcus aureus bacteria that were resistant to penicillin. These bacteria had acquired an enzyme called β-lactamase, which breaks open the β-lactam ring present in all β-lactam antibiotics. This prevents the antibiotic from binding to its target and renders it ineffective. There are many different versions of β-lactamase enzymes that have varying activities and can target specific members of the β-lactam family of antibiotics. However, some β-lactamases, called Carbapenemases, are particularly concerning as they can break down all members of the β-lactam family, including carbapenems, which greatly limits treatment options.

6.2.2 Enzyme modification

Bacteria can develop resistance to antibiotics by acquiring enzymes that modify either the antibiotic or the target site. The first type of enzyme adds chemical groups to the target of the antibiotic within the bacteria, rendering it unable to bind to the antibiotic. For example, the erm gene methylates the ribosome, preventing erythromycin from binding to it. The second type of enzyme modifies the antibiotic itself, making it unable to bind to its target site. Aminoglycoside-modifying enzymes, such as N-acetyltransferases, add an acetyl group to aminoglycoside antibiotics, which prevents them from binding to the ribosome. There are various types of these enzymes that can target different classes of antibiotics.

6.2.3 Modification of the antibiotic target site

Bacteria can become resistant to antibiotics by developing mutations in the genes that encode the target site of the antibiotic. During replication, mistakes can occur in the DNA sequences, and occasionally these mutations are present in bacterial populations in the presence of antibiotics. If the mutation happens in the gene that encodes for the antibiotic target protein, it can result in the antibiotic no longer being able to bind to the target. Bacteria with such mutations have a survival advantage and can resist the antibiotic while the rest of the population dies. This is how Streptococcus pneumoniae develops resistance to penicillin and many bacterial pathogens develop resistance to fluoroquinolone antibiotics like ciprofloxacin. In the case of penicillin resistance, the acquisition of mutations

in the penicillin binding proteins (PBP) prevent penicillin from binding and killing the bacteria, while for fluoroquinolone resistance, mutations in DNA gyrase and DNA topoisomerase IV genes prevent ciprofloxacin from binding to them.

6.2.4 Replacement of the target site

Some bacteria like Streptococcus pneumoniae develop resistance to antibiotics by mutating the targets of the drugs, while others like Staphylococcus aureus acquire an extra copy of a gene that encodes a protein which is still active in the presence of the antibiotic. Staphylococcus aureus, which is commonly known as MRSA, becomes resistant to β-lactam antibiotics like penicillin by producing an additional version of the target protein called penicillin binding protein 2a (PBP2a), which can still function even in the presence of the antibiotic.

6.2.5 Overproduction of the target

Bacteria can develop resistance to antibiotics by overproducing the target of the antibiotics, which means there is an excess of the protein target compared to the antibiotic itself. This mechanism of resistance is seen in Escherichia coli and Haemophilus influenzae with trimethoprim.

Beta-lactam antibiotics, which include penicillin, cephalosporins, carbapenems, and monobactams, are commonly used in clinical practice. They work by inhibiting the enzyme transpeptidase or penicillin binding proteins (PBPs), thereby disrupting the late stage of peptidoglycan synthesis and killing the bacteria.

Resistance to beta-lactam antibiotics is common and can occur through various mechanisms. These include producing proteins that modify PBPs, reducing uptake of the antibiotic into the cell through efflux mechanisms, producing enzymes that inactivate beta-lactam antibiotics (beta-lactamases), and preventing drug entry.

6.2.6 Mechanism of resistance via efflux pump

Gram-negative bacteria have a method of resistance against betalactam antimicrobial agents such as penicillins, cephalosporins, and imipenem. This method involves the use of an efflux pump, a specialized protein that spans the cell membrane and actively transports the antimicrobial agents from the interior of the bacterial cell to the external environment. This reduces the concentration of the betalactam agents in the bacterial cells, making them ineffective as they cannot express their bactericidal activity.

