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Review article ***Antibiotic Resistance***

A Review on Hidden Pandemic of Antibiotic Resistance Super Bugs

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ABSTRACT

Antibiotics have assisted in saving the lives of numerous individuals. Based on their origin, form, and mode of action, antibiotics have been categorized into distinct classes. An innate and acquired mechanism of antimicrobial resistance has been identified in numerous clinically significant bacterial strains. This has posed a significant threat to the use of antibiotics and contributed to the proliferation of microbes resistant to effective first-choice or "first-line" medications. Antibiotic resistance has led to the emergence of so-called superbugs that are immune to the current treatment method. There are fewer antibiotics available to treat these infections, and fewer are in development. In children in developing and underdeveloped nations, infectious diseases are one of the leading causes of mortality. Antibiotics are chemical agents that inhibit bacterial proliferation by preventing or destroying bacterial cell division. However, the widespread use, misuse, and overuse of antibiotics in humans and animals has led to the emergence of resistant bacteria that pose a threat to both animal and human health. Antibiotic-resistant microorganisms have been referred to as "nightmare bacteria" that pose a catastrophic threat to the population of every country on earth. Antibiotic resistance is caused by a variety of factors, including the use of antibiotics in subtherapeutic quantities, non-laboratory-based therapy, and improper storage.

Keywords: Antibiotics, antimicrobial resistance, Superbugs.

INTRODUCTION

Superbugs, or drug-resistant microorganisms, are among the most terrifying threats in the history of medicine. After being exposed to antibiotics, superbugs have evolved. The bacteria develop increased "resistance" to the antibiotic to which they have been exposed. We should be able to eradicate or prevent the spread of the bacteria. A superbug is any microorganism that is resistant to at least one of the most commonly used antibiotics. These are typical causes of the following:

- Rational use of different types of antibiotics
- Overuse of antimicrobial medicines
- Inadequate treatment with these types of drugs
- Poor quality of drugs
- Nostandardized treatment of diseases
- Generic mutation which is likely to be seen among microorganisms

Antibiotics are primarily employed in both human and veterinary medicine to ensure global human and animal health. Antibiotics have also been used to enhance aquaculture and agricultural production, in addition to medical treatment. However, the emergence of therapy-resistant bacteria[1]. A number of studies on bacterial resistance have demonstrated the vast diversity of resistance mechanisms, whose distribution and interaction are largely unknown. However, multiple biochemical and physiochemical pathways can also contribute to the development of antibiotic resistance. The evaluation of the bacterium's genetically inherent resistance or the outcome of its exposure to antibiotics may constitute the resistance mechanism. The majority of antibiotic resistance is the

consequence of mutation or the transfer of genetic material between microbes. Approximately 20,000 potential resistance genes have been identified in nearly 400 distinct bacteria, according to a number of recent studies[2]. It is possible for resistant genotypes to become zoonotic, posing a threat to human health [3]. Antibiotic-resistant infections occur far too frequently and are worsening, making it difficult to treat humans and animals effectively. The introduction of antibiotics into the environment has led to an increase in antibiotic resistance [4].

To maintain the efficacy of antibiotics, it is essential to evaluate their use in both humans and animals. Several new initiatives are being implemented to curtail the alarming trend of antibiotic resistance and to combat the escalating number of infections caused by antibiotic-resistant bacteria [5].

What is antibiotic resistance?

When an antibiotic is no longer effective against bacteria it would ordinarily be able to treat, we refer to these bacteria as "antibiotic-resistant." Bacteria resistant to antibiotics could be resistant to a single antibiotic or multiple antibiotics. The greater a bacteria's resistance to antibiotics, the more hazardous and difficult it is to treat that bacteria..

How does antibiotic resistance happen?

When taking an antibiotic to treat an infection, the dose should be sufficient and the duration of treatment should be sufficient to eradicate all bacteria. If not, the remaining bacteria may adopt antibiotic-resistance and become more difficult to eradicate; what does not kill them literally makes them stronger.

Researchers discovered four distinct mechanisms by which bacteria acquire antibiotic resistance.

Building walls: Some bacteria have outer membranes (or walls) that make antibiotics more difficult to penetrate. If antibiotics cannot reach the microbes, they cannot kill them.

Species of bacteria that previously lacked these defenses have developed biofilm, or restrictive walls, to keep antibiotics out. When this occurs, antibiotics can no longer prevent the multiplication and infection caused by these bacteria.

Super-bug's cell wall buildup process

Gram-negative bacteria have an impermeable lipid-based outer membrane that functions as a defensive barrier against attacks by the body's immune system and antibiotic drugs.

Dong's team determined that the defensive wall was constructed and maintained by a beta-barrel assembly machinery (BAM) consisting of five sub-units named BAMA, BAMB, BAMC, BAMD, and BAME.

The beta barrel assembly apparatus is responsible for the construction of cell wall "gates." Stopping the beta-barrel assembly machine from constructing the cell wall's gates kills bacteria.

The study found that the subunit BAMA, which is located in the outer membrane and is exposed on the outer side of the bacteria, is a crucial component of the Beta-barrel assembly machinery (Bam) complex, making it "a great target." The final component of the BAM (barrel assembly machinery) complex involved in OMP (outer membrane protein) assembly. It is responsible for the ultimate insertion and folding of the beta-barrel trans membrane into the outer membrane.

Escherichia coli's beta-barrel assembly machinery (BAM) complex is a multiprotein mechanism that catalyzes the essential process of outer membrane protein assembly.

