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An overview of antimicrobial agents

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Abstract
Microorganisms can both be useful and are beneficial in human welfare, whilst others are disease-inflicting and poisonous sufficient to make us ill. Antimicrobial agents are mainly used to cure diseases caused by microorganisms. In this review groups of microorganisms, diseases caused by them, antimicrobial agents, their mechanism of action, mechanism of resistance, strategies used to combat antimicrobial resistance and antimicrobials in current clinical development stage have been discussed.

Keywords: microorganisms, antimicrobial agent, antimicrobial resistance, antibacterial

Introduction
Microorganisms or microbes are minute organisms which are invisible to the bare eyes. These microorganisms are so small in length that they cannot be visible with the unaided eye. Microorganisms are so small that they could simplest be visible beneath a microscope. Some of these, such as the fungus that grows on bread, may be visible with a magnifying glass. Others cannot be visible without the assist of a microscope. This is the motive why they're referred to as microorganisms or microbes. The air we breathe, the meals we eat, the water we drink, the ground wherein we stand, the entirety round us is inhabited via some or the opposite sort of microorganism. They are even present inner our body. Few microorganisms also can face up to severe situations like an area as warm as boiling water, or an area as bloodless as ice. Some microorganisms are located alone, whilst the others are located in colonies. Microorganisms can both be useful and are beneficial in human welfare, whilst others are disease-inflicting and poisonous sufficient to make us ill. Useful microorganisms form a massive a part of the atmosphere and take part with in side the manufacturing of minerals and gases like oxygen, carbon dioxide. They additionally feed at the useless and decaying matter by means of changing the complicated compounds into the easier ones. The bio-geochemical cycle, such as the nitrogen cycle is a critical instance of beneficial microorganisms. These microorganisms are utilized in diverse industries for the manufacturing of diverse metabolites together with ethanol, riboflavin, lactic acid, and butanol. There are some of microorganisms which are chargeable for meals spoilage, illnesses and infections. Such microorganisms are referred to as dangerous microorganisms. Bacteria are the maximum risky of all microorganisms and are chargeable for numerous infectious illnesses together with tuberculosis, cholera, diphtheria, etc. Viruses also are chargeable for sure deadly illnesses together with AIDS, influenza, etc. Fungi also are dangerous and may result in sure pores and skin infections and allergies [1, 2].

Group of microorganisms
- Bacteria
- Fungi
- Viruses
- Algae
- Protozoa

1. Bacteria
Bacteria are unicellular microbes belonging to the prokaryotic group wherein the organisms lack some organelles and a real nucleus. They arise in water, soil, air, meals, and herbal environments. They can live on extremes of temperature, pH, oxygen tension and surroundings pressure. Examples of bacteria: *Escherichia coli*, *Staphylococcus aureus*. Bacteria are categorised into five groups consistent with their fundamental shapes: spherical (cocci), rod (bacilli), spiral (spirilla), comma (vibrio) or corkscrew (spirochaetes). They can exist as single cells, in pairs, chains or clusters [3].

▪ Structure of bacteria
The shape of bacteria is easier than that of different organisms as there's no nucleus or membrane bound organelles. Instead, their regulator centre containing the genetic information is contained in a one loop of DNA.

Some bacteria have a further circle of genetic material referred to as a plasmid. The plasmid consists of genes that provide the bacterium a few gains over other bacteria. For instance, it could include a gene that makes the bacterium resistant against a sure antibiotic.
They lack any of the intracellular organelles so typical of eukaryotic cells, such that they do not contain the golgi apparatus, endoplasmic reticulum, lysosomes or mitochondria. Flagella are present which might be composed from a single filament of the protein flagellin. Bacteria multiply by means of binary fission and there's no sexual interaction. A single chromosome, with a closed circle of double-stranded DNA and without a related histone. The plasma membrane is a phospholipid bilayer however consists of no cholesterol or different steroids [4, 5].

- **Types of bacteria**

Bacteria can be grouped as gram-positive or gram-negative depending upon the staining methods.

a. Gram-positive bacteria

The gram-positive bacteria stains purple by retaining the crystal violet colour by gram staining. The high peptidoglycan matter in the cell wall of Gram-positive bacteria is accountable for retaining the crystal violet dye. The cell wall of gram-positive bacteria is mainly composed of multiple layers of peptidoglycan that forms a rigid and thick structure. Its cell wall furthermore contains teichoic acids and phosphate. The teichoic acids found in the gram-positive bacteria are of two types-the lipoteichoic acid and the teichoic wall acid. The cell wall is identified as murein. In gram-positive bacteria outer membrane is absent.

b. Gram-negative bacteria

Gram-negative bacteria retain crystal violet dye in the gram staining protocol. The gram-negative bacteria are stained by a counterstain for example safranin, and they are de-stained by the alcohol wash. Therefore, beneath a microscope, they are markedly pink in colour. Gram-negative bacteria have high resistant against antibodies as their cell wall is impenetrable. In gram-negative bacteria cell wall is comprised of an outer membrane and several peptidoglycan layers. The outer membrane is comprised of phospholipids, lipoproteins, and lipopolysaccharides. The peptidoglycan remains intact to lipoproteins of the outer membrane that is positioned in the fluid-like periplasm among the plasma membrane and the outer membrane. The periplasm is held with proteins and degrading enzymes which help in transporting molecules. The cell walls of the gram-negative bacteria, in contrast to the gram-positive, lacks the teichoic acid. Because of the presence of porins, the outer membrane is penetrable to nutrition, water, food, iron, etc [6, 7].