6.2.7 Mechanism of resistance via modification of PBPS

PBPS are crucial enzymes in bacterial cell wall construction. They catalyze the cross-linking between glycan chains through transglycosylation. Gram-positive bacteria utilize a resistance mechanism by modifying the PBPS. This modification involves altering the structure or quantity of PBPS. As a result, the amount of drug that binds to the target site is affected. If the drug binding is inhibited, the pharmacological action is not exhibited. In other cases, the binding may not be sufficient to produce a therapeutic effect.

6.2.8 Mechanism of resistance via activation of the enzyme beta lactamases

In this course, most beta lactam antibiotics are susceptible to resistance caused by beta lactamase enzymes, except for carbapenems and monobactams which are more resistant. Beta lactamases are produced by bacteria and can break open the beta lactam ring, rendering the antibiotics ineffective and thus causing resistance. Beta lactamases can be found in the bacteria's chromosomes or plasmids, and can be inducible or constitutive. They are classified into four classes based on their peptide sequence, with class A, C, and D having a serine ring at their active site and class D also containing four zinc atoms, making it a metallo-beta-lactamase. Class A beta lactamases are highly effective against benzylpenicillin, while class B enzymes work against penicillin and cephalosporins. Class C enzymes are often inducible but mutations can lead to their overexpression. Class D enzymes are highly effective against oxacillin, a subtype of penicillin.

6.2.9 Mechanism of resistance via preventing drug entry

Changing the frequency, size, and selectivity of the porin channels present on the surface of bacterial cell walls can impede the entry of beta-lactam drugs into the bacteria cells. This impediment prevents the beta-lactam drugs, including cefepime, cefpirome, and imipenem, from performing their intended pharmacological

action, which results in bacterial resistance to these drugs.

Table 3. Table showing various resistance mechanism and the class of beta lactam affected

Mechanism of resistance	Class of betalactam affected
Efflux pump	Carbapenem, cephalosoprin, penicillin
Prevention of drug entry	Cephalosoprin, carbapenem
Modification of PBP	Penicillin and cephalosporin
Activation of beta lactamase	Penicillin and cephalosporin

7. RESISTANCE TO GLYCOPEPTIDE

Glycopeptides are a type of antimicrobial drug used to treat bacterial infections, especially those caused by gram-positive bacteria that are resistant to other antibiotics. These drugs prevent the synthesis of bacterial cell walls by inhibiting peptidoglycan synthesis, with the D-alanyl-D-alanine terminus being the target. Glycopeptides are bactericidal and can stop the growth and replication of invasive bacteria. The first-generation glycopeptides include Vancomycin, Teicoplanin, and Ramoplanin, while the second-generation semi-synthetic glycopeptides are Oritavancin, Dalbavancin, and Televancin.

Vancomycin and teicoplanin are clinically important glycopeptides, but they are not active against gram-negative organisms because of their outer membrane. Vancomycin use increased in response to the rising incidence of methicillin-resistant Staphylococcus aureus (MRSA), and in 1988, resistance was first reported in Enterococci. Vancomycin now accounts for approximately 20% of all enterococcal infections. Five types of resistance are known clinically, VAN A-E, with phenotypic VAN A being the most common and conferring high-level resistance to vancomycin and teicoplanin. VAN-A resistance is mediated by a seven-gene cluster on the transposable genetic element.

8. RESISTANCE TO VANCOMYCIN

Vancomycin works by disrupting the maturation process of the peptidoglycan layer in bacteria by forming a complex network of hydrogen bonds with the d-Ala-d-Ala region of Lipid II. However, resistance to vancomycin can occur when the natural precursor is degraded and replaced with alternatives such as d-Ala-d-lac or d-Ala-d-Ser, which have low affinity for vancomycin.