BamA and BamB recognize the substrate and construct it, whereas BamD recognizes the C-terminal targeting sequence (B-signal) in the precursor OMP.

The insertion of pleated proteins into the outer membrane of Gram-negative bacteria is mediated by the essential beta-barrel assembly process. Here, we describe the native structure and function of BamE, a crucial component of this complex, and demonstrate that while it is exclusively monomeric in the periplasm, where it is normally found, it can adopt a distinct dimeric form in the cytoplasm. Mutagenesis and interaction studies have mapped key determinants for complex binding, outer membrane integrity, and cell viability, in addition to disclosing the function of BamE within the Bam complex. BamE has been shown to bind specifically with phosphatidylglycerol.

A Superbug: What Is It?

A bacterial strain known as a superbug has developed antibiotic resistance. Some genotypes may be resistant to even the most modern antibiotics. If no effective antibiotic treatments are available, individuals infected with superbugs risk suffering catastrophic health consequences.

How hazardous are superbugs, exactly?

Imagine if the antibiotics used to treat these infections abruptly stopped working. Prior to the development of antibiotics, pneumonia and tuberculosis were among the primary causes of death in the United States. Due to this, superbugs pose a significant problem.

Modifying their equipment

Some antibiotics function by traversing a machine within the bacterial cell. By destroying these internal components, the bacteria are deemed incapable of survival and reproduction. Certain microbes are capable of altering their internal structure over time. in order for antibiotics to no longer be effective against them.

Antibiotics that neutralize

Currently, certain microorganisms can neutralize antibiotics. In a manner comparable to how the human immune system generates antibodies to combat disease, bacteria are learning to resist drug invasion by altering the chemical composition of antibiotics. When this occurs, the antibiotic cannot function properly.

Releasing antibiotics

Similar to how your body eliminates toxins, bacteria contain efflux pumps that aid in the elimination of foreign compounds such as antibiotics. These efflux pumps are encoded genetically in microorganisms and have the potential to evolve over time to remove drugs more efficiently.

The causes of antibiotic resistance

When antibiotics are used at recommended dosage levels to treat confirmed bacterial illnesses, the benefit of exposure significantly outweighs the risk of selecting resistant strains [6]. Sadly, a significant portion of antibiotic therapy is neither laboratory-based nor extrapolated in the laboratory. This is in addition to the high proportion of life-threatening infections

that are promptly treatable. Therefore, the prescribed antibiotic must be combined with first-line drugs such as erythromycin, gentamicin, ampicillin, ampiclox, cotrimoxazole chloramphenicol, tetracycline, and metronidazole [7].

Antibiotics mode of action

Understanding how antimicrobial medicines function is essential for comprehending resistance processes. Targeting the cell wall, which is present in prokaryotic (bacterial) cells but absent in human cells, is one of the most common action methods. (eukaryotic cells). Thus, antimicrobial drugs have a negligible or nonexistent effect on host functions, operating only on essential bacterial functions. Antibiotics with distinct mechanisms of action are used to prevent or eradicate bacterial growth[8].

Table 1: A list of antimicrobial agents and their modes of action

Antimicrobial agents	Group	Mode of action
Ampicillin, Agumentin Amoxicillin	Penicillins	Inhibitor of cell wall synthesis
Ceftriaxone	Cephalosporins	Inhibitor of cell wall synthesis
Chloramphenicol	Chloramphenicol	Inhibitor of cell wall synthesis
Erythromycin Azithromycin	Macrolides	Inhibitor of cell wall synthesis
Gentamicin, streptomycin, oxytetracycline, Nalidixic acid, Ciprofloxacin	Aminoglycosides Tetracycline Quinolones	Inhibitors of DNA synthesis
Sulfamethazine Trimethopim	Sulfonamides	Competitive inhibitors of folic acid synthesis

Antibiotic resistance mechanism

As there are numerous ways in which antibiotics can prevent the development and reproduction of microbes or destroy them, there are also numerous mechanisms of resistance that microbes either possess naturally or have developed in response to antibiotic exposure. It is possible for an organism to develop resistance to multiple antibiotic classes via a single mechanism, particularly if the mechanisms of action of the antibiotics are similar. Individual bacteria can occasionally share resistance[9] by generating "resistance plasmids," DNA fragments that can be transferred from one cell to another.

As opposed to mutation, the most common and clinically significant cause of multi-drug resistance (MDR) in Gram-negative bacteria is the transmission of resistance genes between organisms via these mobile genetic elements (MGEs). There is substantial evidence that MGEs can transfer resistance genes between species. Enterococci MGEs, for instance, have been shown to be transferred to Staphylococcus aureus [10].

If a bacterium has "significantly reduced susceptibility" compared to the "original isolate" or a collection of sensitive strains, it is considered resistant. (Chapman, 1998). Changes in housekeeping-related regulatory or structural genes can cause resistance, as can horizontal acquisition of foreign genetic information[11].