- **Disease caused by bacteria**

1. Pneumonia
2. Typhoid fever
3. Cholera
4. Pertussis
5. Tuberculosis

2. Fungi

Fungi are eukaryotic, non-vascular, non-motile and heterotrophic organisms which may be unicellular or filamentous. They exist as a saprophytes, parasites or commensals. They reproduce by means of spores and exhibit the phenomenon of alternation of generation. As fungi lack chlorophyll, they cannot perform photosynthesis. They are aerobic or facultatively anaerobic. Fungi are important sources of antibiotics, enzymes, acids, foods, bakery and alcohol fermentation. Certain fungi also cause human diseases, such as athlete's foot and thrush. A fungus includes yeast, mould, and mushrooms [8, 9].

- **Disease caused by fungus**

1. Mucor mycosis
2. Sporotrichosis
3. Candidiasis
4. Aspergillosis
5. Blastomycosis

3. Viruses

A virus is a genetic material (DNA or RNA) contained within organic particle which lives in a host cell, utilizes host's metabolic processes to reproduce, and releases the replicated nucleic acid chains to invade more cells. A virus is normally held in a protein coat or protein envelope, which is a protective covering that permits the virus to survive between hosts. Viruses are about 20 to 300 nm in size which can only be seen under electron microscope. They are 10 to 100 times smaller than most bacteria. Viruses infect all types of living forms, from plants and animals to microorganisms, including bacteria and archaea. Viruses are seen in almost every ecosystem on earth and are the several type of biological entity. The study of viruses is known as virology. Infections by virus in animals elicit an immune response that usually eliminates the infecting virus as well as immune responses can also be produced by vaccines. Some viruses are responsible for many humane disease

including AIDS, HPV infection, and viral hepatitis. For treating such illness several antiviral drugs have been developed [10, 11].

- **Disease caused by virus**

1. Dengue
2. Yellow fever
3. Gastroenteritis
4. Influenza
5. Viral hepatitis

4. Algae

Algae are unicellular or multicellular, diverse group of photosynthetic eukaryotic organisms. Algae exist in atmospheres ranging from oceans, lakes, and rivers to ponds, brackish waters and even snow. Algae are typically green, but can be observed in a variety of different colours. Algae can be either unicellular or multicellular organisms and do not have definite shape. They are photosynthetic in nature and mode of reproduction can be sexual as well as asexual. Some algae can easily cultivate in the laboratory by using artificial media. They are mainly used as food supplements and in pharmaceutical preparations. Agar, used in culture media is prepared from different types of algae. Examples are Cephaleuros virescens, Oedogonium, Zoochlorella [12, 13].

- **Disease associated with harmful algae**

1. Amnesic Shellfish Poisoning (ASP)
2. Diarrhetic Shellfish Poisoning (DSP)
3. Ciguatera Fish Poisoning (CFP)
4. Neurotoxic Shellfish Poisoning (NSP)
5. Paralytic Shellfish Poisoning (PSP)

5. Protozoa

Protozoa are unicellular, eukaryotic, heterotrophic organisms, either free-living or parasites found in the aquatic environment. They do not have a cell wall but there are many different cell organelles, which accomplish various tasks performed by different organs in higher animals, e.g., mouth, intestinal tract, anus, etc. They are distinguished on the basis of morphological, nutritional and physiological characteristics. They are usually 2 to 200 µm in size. They have complicated life cycles and the cyst stage is dormant and tolerant to environmental stress while the trophozoite stage is reproductive and triggers disease. Some of the protozoal species are simply cultivated in laboratory media like bacteria and others are intercellular parasites. All protozoal species need large amount of moisture for growth and activity. Their reproduction is by sexual as well as asexual processes. There are several protozoal species, that cause various diseases in animals and humans, e.g., Plasmodium (malarial parasite), Trypanosoma (sleeping sickness), Trichomonas (Trichomoniasis), etc [14, 15].

- **Disease caused by protozoa**

1. Malaria
2. Amoebiasis
3. African Sleeping sickness or Trypanosomiasis
4. Giardiasis
5. Leishmaniasis or Kala-azar

Infection

An infection is a disease or the state resulting by the establishment or invasion by one or more pathogenic agents (such as a bacteria, protozoans, or viruses) in the body of a suitable host. Infection usually resulting into illness. One can acquire an infection in several different ways, such as contact with infectious agent or directly from a person with an infection, via contaminated food or water, and even due to the insect bite. Microorganisms which trigger disease are known as pathogens. If a host is to improve from an infection, it must destroy pathogenic microorganisms. Therefore, an infection signifies a fight between the defences displayed by the host and the particular features of virulence factors formed by the pathogen. Particular medicines used to treat infections include antibiotics, antifungals, antivirals, antiprotozoals, and anthelminthics [16, 17].