9. RESISTANCE TO AMINOGLYCOSIDE ANTIBIOTICS

Resistance to vancomycin involves a sensor histidine kinase (VanS) and a response regulator (VanR), with VanH encoding a D-lactate dehydrogenase/alpha-keto acid reductase that generates D-lactate, a substrate for VanA, a D-Ala-D-Lac ligase. This results in cell wall precursors terminating in D-Ala-D-Lac, which vancomycin binds to with low affinity, reducing the concentration of vancomycin in the bacteria's cell and enabling it to confer resistance. The loss of one hydrogen bond mediates the change in affinity, as vancomycin and D-Ala-D-Ala form a stable complex with five hydrogen bonds, whereas only four hydrogen bonds are formed between vancomycin and d-Ala-d-Lac, making the complex unstable.

Aminoglycoside resistance is a growing concern, especially in microorganisms such as Acinetobacter baumannii and Campylobacter spp. that can cause severe infections. A. baumannii is capable of rapidly developing antibiotic resistance due to its ability to upregulate and acquire a variety of antibiotic resistance genes, resulting in multidrug-resistant strains. Resistance mechanisms include enzymatic modification of amino- or hydroxyl-groups of aminoglycosides, resulting in decreased binding to the ribosome of the aminoglycoside molecule. Enzymatic inactivation by aminoglycoside-modifying enzymes (AMEs) such as aminoglycoside acetyltransferases (AAC), aminoglycoside nucleotidyltransferases (ANT), and aminoglycoside phosphotransferases (APH) is the most prevalent resistance mechanism. Anaerobes are inherently resistant to aminoglycosides due to the absence of an oxygen-dependent transport system required for drug uptake. Mutation in the gene responsible for receptor protein deletion or alteration, alteration of cell surfaces that interfere with drug penetration or uptake, and production of AMEs are other mechanisms of aminoglycoside resistance. This high level of resistance to aminoglycosides is concerning as it could limit the use of combination therapy with other antibiotics in treating infections.

10. RESISTANCE TO TETRACYCLINES

"Tetracyclines are effective against a variety of microorganisms, including gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites. They are inexpensive antibiotics that have been widely used to prevent and treat infections in humans and animals. However, tetracycline resistance is now common in many pathogenic, opportunistic, and commensal bacteria, which limits the effectiveness of these agents in treating disease. Resistance can be due to the acquisition of new genes, which code for efflux pumps that expel tetracyclines from the cell, or for ribosome-protecting proteins. Some bacteria acquire resistance by mutations that alter the permeability of the outer membrane, the regulation of efflux systems, or the 16S rRNA. The mechanisms of resistance involve either blocking tetracycline from binding to the ribosome or distorting the ribosome structure to allow t-RNA binding while tetracycline is bound" [53].

11. MECHANISMS OF RESISTANCE TO MACROLIDES AND LINCOSAMIDES

The resistance to macrolides and lincosamides in gram-positive bacteria has increased, and there are multiple ways in which resistance can occur, including changes to the ribosomal target, efflux of the antibiotic, and drug inactivation. These mechanisms can result in different levels of resistance. The clinical relevance of in vitro macrolide resistance has been debated, but recent studies have shown that detecting macrolide resistance is important for guiding therapy and predicting treatment outcomes. Macrolides and lincosamides have a limited spectrum of activity against certain types of bacteria, and resistance mechanisms are often found in bacteria that produce these antibiotics. Target-site modification confers broad-spectrum resistance, while efflux and inactivation affect only some of these antibiotics. The impact of these resistance mechanisms varies among bacteria and has different clinical implications.