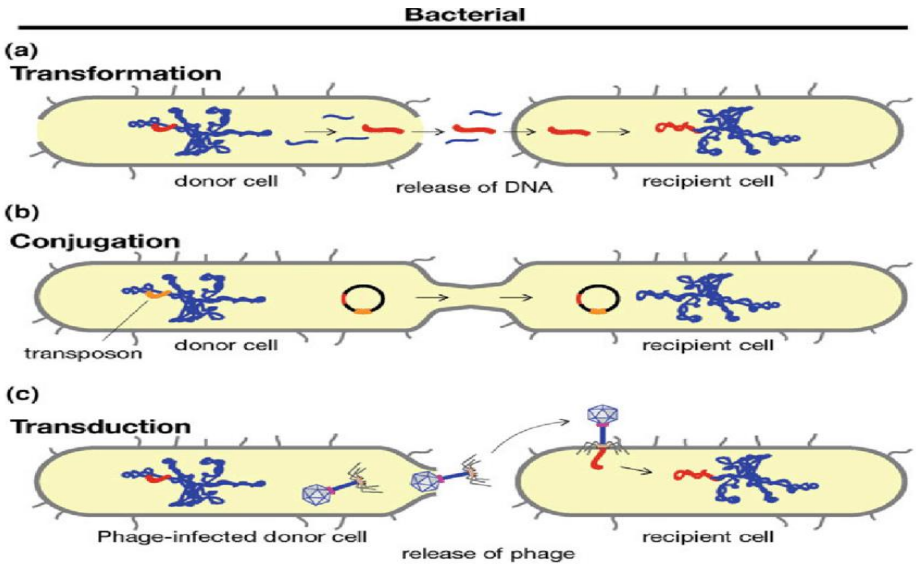

Fig 1: the transfer of a resistance gene horizontally from one bacterium to another.

Microorganisms that naturally lack the drug's target sites and do not respond to it (such as Mycoplasma species resistant to penicillin) or that naturally have low permeability to those agents due to differences in the chemical composition of the drug and the membrane structures of the microorganisms, especially for those that must enter the microbial cell to have an effect, can be classified as intrinsic or natural resistant. The second is acquired resistance, which occurs when a microorganism that is normally susceptible to a drug learns how to resist its effects.

A decrease in membrane permeability: Stopping the drug from accessing the cell is an additional common method of antibiotic interference. The drugs must pass through the cell pores, which are channels that span the outer membrane of gram-negative bacteria and allow materials to enter or depart the cell. Gram-negative bacteria possess a cell envelope. To enter the cell or interact with the cell wall, the medications must be capable of passing through the pores. A gene mutation can alter the physical composition or electrical charge of pores, making it more difficult for antibiotics to penetrate the cell.

Although functional, the antibiotic will be unable to reach its intended destination. Thus, a microbe can simultaneously acquire resistance to multiple forms of medication. However, some gram-negative bacteria possess innate resistance to potent medications such as vancomycin, which is too large to travel through the pores.

Target site modification: Numerous antibiotics function by attaching to a specific bacterial molecular component. If the target molecule undergoes a minute structural change as a result of an organism, the antibiotic may lose its ability to bind to the target molecule, thereby diminishing the drug's efficacy. For instance, tetracyclines bind to the transfer RNA access site and inhibit it. Mild modifications to the access point may induce tetracycline resistance in microorganisms [12].

Antibiotic efflux or transport: Utilizing an efflux pump is another method by which microorganisms acquire antibiotic resistance. An antibiotic can be expelled from the cell by an efflux pump, preventing it from reaching or maintaining contact with its target. This form of antimicrobial resistance may frequently result in resistance to more than one class of antibiotics, especially macrolides, tetracyclines, and fluoroquinolones, as these medications must be intracellular to function and inhibit various portions of protein and DNA biosynthesis..

There are four primary mechanisms by which genetic changes in bacteria cause antibiotic resistance. Target molecules are structurally altered to prevent antibiotic binding; membrane permeability is decreased (antibiotics are excluded from cell entrance); antibiotics are degraded by enzymes; or antibiotics are pumped out of the cell by efflux pumps.

Transmission of microorganisms resistant to antibiotics to humans

Numerous antibiotics used in animal nutrition are also employed in the treatment of human diseases. Because of the potential for bacterial resistance in the gastrointestinal tracts (GITs) of these animals, public health officials and consumers are alarmed by such levels of antibiotic use in animal feed.

This resistance can also propagate through the food chain to the bacteria that inhabit the GIT.

As a consequence of feeding calves, pigs, and poultry low doses of antibiotics such as tetracycline and penicillin to promote growth, the reservoir of antibiotic-resistant bacteria has increased significantly. These pathogenic bacteria may propagate from animals to humans. It is well-known that Salmonella infections cause this. Animal-to-human transmission of antibiotic-resistant bacteria can occur indirectly through food (such as when carcasses are contaminated during slaughter) or less frequently through direct contact.

Control of antibiotic resistance Guidelines exist for the responsible (proper, appropriate, prudent, or judicious) use of antibiotics in veterinary and human medicine, and the medical and agricultural sectors have similar guidelines[13]. In numerous nations, veterinary and animal producer organizations have developed and implemented responsible use guidelines. These include applications for poultry, swine, dairy and beef cattle, as well as lambs. Additionally, international organizations such as the OIE and WHO have devised principles or codes of conduct to limit antibiotic resistance. The WHO has published global guidelines for the control of antimicrobial resistance in food-producing animals.

Guidelines for the appropriate and prudent use of antimicrobial agents in Veterinary Medicine is one of five documents regarding antibiotic resistance published by the OIE. The remaining four documents address laboratory procedures, monitoring of use quantities, surveillance programs, and methods for risk analysis. The majority of the numerous guidelines' recommendations can be summed up in three objectives: Prioritize disease prevention measures to reduce the therapeutic use of antibiotics; if a disease affects or threatens animals, consider alternatives to using antibiotics to mitigate or prevent the disease's effects; and if antibiotics are required to prevent, control, or treat a disease, prioritize the use of antibiotics that are less important to humans.