Antimicrobial agent

Antimicrobial agent is a universal term that is mainly related with antibiotic, antibacterials, antifungals, antivirals and antiprotozoans. Antimicrobial agents are drugs, chemicals or other substances that are able to act via two modes: either kill (microbicidal) or prevent the growth of microbes (microbiostatic). Generally, they can be grouped according to the microorganisms they act mainly against. For example, antibacterials are used against bacteria and antifungals act against fungi [18].

History of antimicrobials

Antimicrobials are perhaps one of the most effective forms of chemotherapy in the history of drug. Antibiotics have been consumed for ages to treat infections, though till the preceding century or so people did not recognize

the illnesses were caused by bacteria. Several moulds and plant isolates were used to cure infections by some of the initial civilisations, for example-the earliest Egyptians, put on mouldy bread to cure infected wounds. However, till the 20th era, diseases which are now possible straightforward to treat, for instance pneumonia and diarrhoea, that are caused by bacteria, were the primary reason behind human death in the developed world [19].

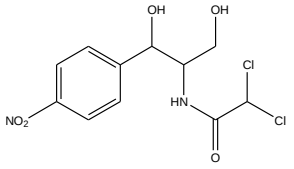
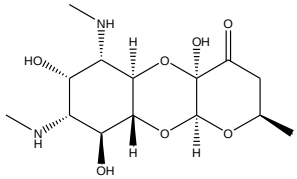
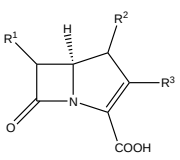
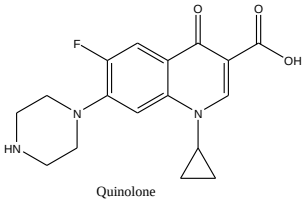
- After 19th century scientists began to observe antibacterial chemicals in action. A German physician, Paul Ehrlich, observed that some chemical dyes coloured a few bacterial cells but not others. He came to conclusion that, in accordance with this principle, it must be probable to produce substances which can kill certain bacteria selectively with no harm to other cells.
- In 1909, he exposed a new chemical called arsphenamine which was an effective treatment for syphilis. Later, this turn out to be the first modern antibiotic, while Ehrlich himself mentioned to his finding as 'chemotherapy'-the use of a chemical to cure an illness.
- Over 30 years later, the Ukrainian-American inventor and microbiologist Selman Waksman, first used the word ‘antibiotics’, who in his lifetime found over 20 antibiotics.
- Alexander Fleming during his work accidentally discovered penicillin. In 1928, upon returning from a holiday in Suffolk, he observed that a fungus, *Penicillium notatum*, had spoiled a culture plate of *Staphylococcus* bacteria he had unintentionally left open. He noticed that the fungus had formed bacteria-free zones everyplace it grew on the plate. So, he isolated and grew the mould in clean culture. He noticed that *P. notatum* shown extremely effective still at very little concentrations, stopping *Staphylococcus* growth even after diluting 800 times, and was less toxic as compared to the disinfectants used at the time.
- During the earlier days of antibiotics research, the systematic screening approach presented by Paul Ehrlich led to the discovery of sulfa drugs, namely Prontosil (sulfonamidochrysoidine), which was produced by Bayer chemists Josef Klarer and Fritz Mietzsch and verified by Gerhard Domagk for its antibacterial activity in a number of infections.
- In 1944, the finding and isolation of streptomycin led to a universal exploration for sources of new antibiotics.

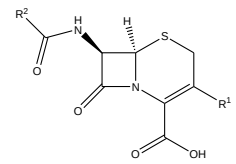
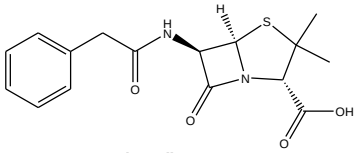
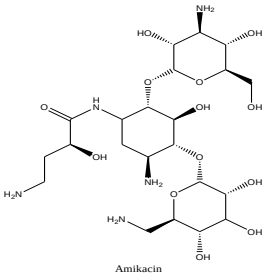
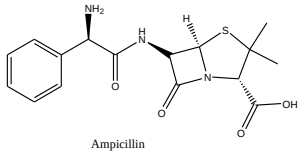
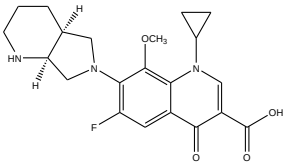
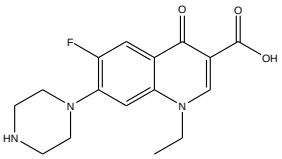
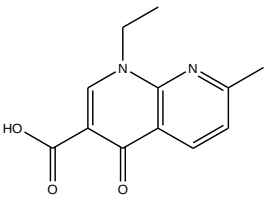
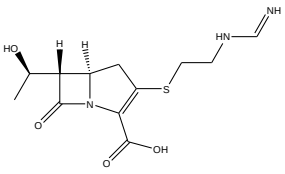
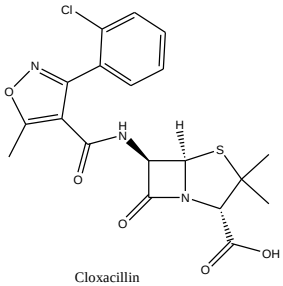
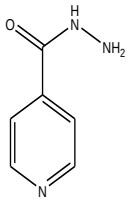
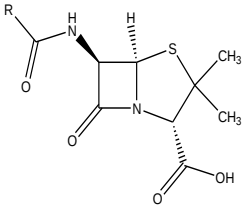
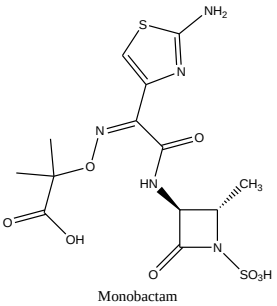
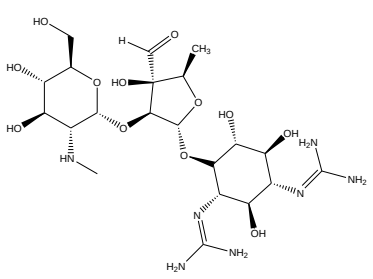
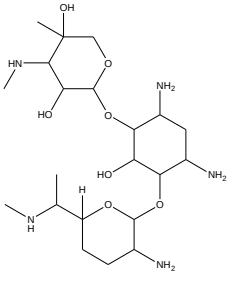
Since then, several different antimicrobials have been formed from both natural as well as synthetic sources [20, 21].