11.1 An Emerging Mechanism: Target Mutation

The process of selecting Escherichia coli mutants that are highly resistant to erythromycin in a laboratory setting has helped to understand how this antibiotic binds to the ribosome. Recently, mutations at specific locations in the rRNA have been identified as causing resistance to erythromycin and related antibiotics in various bacterial species, including Mycobacterium avium, Helicobacter pylori, Treponema pallidum, and Propionibacterium. These mutations typically occur in pathogens with only one or two copies of the rRNA operon. In S. pneumoniae, mutations in ribosomal proteins L4 and L22 have been found to cause erythromycin resistance. Although these resistance mechanisms are generally considered to be non-transferable, the ease with which S. pneumoniae can acquire new genes through transformation and recombination could potentially facilitate their spread. The prevalence and clinical significance of these resistant strains is not yet fully understood, as research on the conditions that lead to their selection in vivo has been limited. Nonetheless, it is believed that these new forms of resistance may be more important than previously thought.

11.2 Antibiotic Efflux Mechanism

Gram-negative bacteria have natural resistance to certain hydrophobic compounds, such as macrolides, due to chromosomally encoded pumps. These pumps are part of the resistance/nodulation/division family and have 12 membrane-spanning regions. In gram-positive bacteria, two classes of pumps, ABC transporters and MFS, are responsible for acquired resistance to macrolides through active efflux. The msr(A) gene encodes an ABC transporter in Staphylococcus species, including S. aureus, which requires ATP to function. The pump is made up of two membrane-spanning domains and two ATP-binding domains. The msr(A) gene works in conjunction with other chromosomal genes to form a multicomponent efflux pump with specificity for 14- and 15-membered macrolides and type B streptogramins, known as the MSB phenotype. The resistance is inducibly expressed, with erythromycin and other macrolides being inducers but not streptogramins B. Clindamycin is not an inducer or a substrate for the pump, and strains are fully susceptible to it.

11.3 Trimethoprim Resistance Mechanism

The resistance of bacteria to trimethoprim, an antibiotic used to treat various infections, can be caused by several mechanisms, including chromosomal and plasmid-mediated ones. The most significant mechanism in clinical settings is

plasmid-mediated resistance. The emergence of clinical resistance to trimethoprim may result from bacterial cells with altered permeability, loss of drug-binding capacity, overproduction or changes in DHFR, or a combination of these factors. DHFRs that are distinctive and mediated by dfr genes have been described in several bacterial species, including Enterobacteriaceae, P. aeruginosa, H. influenzae, Streptococcus pneumoniae, S. aureus, and Campylobacter spp. These resistant enzymes can be plasmid-mediated and spread by highly mobile transposons, leading to outbreaks of trimethoprim-resistant conjugative plasmids in various regions worldwide. The use of trimethoprim alone in some countries may also contribute to increasing resistance to TMP-SMX, although this is not certain.

A study was conducted to assess the susceptibility/resistance of E. coli and Klebsiella spp. isolates to trimethoprim using urine samples and to demonstrate the molecular detection of dfrA genes. The results showed that 29.8% of the isolates were resistant to trimethoprim, and dfrA genes were detected in 78.4% of the trimethoprim-resistant isolates. The detection of dfrA genes using a culture-independent PCR method was highly sensitive and specific in predicting phenotypic trimethoprim resistance in isolates and urine samples. There was a significant association between the presence of dfrA and trimethoprim resistance in urine samples containing Gram-negative bacteria. Rapid detection of trimethoprim resistance using molecular methods prior to prescribing an antibiotic could help avoid treatment failure and longer hospitalizations. Therefore, timely and appropriate initiation of antimicrobial therapy is crucial for effective antimicrobial stewardship policies.

Mupirocin is a topical antibiotic that is sold under the brand name Bactroban and is primarily used to treat superficial skin infections such as impetigo or folliculitis. It is also effective against methicillin-resistant S. aureus (MRSA) present in the nose without symptoms. However, using it for more than ten days is not recommended due to concerns about developing resistance. Mupirocin is available in the form of a cream or ointment that is applied to the skin.

Some common side effects of Mupirocin include itchiness and rash at the site of application, headache, and nausea. Long-term use may lead to increased growth of fungi. It belongs to the carboxylic acid class of medications, and its mechanism of action involves blocking a bacteria's ability to produce protein, which leads to bacterial death.