Preventing animal infectious diseases: Focus should be placed on the continuous implementation of appropriate disease prevention measures in order to reduce the demand for antibiotics. To mitigate infection in food animal production and reduce antibiotic use, efforts should focus on improving animal health, thereby eliminating or reducing the need for antibiotics for treatment or prevention. This can be accomplished by enhancing hygiene, bio-security, and health management on farms and preventing disease through the use of vaccines and other measures such as probiotics, prebiotics, and competitive exclusion products. (intestinal bacterial flora that limit the colonization of some bacterial pathogens). Vaccines have been an integral part of disease prevention for many years due to their low cost, simplicity of administration, efficacy, multiple agent efficacy (viruses, bacteria, mycobacteria, and parasites), and safety. (worker, animal, environmental, lack of food residue). Sometimes, adjuvants are added to vaccines to enhance the immune response. Various delivery systems or routes of administration (such as injection into muscle, aerosol, topical, or oral (mucosal)) are used to administer the vaccine to the animal.

Future research on veterinary vaccine adjuvants will concentrate on particle delivery to antigen-presenting cells and immune stimulatory adjuvants in order to induce a more robust and durable immune response[14]. New oral delivery

systems, such as vaccines derived from plants, are being developed that offer simplicity of administration, production, and other advantages; however, the regulatory acceptance of these products remains unclear. Bacteriophages have been used successfully in Russia to prevent and treat bacterial diseases in humans and animals, but they have failed to obtain acceptance in Western nations due to the prevalence of antibiotic use[15]. The anti-infective properties of bacteriophages include their specificity because they target a single type of bacterium (limited host range), as well as their lethality, projected low cost, and lack of residues in food products. However, concerns remain regarding the safety of recombinant therapies, environmental containment, and phage resistance.

Bacteriocins are pore-forming antibacterial proteins produced by microorganisms, and their potential use in the control of certain zoonotic pathogens in the avian intestinal tract has been investigated. Nisin, a bacteriocin, has been approved for use in a variety of culinary products.

After the discovery of the antibiotic substance penicillin in 1928 by Sir Alexander Fleming from the fungus Penicillium notatum, antimicrobial agents (antibiotics and related medicinal medicines) were discovered in 1935 by German chemist Gerhard Domagk. Prontosil was the first sulfa drug. (1895-1964). The 1945 Nobel Prize in medicine was shared by Fleming, Florey, and Chain for their work on penicillin[16,17]. In the year 1950, aminoglycosides, chloramphenicol, tetracycline, and macrolides were discovered. (Table 1). These antibiotics acted effectively on both Gram-positive and Gram-negative bacteria and were the preferred treatment for a number of bacterial diseases. Later in 1956 and 1960, vancomycin and methicilin were discovered, which represented a significant advancement in the treatment of infectious diseases. (Table 1). It is highly effective at curing infection, especially when Gram-positive bacteria are involved. 1962 saw the discovery of nalidixic acid, and 1967 saw its introduction to clinical use[18]. This is the first synthetic quinolone antibiotic that is effective against both Gram-positive and Gram-negative bacteria, and it, along with its more recent subset of fluoroquinolones, is used very effectively in the treatment of Gram-negative urinary tract infections. In the late 1990s, the development of the first, second, and third generations of cephalosporins increased the arsenal for fighting infections caused by Gram-positive and Gram-negative bacteria[19]. First-generation cephalosporins are primarily effective against Gram-positive bacteria, whereas subsequent generations are increasingly effective against Gram-negative bacteria [14-20]. These antimicrobial agent discoveries have saved lives and alleviated the distress of countless individuals. However, emerging antimicrobial resistance in microbes has put its use in jeopardy and contributed to the spread of microbes resistant to effective first-choice, or "first-line," antibiotics[21].

Years	***Development of antimicrobial agents***
1928	Discovery of penicillin
1935	Discovery of sulfonamide
1940	Clinical application of penicillin
1950	Discovery of aminoglycoside, chloramphenicol, Tetracycline and macrolide
1950	Discovery of vancomycin
1960	Synthesis of methicillin
1962	Synthesis of Nalidixic
1967	Development of first generation cephems Development of second generation cephems Development of third generation cephems
1983	Development of carbapenem and monobactam Increased use of third generation cephem, carbapenem, oral cephem and new Quinolone antimicrobial
2000	(Decrease in newly developed antimicrobial agents)