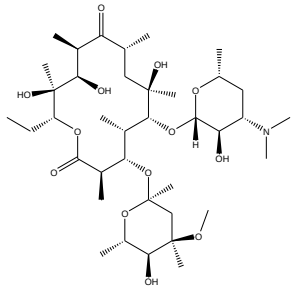
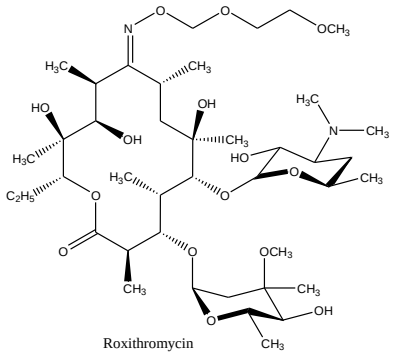
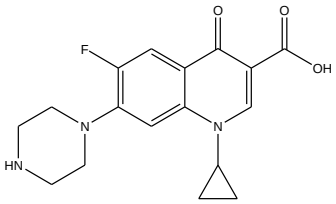
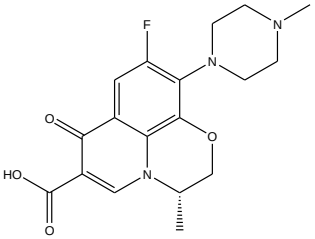
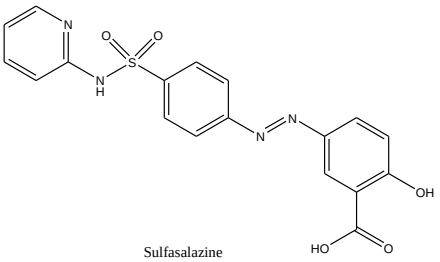
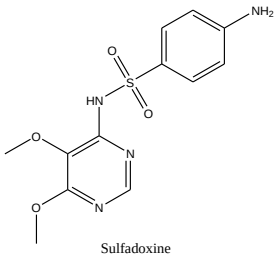
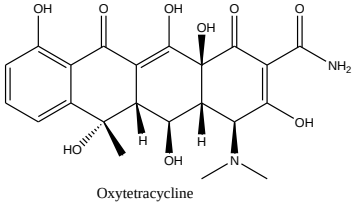
Classification of antimicrobial agents

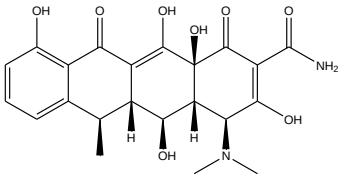
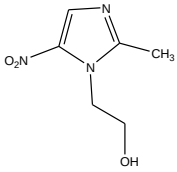
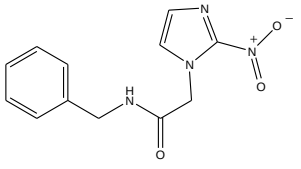
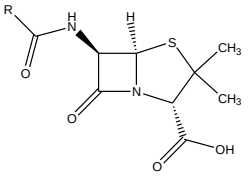
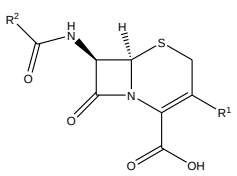
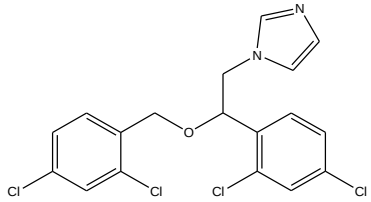
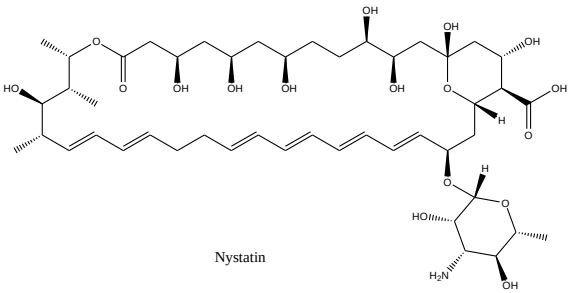
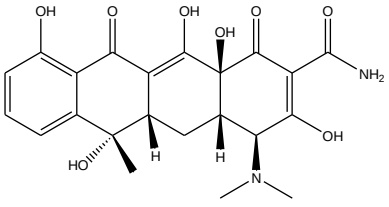
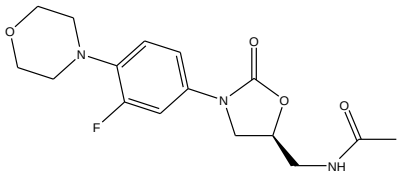
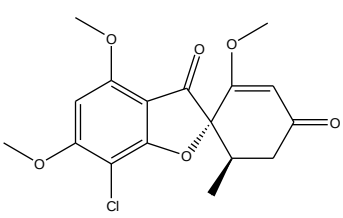
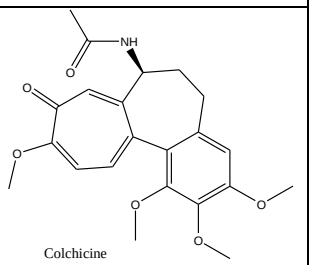
The antibacterial agents have been classified previously in numerous ways: however, to make it more easily understandable, one can classify antibacterial agents into five major groups, i.e., based on type of action, source, spectrum of activity, chemical structure, and mechanism of action [22, 23].