Mupirocin is considered safe for use during pregnancy and breastfeeding.

11.4 Mechanism of Action

Pseudomonic acid is an antibacterial compound that works by blocking the activity of isoleucine tRNA synthetase, an enzyme responsible for attaching isoleucine to tRNA molecules during protein synthesis in bacteria. As a result, the supply of isoleucyl-tRNA is reduced, leading to the accumulation of uncharged tRNA molecules that cannot participate in protein synthesis. The uncharged tRNA molecules bind to the ribosome, causing the formation of a molecule called (((p)ppGpp, which further inhibits the synthesis of RNA, a critical component of protein synthesis. This dual inhibition of protein and RNA synthesis stops bacterial growth and is similar to the mechanism of action of furanomycin, a compound that resembles isoleucine.

11.5 MUP Resistance *in S. aureus*

“Mupirocin (MUP) is an antibiotic used to treat methicillin-resistant Staphylococcus aureus (MRSA) infections. However, MUP resistance is increasing among S. aureus, particularly MRSA, due to over-the-counter, unjustified, and long-term usage. The frequency of MUP resistance varies between MRSA strains and is influenced by several factors, including the patient population, surveillance nature, and resistance profile. MUP resistance can be classified as low-level resistance (LLR) or high-level resistance (HLR) based on the minimum inhibitory concentration (MIC). LLR arises due to spontaneous mutations in the Ile-tRNA synthetase gene, leading to reduced binding affinity of MUP to the enzyme. LLR is clinically insignificant and non-transferable, but further mutations can lead to HLR via the acquisition of a staphylococcal multi-resistant conjugative plasmid (pSK41-like plasmid). HLR is plasmid-coded and can occur through the acquisition of plasmid-mediated mupA or Ile-tRNA synthetase-2 genes, which can also confer resistance to other antibiotics. The mupA gene is responsible for HLR in most S. aureus isolates, and it can transfer resistance to other antibiotics through self-transmission. Another paralog, mupB, is also responsible for MUP resistance” [53].

12. RESISTANCE TO ANTIFUNGAL AGENTS

Antifungal resistance is a problem where fungal infections no longer respond to medications designed to treat them. This type of antimicrobial resistance happens when fungi, viruses, bacteria, and parasites are not affected by the drugs developed to treat them. The issue is becoming a significant concern for clinicians caring for patients at high risk for invasive mycoses. Resistance can develop due to acquired mechanisms following exposure to antifungal drugs or because of intrinsic resistance in some fungal species. Some fungi, known as superbugs, have become more resistant to antifungal medicines and do not respond to standard treatments. The development of antifungal resistance can occur spontaneously or due to the overuse or misuse of antifungal medications. Those with weakened immune systems are at the greatest risk of developing fungal infections that can lead to antifungal resistance. Currently, there are only three classes of antifungal medications available, and a fungus that develops resistance to one drug may not respond to any available treatments:

12.1 Resistance in *Aspergillus fumigates*

Recently, there has been a growing interest in Aspergillus species that are resistant to azoles, particularly A. fumigatus. Similar to Candida species, resistance to itraconazole, posaconazole, voriconazole, and isavuconazole, which are triazoles that are effective against mold, can develop with prolonged clinical use. This resistance has been well documented in patients with chronic pulmonary aspergillosis who are often treated with azoles for many years. In *A. fumigatus*, acquired resistance is caused by mutations in the CYP51A gene, which codes for the Cyp51 enzyme responsible for converting lanosterol to ergosterol. These mutations can affect the azoles differently, with some causing resistance to voriconazole and isavuconazole, others to posaconazole and itraconazole, and still others causing resistance to all azoles.