Different groups of antimicrobial

Since it is the lowest, safest, and most effective antibacterial treatment available, penicillin G is the most commonly used antibiotic. Penicillin G and V continue to be the treatment of choice for numerous Gram-positive bacterial infections. Gram-positive Staphylococcus pyogenes (strep pharynx) and Streptococcus pneumonia (respiratory tract infections) are treated with penicillin G and V [22]. Methicillin was the first penicillin to be effective against penicillin G-resistant Staphylococcus strains.Ampicillin and amoxicillin have a wider spectrum of activity than earlier penicillin formulations. It is effective against both prevalent Gram-negative and Gram-positive bacteria. However, they are ineffective against staphylococci resistant to penicillin G. Both are efficacious when administered orally and are active against Escherichia coli, Haemophilus influenza, and Salmonella typhi [23]. Carbenicillin was the first penicillin synthesized with anti-Pseudomonas aeruginosa activity. This bacterium typically causes infections in hospitalized patients and has proven to be particularly difficult to treat. Cephalosporins are an essential class of antimicrobial agents in clinical practice. This group's injectable forms are typically broad-spectrum. The bactericidal mode of action is restricted to hospital use for the treatment of severe infections. Tetracycline is a bacteriostatic, broad-spectrum antibiotic used to treat a variety of infections [24]. Erythromycin (Macrolide group) is a very safe antibiotic that is effective orally, bacteriostatic, and active against Gram-positive infections, particularly respiratory tract infections caused by streptococci. For patients who cannot tolerate penicillin, erythromycin has proven to be a valuable alternative [25]. Antibiotics with a broad spectrum and bactericidal activity are quinolones. It is increasingly utilized due to its relative safety, oral and parenteral availability, and favorable characteristics. 1st generation quinolones (Nalidixic acid) are limited to Gram negative enteric bacteria, whereas 2nd and 3rd generation fuoroquinolones (norfoxacin, ciprofoxacin) have enhanced activity against Gram positives, such as staphylococci and pneumococci, and also have activity against mycoplasma and legionella [26]. Against Gram-negative bacteria, Aminoglycoside Group is exceedingly active. Bactericidal, it is only efficacious when administered intravenously. Newer aminoglycosides, such as gentamicin[27], have essentially supplanted streptomycin. The Aminoglycosides group has the potential to induce kidney damage and hearing loss. Chloramphenicol is an orally efficacious, broad-spectrum bacteriostatic antibiotic. Chloramphenicol is a significant alternative treatment for typhoid fever and bacterial meningitis due to its ability to efficiently enter the central nervous system. In most nations, the use of these antibiotics has decreased due to fears that they may induce an extremely rare but fatal anemia and the availability of safer alternatives. Florfenicol, a fuorinated chloramphenicol derivative, is an antimicrobial agent with

broad spectrum activity against a wide variety of Gram-positive and Gram-negative bacteria[18,19].

The antibacterial activity

Antibiotics target and inhibit multiple essential bacterial metabolic, growth, and multiplication mechanisms. In addition, it causes bacterial lysis by distorting and damaging the cell membrane, resulting in the leakage of vital cell components and mortality. Polymyxins damage the osmotic barrier by interfering with phospholipids in the bacterial cell membrane. Changes to the lipid A-binding site or efflux channels may contribute to colistin resistance. A mutation of lipid A that causes a defective cell membrane and osmotic trauma in the absence of colistin is one possible mechanism for colistin dependence. Inhibition of cell wall synthesis by binding to transpeptidases and inhibiting the formation of peptidoglycan is an additional important antibiotic mechanism. These transpeptidase enzymes and certain other bacterial proteins to which penicillin binds are referred to collectively as penicillin-binding proteins. (PBPs). Gram-positive and Gram-negative bacteria, as well as anaerobic taxa, have distinct PBPs. -lactams are only effective against bacteria that are actively dividing, as this is when a new cell wall is being created[1,18].

Several classes of antimicrobials are able to halt cell division by interfering with the ribosome's protein synthesis process. Certain antimicrobials bind to one or both subunits (30S, 50S) and cause misreading of the genetic code or aberrant, nonfunctional protein complex formation. Aminoglycosides (gentamicin, tobramycin, amikacin, streptomycin) predominantly bind to the 30S subunit to exert their effects. Tetracylines are an additional class of biochemical antibiotics that bind to the 30S ribosome[28]. Tetracylines are bacteriostatic rather than bactericidal due to their transient ribosome binding. Multiple antimicrobial classes inhibit the 50S ribosomal subunit. Macrolides (erythromycin, chloramphenicol, and clindamycin) are predominately bacteriostatic and reversibly bind to the 50S subunit, interfering with the linking of amino acids.

Several antimicrobials effectively increase the inhibition of nucleic acid (DNA) replication. They bind to the DNA-gyrase complex, inhibiting its function and causing cell demise in bacteria. Important antimicrobial compounds include the quinolone naladixic acid, which only acts on aerobic Gram-negative organisms, and the fluoroquinolones ciprofoxicin, norfoxacin, and oxacin, which have a much broader spectrum of activity. Typically, bacteria are incapable of absorbing folic acid from the environment and must synthesize it internally. Trimethoprim and sulfonamides inhibit the synthesis of tetrahydrofolate, thereby interfering with folate metabolism. Typically, trimethoprim and sulfonamides are administered together because trimethoprim enhances the efficacy of sulfonamides [29].

Mechanisms of antimicrobial resistance

Antibiotic resistance is the capacity of a bacterium or other microorganism to survive and proliferate in the presence of antibiotic doses that were once believed to be efficacious against them. Different mechanisms are known to contribute to antimicrobial resistance enhancement. It is possible that microbes are intrinsically resistant and lack a target for antibiotics[30]. Chlamydiae lack peptidoglycan and are therefore not susceptible to penicillins. The target of the antibiotic may be inaccessible. Membrane modifications prevent antibiotic entry and cell penetration. Penicillins incapable of penetrating the Gram-negative outer membrane cannot access peptidoglycan in Gram-negative bacteria. Antibiotics can be actively pumped out of cells by Effux pumps. This essential mechanism allows Gram-negative bacteria to resist the activity of tetracycline antibiotics.