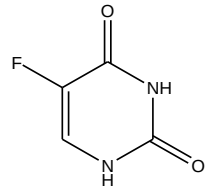
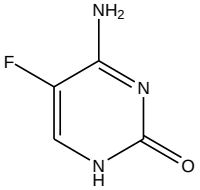
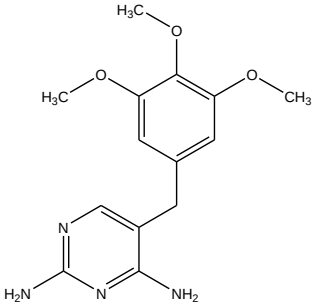
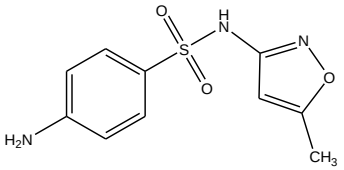
Table 1: Classification of antimicrobial agents along with their examples.

Basis for classification	Class	Example
A. Classification based on type of action	Bacteriostatic	 Chloramphenicol  Spectinomycin
	Bactericidal	 Carbapenem  Quinolone

B. Classification based on source of antibacterial agents	Natural	 Cephalosporin  Benzylpenicillin
	Semi-synthetic	 Amikacin  Ampicillin
	Synthetic	 Moxifloxacin  Norfloxacin
C. Classification based on spectrum of activity	Broad-spectrum	 Nalidixic acid  Imipenem
	Narrow-spectrum	 Cloxacillin  Isoniazid
D. Classification based on chemical structure	β-Lactams	 Penicillin  Monobactam
	Aminoglycoside	 Streptomycin  Gentamicin

	Macrolides	 Erythromycin  Roxithromycin
	Quinolones and fluoroquinolones	 Ciprofloxacin  Levofloxacin
	Sulfonamides	 Sulfasalazine  Sulfadoxine
	Tetracyclines	 Oxytetracycline

		 Doxycycline
	Nitroimidazoles	 Metronidazole  Benznidazole
E. Classification based on mechanism of action	Cell wall synthesis inhibitors	 Penicillin  Cephalosporin
	Inhibitors of membrane function	 Miconazole  Nystatin
	Protein synthesis inhibitors	 Tetracycline  Linezolid
	Interference with microtubules and microfilaments	 Griseofulvin  Colchicine

	Inhibition of nucleic acid synthesis	 Fluorouracil  Flucytosine
	Inhibitors of bacterial folic acid synthesis	 Trimethoprim  Sulfamethoxazole

Mechanism of action of antimicrobial agents

Six microbial targets have been utilized in the growth of antimicrobial drugs i.e., cell wall synthesis, plasma membrane, protein synthesis, ribonucleic acid synthesis, deoxyribonucleic acid (DNA) synthesis, and intermediary metabolism. As resistance to drugs which inhibit these targets is widespread, new antimicrobials and an understanding of their mode of action are vital [24, 25].

1. Inhibitors of cell wall synthesis

The cell wall of a bacterium made up of macromolecular network termed Peptidoglycan. Peptidoglycan is observed only in bacterial cell walls. Penicillin and certain other antibiotics avoid the synthesis of intact peptidoglycan: subsequently, the cell wall is greatly destabilised, and the cell suffers lysis. Penicillin and cephalosporins mainly act by inhibiting transpeptidases, the enzymes which catalyse the final cross-linking step in the peptidoglycan synthesis. As penicillin targets the synthesis process, thus only actively growing cells are affected by these antibiotics and, since human cells do not contain peptidoglycan cell walls, penicillin has very minute toxicity for host cells [26].

2. Inhibitors of membrane function

A small group of antimicrobials target the cell membrane as their mode of action. The polymyxins are natural polypeptide antibiotics that were interacts with lipopolysaccharide in the outer membrane of gram-negative bacteria, resulting in cell death through the eventual disruption of the outer membrane and cytoplasmic membrane. Lipopeptides like daptomycin get inserted into the cytoplasmic membrane of gram-positive bacteria, interrupting the membrane and killing the cell. While, in distinction to polymyxin B and colistin, that target only gram-negative bacteria, daptomycin definitely targets gram-positive bacteria.