12.2 Resistance in Candida

Candida is a yeast that naturally exists in the human body and on the skin. It can cause candidemia, a potentially life-threatening bloodstream infection, and it is becoming resistant to azole medicines. Candida glabrata affects the urinary system, and it is increasingly resistant to azoles and echinocandins, leaving patients with few safe treatment options. Candida auris is a new fungal superbug that emerged in 2009, causing problems worldwide and becoming more common in the United States. Antifungals that usually work against Candida infections do not always work against this strain, and some strains are multidrug-resistant, with no response to any antifungal drugs. C. auris causes bloodstream infections that can affect the heart and brain, and more than one-third of infected people die. The fungus spreads quickly in hospitals and nursing homes through contact with infected people or contaminated surfaces, and it can live on surfaces for several weeks, making it challenging to eliminate.

12.3 Resistance in non-*C. albicans*

12.3.1 Azole resistance

Candida albicans is the most commonly found species causing candidiasis in patients, but in various regions of the world, other species like C. glabrata, C. parapsilosis, and C. tropicalis are increasingly causing infections. These non-C. albicans species have been found to be more resistant to fluconazole, which is a low-cost and well-tolerated antifungal drug that can be easily administered orally. The concern is that resistance to fluconazole could also result in resistance to other azole drugs because the mechanisms that reduce susceptibility to fluconazole also affect other azoles. For example, mutations in the ERG11 gene increase transcription of the gene, leading to an increased amount of the enzyme, which is the target of the azoles. Additionally, efflux pumps such as Cdr1 and Cdr2 also affect this class of antifungal drugs. The World Health Organization has reported increasing fluconazole resistance in non-C. albicans species, which is worrying because these species are becoming more important causes of candidiasis, and alternative antifungal drugs may not be as accessible or well-tolerated as fluconazole.

The echinocandins are the recommended initial treatment for invasive candidiasis in patients who have weakened immune systems or who have previously been treated with azoles, as they are less likely to develop resistance. Unlike azoles, echinocandins work differently and are effective against many Candida strains that are resistant to azoles. However, resistance to echinocandins can still occur with prolonged exposure, usually

due to mutations in the FKS1 and FKS2 genes, which are responsible for producing parts of the glucan synthase enzyme.

13. MULTI DRUG RESISTANCE

The past few decades, there has been a significant increase in the occurrence of microbial infections. This is partly due to the continuous use of antimicrobial drugs in treating infections, which has led to the emergence of resistance among various strains of microorganisms. Multidrug resistance (MDR) refers to the inability of a microorganism to be affected by different antimicrobial medicines (that are structurally unrelated and have different molecular targets), even though it was previously sensitive to them.

Despite the administration of appropriate doses of drugs for a specific duration of time, various microbial strains can survive, indicating the high levels of resistance developed in them. This clinical failure is not solely due to antimicrobial resistance but can also be due to suppressed immune function, poor drug availability, or increased drug metabolism. The persistence of microbes after conventional treatments indicates the existence of different types of antimicrobial drug resistance, which is becoming a growing problem in the medical field. MDR can be categorized as primary, secondary or clinical resistance.

Primary resistance refers to the inability of a microorganism to be affected by a specific drug because it has not been exposed to it before.

On the other hand, secondary resistance or acquired resistance occurs when microorganisms become resistant to a drug after exposure. This resistance can be classified as intrinsic resistance, where all microorganisms of a single species are insensitive to common drugs, or extensive resistance, which is the ability of organisms to withstand the effects of the most effective antimicrobial drugs.

Clinical resistance occurs when the concentration of an antimicrobial agent required to inhibit a pathogen is too high to be safely achieved through normal dosing, leading to a high likelihood of treatment failure or reappearance of infections due to impaired host immune function.