The antibiotic target can be altered to prevent the drug's action: Ribosomes undergo alterations and mutations, and chemical and physical changes prevent the attachment of antibiotics to these ribosomes. By synthesizing a new metabolic pathway, bacteria are able to produce a new enzyme that is unaffected by the antimicrobial. Resistance to trimethoprim-sulfamethoxazole is caused by bacteria that produce a new dihydrofolate reductase that is not inhibited by trimethoprim and a new dihydropteroate synthase that is resistant to sulfonamides. Quinolone resistance is caused by DNAgyrase point mutations that prevent the drug from binding to its target.

The antibiotic may be chemically modified to destroy

Enzymes degrade or inactivate antibiotics through phosphorylation, adenylation, or acetylation reactions. Resistance to aminoglycosides is primarily caused by bacterial enzymes that acetylate, phosphorylate, or adenylate aminoglycosides in the periplasmic space. This modification of the compound causes binding to bacterial ribosomes and inadequate cellular uptake. The genes coding for antibiotics-altering enzymes are frequently found on transposons and have been identified in Enterobacteriaceae and P. aeruginosa, S. pneumonia, and Gram-positive bacteria including S. aureus, S. faecalis, and S. pyogenes. The vast array of -lactamases is a significant example.Chloramphenicol resistance is caused by the presence of chloramphenicol transacetylate, an intracellular enzyme. This enzyme acetylates hydroxyl groups on the structure of chloramphenicol, reducing its binding to the 50S ribosome. Photobacterium piscicida is the source of the first forfenicol resistance gene (pp-fo) that confers resistance to both chloramphenicol and forfenicol. Similarly, among Salmonella enterica serovar Typhimurium DT104, a fostgene with 97% homology to the pp-fo gene was reported. Since then, the for gene has also been discovered in Escherichia coli and Salmonella spp plasmid and chromosomal loci. Despite having a similar mode of action to chloramphenicol, forfenicol is highly efficacious against a wide range of Gram-positive and Gram-negative clinical bacterial isolates. Florfenicol has acquired popularity as the demand for alternative antimicrobial agents has increased due to the emergence of microorganisms resistant to antibiotics. Forfenicol description in multidrug resistance Salmonella enterica serovar Typhimurium Phage type DT104 worldwide epidemic variants have added to its public health significance[22-30]. Bacteria may develop alternate routes to circumvent the drug target: Meticillin-resistant Staphylococcus aureus produces an additional penicillin-binding protein, PBP2', that is resistant to inhibition by penicillin.

Molecular pumps transfer antibiotics out of the cell with vigor: Active efflux is the mechanism responsible for the expulsion of toxic substances and antibiotics from the cell; it is regarded as a crucial component of xenobiotic metabolism.

This mechanism is essential in medicine because it contributes to antibiotic resistance in bacteria. Efflux systems use an energy-dependent mechanism (Active transport) to expel unwanted noxious substances via specific efflux pumps. Some efflux systems are drug-specific, while others can accommodate multiple drugs and thus contribute to multidrug resistance in bacteria (MDR).

Antibiotic Resistance by Mutation and Selection

Normal intestinal bacteria divide and proliferate rapidly, requiring only 15 to 20 minutes to double through binary fusion. The human large intestine contains approximately 100 billion bacteria per gram of solid matter and more than 100 distinct bacterial species. At a rate of 1 in 100,000 to 1 in a million, bacteria multiply and mutate at a rapid rate. Mutations are random occurrences that are not typically induced by antibiotics. Frequently, biochemical alterations occur when mutations occur. Proteins, enzymes, and ribosomes that lack a membrane can be altered. DNA base-pair mutations frequently result in single, distinct amino acid changes in the protein, accompanied by alterations in protein structure or function. Numerous potential mutations anywhere along a DNA-molecule (the fundamental hereditary material) increase the likelihood that antibiotic-resistant bacteria will develop.

Transfer of antibiotic resistance

DNA and associated traits - such as antibiotic resistance - may be transferred between bacteria. DNA transfers may be rare, or fairly common, depending upon circumstances. Large populations of closely-related bacteria increase the chances for gene transfer, including resistance genes, which are among the preferred bacterial gene transfers. The three common gene transfers are:

Conjugation

One bacterium attaches to another via a protein transfer tube (pilus) that transfers a portion of its DNA to the receiving bacterium. F+ or Hfr bacteria that transfer to F- bacteria are examples. One or multiple alleles may be transmitted in this way. A plasmid is a circular body of double-stranded DNA that is distinct from the chromosome and bears genes that code for various characteristics, including virulence and antimicrobial resistance. According to their capacity to transfer from one bacterium to another, plasmids can be divided into two categories. Nonconjugative plasmids are incapable of transferring to other bacteria via sex pili. Conjugation requires cell-to-cell contact, and both donor and recipient end up with a copy of the plasmid. R-factors are plasmids with both conjugation and antimicrobial resistance properties. The transfer of plasmids by conjugation is a crucial mechanism because it can occur in a wide variety of bacterial species and can extend to organisms that are distantly related. Multiple classes of antimicrobial resistance genes can be contained on a single plasmid.

Transduction

A virus carries a portion of the genes of one bacterium into another bacterium by attaching to it, injecting viral DNA and some bacterial DNA, which are then incorporated into the host, recipient bacterium. If the organism survives the infection and proliferates, the gene is maintained and transmitted to all progeny. By means of bacteriophages, chromosomal or plasmid DNA is transferred from one bacterium to another. Bacteriophages are viruses that target microorganisms. Since bacteriophages have a very limited host range, this is a less significant method for transferring resistance genes into the recipient host bacterium. If the organism survives the infection and proliferates, the gene is maintained and transmitted to all progeny.