Several antifungal drugs, such as amphotericin B, miconazole, and ketoconazole, are active against a wide range of fungal diseases. Such drugs fuse with sterols in the fungal plasma membrane to disrupt the membrane. As bacterial plasma membranes usually lack sterols, these antibiotics are inactive against bacteria [27].

3. Protein synthesis inhibitors

Various drugs prevent protein synthesis in bacteria with no significant interference with protein synthesis in human cells. This selectivity is because of the differences between prokaryotic and eukaryotic ribosomal proteins, RNAs, and associated enzymes. Prokaryotic cells have 70S ribosomes with 50S and 30S subunits, however eukaryotic cells have 80S ribosomes with 60S and 40S subunits. Chloramphenicol, clindamycin, linezolid and erythromycin act on the 50S subunit, while tetracyclines and aminoglycosides have an effect on the 30S subunit. These classes of drugs have distinct modes of action.

Reacting with the 50S portion of the 70S prokaryotic ribosome, chloramphenicol inhibits the formation peptide bonds in the growing polypeptide chain. It inhibits protein chain elongation by blocking peptidyl transferase activity of bacterial ribosome. Most drugs which prevent protein synthesis have broad spectrum activity except erythromycin. As it does not enter the gram-negative cell wall, it impacts mostly gram-positive bacteria.

The Tetracyclines block the attachment of amino-acyl-tRNA to the acceptor site on the mRNA ribosome complex by binding to the 30S ribosome subunit, thus peptide chain fails to grow. Tetracyclines are primarily bacteriostatic with no interference with mammalian ribosomes as they do not penetrate absolutely into intact mammalian cell. Though, at least amounts they are capable of entering the host cell, as it is clear from the point that the intracellular pathogenic rickettsia and chlamydia are susceptible to tetracycline. The selective harm of the drug in this instance is because of a better sensitivity of bacteria at the ribosomal level.

Aminoglycoside antibiotics, such as streptomycin and gentamycin, blocks functioning of initiation complex thus interfering with the initial steps of protein synthesis through changing the shape of the 30S portion of the

prokaryotic ribosome. The interference causes misreading of mRNA. They are active in a wide range of bacteria, but only in those organisms that can transport them over an oxidative phosphorylation mechanism into cells [28, 29].

4. Inhibitors of DNA synthesis

The synthesis of DNA is an essential function of dividing and growing cells. Inhibition of DNA synthesis quickly outcomes in inhibition of cell division. DNA inhibitors block nucleic acid synthesis by binding to the DNA template, usually by preventing both DNA replication and transcription into RNA. Quinolones and fluoroquinolones such as nalidixic acid, ciprofloxacin, moxifloxacin prevent DNA replication by inhibiting DNA gyrase or topoisomerase. DNA gyrase facilitates the unwinding and rewinding of DNA strands which prevents the DNA from becoming tangled or supercoiled. It is an important enzyme for mediating transient double-strand breaks and participate in DNA replication [30]. For the polymerization of deoxynucleotides by DNA polymerase, DNA gyrase opens DNA strands according to each circular template strand of the chromosome. Hydroxyurea, 5-fluorodeoxyuridine, and 5-fluorouracil can inhibit the synthesis of deoxynucleotide precursors that are used in DNA replication. Hydroxyurea inhibits ribonucleotide reductase that catalyses deoxynucleoside diphosphate and this inhibition resulted in inhibition of DNA synthesis, producing cell death in the S phase. Resistance to hydroxyurea can be developed by mutating microorganisms of gene coding ribonucleotide reductase. 5-Fluorodeoxyuridine and 5-fluorouracil can block precursor synthesis with competitive inhibition [31-32].

5. RNA Synthesis inhibitors

Transcription is the process by which involves the synthesis of RNA from a particular segment of DNA by the enzyme RNA polymerase. Transcription takes place in three steps: initiation, elongation, and termination. Drugs that inhibit RNA synthesis can either inhibit the initiation or elongation step. Rifampin is a rifamycin derivative that blocks initiation of transcription by binding to β subunit of RNA polymerase. Rifampin inhibits bacterial DNA transcription into mRNA by inhibiting DNA-dependent RNA polymerase and is used in the treatment of infections triggered by *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and bacteria. Actinomycin inhibit transcription by binding at the initiation complex and prevents the elongation of the RNA chain by RNA polymerase [33, 34].

6. Metabolic antagonists

Antimetabolites are the drugs which antagonize or block the functioning of metabolic pathway. They are structurally identical to the substrates of key enzymes and compare with the metabolites for binding site of these enzyme. Once attached to the enzyme they prevent enzyme activity, further progression of the pathway. An example of competitive inhibition is the connection between the antimetabolite sulfanilamide and *p*-aminobenzoic acid (PABA). PABA is an essential co-factor of many enzymes and required for folic acid synthesis. Folic acid is a precursor of purines and pyrimidines and another important cell component. Sulfa drugs compete with PABA for active site of enzyme involved in folic acid synthesis. As humans do not generate folic acid from PABA, sulfanilamide exhibits selective toxicity, it only affects microorganism that synthesize their own folic acid but does not harm the human host [35].