13.1 Mechanisms of MDR

The cell wall is essential for the survival of bacteria and fungi, and drugs target it by inhibiting cell wall synthesis. However, organisms can develop resistance to these drugs through mutations or horizontal gene transfer, leading to changes in the cell membrane composition that decrease drug permeability or eliminate drug target sites. Mutations in genes encoding drug target enzymes can also lead to alternate target molecule production, reducing drug efficacy. The primary mechanism of multidrug resistance is the overexpression of genes that encode ATP-binding cassette transporter membrane proteins, such as P-glycoprotein, which export drugs out of the cell, allowing cellular functions to continue without interference.

13.2 AMR: A Growing Concern

Antimicrobial resistance (AMR) is a major global public health concern in the 21st century, particularly with regard to antibiotic resistance in bacteria. Bacteria causing common or severe infections have developed resistance to each new antibiotic over several decades. To prevent a global health crisis, the World Health Organization (WHO) has long recognized the need for a coordinated effort to contain AMR. In 2001, the WHO Global Strategy for Containment of Antimicrobial Resistance provided a framework for interventions, and in 2012, WHO published The Evolving Threat of Antimicrobial Resistance - Options for Action, which proposed a combination of interventions. These included strengthening health systems and surveillance, improving the use of antimicrobials in hospitals and communities, infection prevention and control, encouraging the development of appropriate new drugs and vaccines, and political commitment. Surveillance is particularly crucial, and in April 2014, WHO published the first global report on surveillance of AMR, which showed that surveillance data can be useful in orienting treatment choices, understanding AMR trends, identifying priority areas for interventions, and monitoring the impact of interventions. Our review focuses on the impact of antibiotic resistance in species commonly associated with infection, such as Staphylococcus aureus, Klebsiella pneumoniae, non-typhoidal Salmonella, and tuberculosis, in different settings. We also examine the main factors contributing to the development of antibiotic resistance and its consequences for human health.

13.3 Antibiotics Resistance Impact

Antibiotic resistance is a significant public health issue, and its impact is challenging to quantify. In

the US, over two million people are affected by antibiotic-resistant infections each year, resulting in at least 23,000 deaths. Similarly, in Europe, around 400,000 infections and 25,000 deaths are caused by multidrug-resistant bacteria annually. Antibiotic-resistant bacterial strains pose a severe threat to modern medicine as various medical procedures such as cancer treatment, organ transplantation, and surgery rely heavily on effective antibiotics. For instance, cancer patients with chemotherapy-related neutropenia are vulnerable to high antibiotic resistance rates in infections, and orthotopic liver transplant patients have a high percentage of antibiotic-resistant bacterial isolates. The economic impact of antibiotic resistance is challenging to calculate, and it encompasses several factors such as increased treatment costs, hospitalization, and societal costs. In Europe, the economic burden of antibiotic resistance was estimated to be at least 1.5 billion euros, with 40% of the cost attributed to productivity loss due to absence from work or death from infection. The CDC in the US estimated that the cost of antibiotic resistance was $55 billion per year, with $20 billion in direct healthcare costs and up to $35 billion in societal costs for lost productivity.

13.4 Global Threat: AMR

Antimicrobial resistance (AMR) is a serious global threat to public health and development that requires immediate action. According to WHO, AMR is among the top 10 global public health threats facing humanity. The overuse and misuse of antimicrobial drugs are the leading causes of drug-resistant pathogens.

Lack of access to clean water and sanitation, as well as inadequate infection prevention and control, promote the spread of microbes that can resist antimicrobial treatment. The economic cost of AMR is significant, as prolonged illness results in longer hospital stays, the need for more expensive medicines, and financial difficulties for those affected.

Effective antimicrobials are crucial for modern medicine to treat infections, especially during major surgeries and cancer chemotherapy. However, the emergence and spread of drug-resistant pathogens, including superbugs that are resistant to existing antimicrobial medicines, threaten our ability to treat common infections.

The development of new antimicrobials is not keeping pace with the emergence of drug-resistant pathogens. WHO identified only six innovative antibiotics out of 32 in clinical development that address priority pathogens. A lack of access to quality antimicrobials remains a significant challenge, leading to antibiotic shortages in healthcare systems.