Current research

Numerous studies have been conducted around the world in an effort to comprehend the extant and emerging antimicrobial resistance in microbes from various environmental niches. According to the research findings, antimicrobial resistance mechanisms are highly influenced by the manner in which antibiotics are used locally, and microbes can efficiently transfer resistance either horizontally or vertically due to the different mechanisms discussed above. It has been discovered that microbes from vast geographical distances and unrelated niches share a comparable antimicrobial resistance mechanism. Thus, once a resistance mechanism has emerged for any antibiotic, a similar mechanism can be predicted in other regions, despite the low or brief duration of selection pressure imposed by any antibiotic use. Staphylococcus aureus developed penicillin resistance shortly after the discovery and therapeutic use of penicillin. (1940-1961). Emerging between 1967 and 1977, the penicillin intermediate and resistant clone of Streptococcus pneumonia has recently become a significant concern in many regions of the world. Since then, numerous studies have sought to comprehend the mechanisms and distribution of Streptococcus pneumonia resistance clones and types. Between 1983 and 1986, the emergence of ESBLs producing Gram-negative bacilli and VRE was observed. Since then, a mechanism of resistance to cephalosporins and cephamycin has been identified in microorganisms from hospital and community-acquired infections that pose a significant clinical risk. In this group of microorganisms, four major classes of -lactamases enzymes have been identified to date. Class are derived from the older, broad-spectrum -lactamases (e.g., TEM-1, TEM-2, SHV-1) and have an extended substrate profile that allows for the hydrolysis of all cephalosporins, penicillins, and aztreonam.

These enzymes are typically produced by Klebsiella spp. and Escherichia coli, but other Gram-negative bacteria, such as Enterobacter, Salmonella, Proteus, and Citrobacter spp., may also produce them. Class B enzymes are relatively uncommon and contain zinc. Class C Amp C -lactamases are plasmid-mediated enzymes created by the transfer of chromosomal genes for inducible AmpC -lactamases onto plasmid. OXA-class enzymes of the Class D -lactamases are uncommon. In numerous Gram-negative bacteria, including Pseudomonas aeruginosa and Enterobacter spp., chromosome-mediated AmpC -lactamses have been identified. In hospital and community acquired infections, plasmid-mediated ESBLs and AmpC-type -lactamases have been increasingly reported in recent years. AmpC enzymes such as DHA-1 have been identified in K. pneumoniae and Salmonella, which naturally lack chromosomal AmpC -lactamases. Plasmids encoding these AmpC -lactamases were all derived from the chromosomally encoded AmpC -lactamases of representative bacterial species and have been identified in a vast array of microorganisms. TEM and SHV-

ESBLs are efficient and clinically significant class A-lactamases that play a significant role in antibiotic resistance. (Fig. 2). SHV-1 activity is comparable to TEM-1, but it is more effective against ampicillin. Extended-spectrum -lactamases are derived from TEM-1, TEM-2, or SHV-1 through mutations that modify the amino acid configurations surrounding their active sites. CTX-M family members have recently been the most successful plasmid-encoded -lactamases in terms of clinical significance. These -lactamases catalyze the hydrolysis of -lactam antibiotics, rendering them inactive. In response to clinical use of extended-spectrum -lactam antibiotics, naturally occurring variants of CTX-M have been isolated containing amino acid substitutions that modify the enzyme's substrate specificity, similar to TEM and SHV enzymes. Some of the new variants displayed enhanced activity (Kcat/Km) against the extended-spectrum antibiotics without losing activity against penicillin. Similarly, resistance microorganisms to antibiotics used in hospitals and farms have been identified in farm-bred animals. As it can serve as a reservoir and promote the spread of multidrug-resistant organisms and their determinants in the environment, a great deal of research has been devoted to the surveillance and monitoring of antibiotic use in farms. Specifically, the comparative study of phenotype and genetic resistance mechanisms in microorganisms of human and animal origin would be useful for gaining insight into the current situation of local selection pressure imposed by the use of antibiotic agents in both humans and animals. Because of the emergence of antibiotic resistance and its impact on public health, the use of antibiotics in animals has been hotly contested for a long time, and various preventive measures are being taken to lessen the negative impact of antimicrobial use in animal farms.

CONCLUSION

Antibiotics are put to significant use in both human and animal health practices across the globe, in both developed and developing countries, primarily for the treatment and prevention of a wide variety of diseases. However, the usage of these drugs, including their improper administration and excessive use, contributed to conditions that were conducive for the appearance, incidence, and evolution of bacteria resistant to antibiotics. In a similar vein, some of the other aspects that may play a role are the utilization of sub-therapeutic doses, non-laboratory-oriented antibiotic therapy, inefficient medications, and inadequate drug storage. All of these things have the potential to lead to infections that are far more difficult to treat. Even though there are guidelines in human and veterinary medicine for the responsible use of antibiotics, vaccination, competitive exclusions, and others for rational use and the control of antibiotic resistance, there are still some indications of the misuse of antibiotics by health care providers, unskilled practitioners, and drug consumers. This is a problem because antibiotic resistance is a growing problem in both human and veterinary medicine. All of these factors, along with the rapid spread of microorganisms that are resistant to treatment, may ultimately result in higher mortality.