Other chemotherapeutic agents that act as an antimetabolite are the sulfones and trimethoprim. Trimethoprim inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF) via binding to dihydrofolate reductase. THF is a vital precursor in the thymidine synthesis pathway and intrusion with this pathway prevents bacterial DNA synthesis. The affinity of trimethoprim for bacterial dihydrofolate reductase is several thousand times better than its affinity for human dihydrofolate reductase [36].

Antimicrobial Resistance

Antimicrobial resistance is the capability of a bacterium or other microorganisms to persist and reproduce in the presence of antibiotic quantities that were formerly thought effective against them. Resistant microorganisms are more difficult to treat, requiring higher doses, or alternative medications that may prove more toxic. These strategies may also be more costly. Microorganisms resistant to several antimicrobial agents are named multidrug-resistant (MDR). All classes of microbes can develop resistance such as fungi evolve antifungal resistance, viruses develop antiviral resistance, bacteria evolve antibiotic resistance. A person cannot become resistant to antimicrobials. Resistance is a property of the microbe, not a person or other organism infected by a microbe [37].

Type of Resistance

Bacterial resistance to the antimicrobial is either natural or acquired. A related phenomenon is dependent, which occurs rarely. The development of bacterial resistance is an expression of bacterial evolution, with the survival of fittest.

A. Natural resistance: This type of resistance is genetically determined and depends upon the absence of the metabolic process or pathway in the bacterium, which is affected by the antibiotic. Clinically natural resistance is a rare problem because other drugs are available with antibacterial activity to which the pathogen is susceptible. Natural resistance is normally a characteristic of a whole species, but occasionally

as in the case of penicillin-resistant staphylococci, the resistance is confined to a particular strain within that species.

B. Acquired resistance: Acquired resistance refers to developing in a previously sensitive bacterial species. This kind of resistance poses a serious clinical problem because the one effective drug becomes useless for treating infection caused by the resistant strains of the previously sensitive species.

a. Mutation: Any big populace of antibiotic susceptible bacteria is plausible to contain some mutants that are relatively resistant to the drug. As the drug exerts its action to eliminate most of the sensitive member of the species, some bacterial cells that are congenitally resistant to the drug reproduce freely until they become the majority of the bacterial population.

b. Adaptation: Adaptation presumes that organisms contain a low concentration of drug destroying enzyme or the potential for synthesizing such enzyme and the lethal enzyme concentration.

c. Transformation: Transformation involves incorporation by a sensitive bacterium of free genes from drug resistance cells. It happens infrequently and is of slight clinical significance.

d. Transduction: Transduction indicates the transfer of an R factor bearing plasmid by a bacterial virus (bacteriophage) vector along with its gene. It is an important phenomenon in the transfer of antibiotic resistance among the strain of *S. aureus*, where some phases can carry plasmid that code for penicillinase, while other transfer information for resistance to erythromycin, tetracycline, or chloramphenicol.

e. Conjugation: Conjugation refers to the passage of resistant genes (R factor) from cell to cell by direct contact through a sex pilus or bridge. This is now familiar as an extremely important mechanism for the spread of antibiotic resistance, as DNA that codes resistance to multiple drugs may be so transferred [38, 39].

Mechanisms of Antimicrobial Resistance

Antimicrobials have been conventionally separated into agents that directly kill the bacteria (bactericidal) and that inhibits cell growth (bacteriostatic). Though, in modern therapeutics, these limits have become indistinct. Forms of resistance to antimicrobials have been advanced in several ways and these patterns of resistance have been progressed alongside different modes of action of respective drug molecules (Table-2) [40].

Table 2: Antibiotic targets and patterns of antibiotic resistance.

Antibiotic Targets	Antibiotic Resistance
1. Cell Wall β-lactams Vancomycin 2. DNA/RNA Synthesis Fluoroquinolones Rifamycins 3. Folate Synthesis Trimethoprim Sulfonamides 4. Cell Membrane Daptomycin 5. rotein Synthesis Linezolid Tetracyclines Macrolides Aminoglycosides	1. Efflux Fluoroquinolones Aminoglycosides Tetracyclines β-lactams Macrolides 2. Immunity and Bypass Tetracyclines Trimethoprim Sulfonamides Vancomycin 3. Target Modification Fluoroquinolones Rifamycin Vancomycin Penicillins Macrolides Aminoglycosides 4. Inactivating Enzymes β-lactams Aminoglycosides Macrolides Rifamycins

There are several mechanisms through which microorganisms may develop resistance to antimicrobial agents. The following are fairly well supported by evidence.

1. Limiting uptake of a drug

There is a natural variance in the capability of bacteria to limit the uptake of antimicrobial agents. The structure and functions of the lipopolysaccharide layer in gram-negative bacteria offer a barrier to certain kinds of molecules. This offers those bacteria innate resistance to particular groups of large antimicrobial agents. The mycobacteria possess an outer membrane that has high lipid content, and so hydrophobic drugs such as rifampicin and the fluoroquinolones have effortless access to the cell, but hydrophilic drugs have limited access. Gram-positive bacteria do not have an outer membrane, and restricting drug access is not as predominant. In the case of enterococci, the fact that polar molecules have struggle penetrating the cell wall imparts intrinsic resistance to aminoglycosides [41].