Antibiotics are becoming less effective as drug resistance spreads globally, making infections more difficult to treat and leading to deaths. New antibacterials are urgently needed, but they will suffer the same fate as current ones if people do not change how antibiotics are used.

AMR has significant economic and health system costs, affecting patient productivity, prolonged hospital stays, and expensive intensive care. Without effective prevention and treatment tools for drug-resistant infections, the number of treatment failures and deaths will increase. Medical procedures, such as surgeries, chemotherapy, and organ transplantation, will become riskier.

13.5 Drivers of AMR (Factors that Accelerate AMR)

Antimicrobial resistance (AMR) is accelerated by several factors such as the misuse and overuse of antimicrobial drugs, lack of access to clean water, sanitation and hygiene, poor infection and disease prevention and control, poor access to quality, affordable medicines, vaccines and diagnostics, lack of awareness and knowledge, and lack of enforcement of legislation. Additionally, AMR occurs naturally over time, usually through genetic changes, and antimicrobial-resistant organisms can be found in people, animals, food, plants, and the environment. A united multisectoral approach is needed to tackle the problem of AMR. The One Health approach brings together multiple sectors and stakeholders engaged in human, terrestrial and aquatic animal and plant health, food and feed production, and the environment to work together to attain better public health outcomes. To ensure global progress, countries need to ensure the costing and implementation of national action plans across sectors to ensure sustainable progress. The Global Antimicrobial Resistance and Use Surveillance System (GLASS), the Global Antibiotic Research & Development Partnership (GARDP), the Antimicrobial Resistance Multi-Partner Trust Fund (AMR MPTF), and other funds and initiatives could fill a major funding gap. The WHO priority pathogens list guides research and

development into new antimicrobials, diagnostics and vaccines.

13.6 Preventing Antibiotics Resistance

Antibiotic resistance is a serious global health concern that occurs when bacteria develop the ability to resist the effects of antibiotics, making them harder to treat. The overuse and misuse of antibiotics contribute to the development of resistance. This results in longer and more complicated illnesses, more doctor visits, the use of stronger and more expensive drugs, and even more deaths caused by bacterial infections.

To prevent antibiotic resistance, individuals can take simple steps such as washing their hands regularly, getting vaccinated, and taking antibiotics only as prescribed by a healthcare professional. It is essential to understand that antibiotics are not effective against viral infections such as colds or flu, and taking them unnecessarily can lead to harmful side effects and contribute to antibiotic resistance.

Healthcare professionals have a crucial role to play in combating antibiotic resistance by prescribing antibiotics only when necessary and following appropriate prescribing guidelines. In hospitals, it is vital to use the CDC dedicated network to prevent the spread of resistant bacteria between patients.

In the agricultural sector, the use of antibiotics in animal production can lead to the emergence of resistance and the transmission of resistant bacteria. This has consequences such as reduced food production, increased food safety concerns, and contamination of the environment. It is essential to prioritize access to effective and cost-efficient antimicrobials to maintain animal health, welfare, and food security while preventing the emergence of resistance.

14. CONCLUSION

The reviewed literature highlights the urgency of developing innovative approaches to tackle the rising problem of antimicrobial resistance (AMR) worldwide. It emphasizes the significance of a coordinated global effort to confront this public health threat, given the potential dire consequences of uncontrolled AMR. This review should prove useful to professionals in the field of infectious diseases and AMR, providing them with valuable insights and guiding their research and clinical practice. As AMR poses a challenge to multiple sectors, including healthcare, agriculture, and environment, it is crucial to engage stakeholders from various domains and disciplines to address this multifaceted issue. Furthermore, tackling AMR requires a comprehensive approach, encompassing measures such as promoting responsible use of antibiotics, strengthening infection prevention and control, investing in new drug development, and fostering international collaboration and partnerships.

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CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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