REFERENCES

1. Wang HJ, Entire MC, Zhang LX, Doyle LM. The transfer of antibiotic resistance from food to humans: facts, implications and future directions. Rev Sci Tech Off Int Epiz. 2012;31(1):249-60.
2. Davies J. Origin and evolution of antibiotic Resistance, Microbiologyand Mol. Biol Rev. 2010:417-33.
3. Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere. 2006;65(5):725-59. doi: 10.1016/j.chemosphere.2006.03.026, PMID 16677683.
4. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care symptomatic for longer and increased workload: outcomes for patients with E. coli UTls. Br J Gen Pract. 2006;56(530):686-92. PMID 16954001.
5. Center for Disease Control (CDC). National Antimicrobial Resistance Monitoring System (NARMS); 2008. Human isolates of enteric bacteria final report.
6. Young KD. Peptidoglycan. In: Wiley Online Library. Available from: http://www.els.net/WileyCDA/ElsArticle/refId-a0000702. html.2011.
7. Young KD. Peptidoglycan. In: Wiley Online Library. Available from: http://www.els.net/WileyCDA/ElsArticle/refId-a0000702. html.2011.
8. World Health Organization (WHO). Tackling antibiotic resistance from a food safety perspective in Europe. WHO library cataloguing in publication data. Copenhagen, Denmark. 2011.
9. Rafailidis PI, Pitsounis AI, Falagas ME. Meta analyses on the optimization of the duration of antimicrobial treatment for various infections. Infect Dis Clin North Am. 2009;23(2):269-76. doi: 10.1016/j.idc.2009.01.009, PMID 19393908.
10. Gordon MA, Banda HT. Non-typhoidalbacteraemia among HIVinfected Malawian adults: high mortality and frequent recrudescence. AIDS. 2002;16:1633-41.
11. Sykes R. Penicillin: from discovery to product. Bull World Health Organ. 2001;79(8):778-9. PMID 11545336.
12. John s. Haller Jr. Prontosil. In: Lesch JE, editor. The first miracle drugs: how the sulfa drugs transformed medicine. New York: Oxford University Press; 2007. p. 119-21.
13. Saga T, Yamaguchi K. History of antimicrobial agents and resistant bacteria. JMAJ. 2009;52(2):103-8.
14. Pegler S, Healy B. In patients allergic to penicillin, consider second and third generationcephalosporins for life threatening infections. BMJ. 2007;335(7627):991. doi: 10.1136/bmj.39372.829676.47, PMID 17991982.

15. Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14(4):933-51. doi: 10.1128/CMR.14.4.933-951.2001, PMID 11585791.
16. Matagne A, Lamotte-Brasseur J, Frère JM. Catalytic properties of class A β-lactamases: efficiency and diversity. Biochem J. 1998;330(2):581-98. doi: 10.1042/bj3300581, PMID 9480862.
17. Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for β-lactamases and its correlation with molecular structure. Antimicrob Agents Chemother. 1995;39(6):1211-33. doi: 10.1128/AAC.39.6.1211, PMID 7574506.
18. El-Shaboury SR, Gamal SA, Mohamed FA, Rageh AH. Analysis of cephalosporin antibiotics. J Pharmacol Biomed Anal:200745:1-19.
19. Livermore DM, Canton R, Gniadksowski M, Nordmann P, Rossolini GM, Arlet G et al. CTX-M: changing the face of ESBLs in Europe. J Antimicrobche-Mother. 2006;2:165-74.
20. Jacoby GA, Medeiros AA. More extended spectrum of β-lactamses. Antimicrob Agents Chemother. 1991;35(9):1697-704. doi: 10.1128/AAC.35.9.1697.
21. Nelson N, Joshi M, Kirika R. Antimicrobial resistance: the need for action in the east, central and Southern Africa region, Arlington, 2009. Dargatz, JL, Weese JS. Antimicrobial drug use in veterinary medicine. Intern Med. 2005;19(2):617-29. View publication stats.
22. Morley PS, Apley MD, Besser TE, Burney DP, Fedorka-Cray PJ, Papich MG et al.
23. Federal Ministry of Health (FMOH). Ethiopia and WHO. Assessment of pharmaceutical sectors in Ethiopia; 2003.
24. Spanu T, Luzzaro F, Perilli M, Amicosante G, Toniolo A, Fadda G. Italian ESBL Study Group.
25. Merril CR, Scholl D, Adhya SL. The prospect for bacteriophage therapy in Western medicine. Nat Rev Drug Discov. 2003;2(6):489-97. doi: 10.1038/nrd1111, PMID 12776223.
26. Joerger RD. Aternatives to antibiotics: bacteriocins, antimicrobial peptides and bacteriophages. Poult Sci. 2003;82(4):640-7. doi: 10.1093/ps/82.4.640, PMID 12710486.
27. Henzler Wildman KA, Lee DK, Ramamoorthy A. Mechanism of lipid bilayer disruption by the human antimicrobial peptide, LL-37. Biochemistry. 2003;42(21):6545-58. doi: 10.1021/bi0273563.
28. Hancock RE, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006;24(12):1551-7. doi: 10.1038/nbt1267, PMID 17160061.
29. Watkinson AJ, Murby EJ, Kolpin DW, Costanzo SD. The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. Sci Total Environ. 2009;407(8):2711-23. doi: 10.1016/j.scitotenv.2008.11.059, PMID 19138787.
30. Li D, Yang M, Hu J, Zhang J, Liu R, Gu X et al. Antibiotic-resistance profile in environmental bacteria isolated from penicillin production wastewater treatment plant and the receivingriver. Environ Microbiol. 2009;11(6):1506-17. doi: 10.1111/j.1462-2920.2009.01878.x, PMID 19226301.