2. Modification of drug targets

There are numerous components in the bacterial cell that may act as a target of antimicrobial agents and some targets may be altered by the bacteria to enable resistance to those drugs. One mechanism of resistance by gram-positive bacteria to the β-lactam drugs used almost exclusively is via alterations in the structure and/or number of

PBPs (penicillin-binding proteins). A change in the quantity (increase in PBPs which cause a decrease in drug binding ability, or decrease in PBPs with normal drug binding) of PBPs influences the amount of drug that can bind to that target. A change in structure may decrease the drug's ability to bind or inhibit drug binding.
Resistance to drugs that affect the ribosomal subunits may happen through the ribosomal mutation (aminoglycosides, oxazolidinones), methylation of ribosomal subunit (aminoglycosides, oxazolidinones, streptogramins), or ribosomal protection (tetracyclines). These processes interfere with the capability of the drug to bind to the ribosome. The intensity of drug inhibition varies significantly among these mechanisms [42].
For drugs that interfere with nucleic acid synthesis (For example, fluoroquinolones), resistance occurs through the modifications in DNA gyrase or topoisomerase IV. Resistance in the drugs that target metabolic pathways, is via mutations in enzymes (dihydropteroate synthase, dihydrofolate reductase) included in the folate biosynthesis pathway and/or overproduction of resistant enzymes (sulfonamides, trimethoprim) [43].

3. Drug inactivation
Bacteria can inactivate drugs through two main ways: by actual degradation of the drug, or via transport of a chemical group to the drug. The β-lactamases are the very largest group of enzymes that can hydrolyses drugs. Another example is tetracycline which can be inactivated by hydroxylation, via the *tetX* gene. Inactivation of a drug by transfer of a chemical group to the drug most commonly occurs through the transfer of acetyl, phosphoryl, and adenyl groups. There are a vast number of transferases that have been known. Acetylation is the reason behind the inactivation of most aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones. Phosphorylation and adenylation are most commonly used primarily against the aminoglycosides [44].

4. Drug efflux
Bacteria contains chromosomally encoded gene especially for efflux pumps, a few of which are expressed constitutively, and others are induced or overexpressed under some environmental stimuli or when an appropriate substrate is extant. The efflux pumps act primarily to clear the bacterial cell of toxic substances. The resistance ability of many of these pumps is affected by what carbon source is available. Efflux pump cause resistance by pumping the drug out of the cell before it reaches its site of action. One notable example is efflux pump of ABC transporter family is found in *Vibrio cholerae* (VcaM), and is capable of transporting fluoroquinolones and tetracycline [45].

Strategies to combat antimicrobial resistance
Antibiotic resistance is a growing public health concern worldwide. When a person is infected with an antibiotic-resistant bacterium, not only is treatment of that patient more difficult, but the antibiotic-resistant bacterium may spread to other people. Drug-resistant infections can lead to poor health outcomes, increased health care costs and limited treatment options for patients. Numerous antimicrobial stewardship programs have been developed over the years to address the growing problem of inappropriate prescribing of antibiotics and to increase our medical arsenal against infectious diseases.

1. New Drugs
While new approaches to avoid drug, resistance are researched and developed continually, antibiotic discovery is not keeping pace with rates of drug resistance. Since 2015, FDA approved new antibiotics that can treat certain resistant bacteria. Health care professional are encouraged to use the new antibiotics appropriately and for some antibiotics, use only in patients who have limited or no other treatment options. Oxazolidinones Considered to be the first truly new class of antibacterial drugs introduced in the past 3 decades. Linezolid-approved for adults use in 2000, approved for paediatric use in 2005. Resistance to older oxazolidinones occurs due to mutations in ribosomal RNA (rRNA) which is overcome by newer oxazolidinones by additional hydrogen bond interactions with 23S rRNA [46].

2. Combinations of two or more antibiotics
One approach to combating MDR infections is combination of two or more antimicrobial drugs during a treatment regimen. Although the possibility of drug-drug interactions is a possible drawback to this approach, and must be taken into consideration during the drug development process, combination therapy is common and critical in many areas of medicine. For example, drug combinations are key to most cancer treatments, bacterial infections, HIV infected patients [47]. Antibiotic combination therapy can be divided into three categories:

1. Inhibition of targets in different pathways, as is the case for the combination of isoniazid, rifampicin, ethambutol, and pyrazinamide for the treatment of *M. tuberculosis* infections.
2. Inhibition of different targets in the same pathway, for example, the combination of sulfamethoxazole and trimethoprim (marketed as co-trimoxazole in the UK and various other trade names worldwide), which inhibits successive steps in the folic acid biosynthetic pathway.
3. Inhibition of the same target in different ways, for example, with the streptogramins.

3. Antibiotic/adjuvant combinations
An alternative to the combination of two or more drugs with known antibiotic activity for the treatment of MDR bacterial infections is to combine an antibiotic with a compound that is not, when administered alone, microbicidal but increases the activity of the antibiotic, for example, by blocking the mechanism of resistance to

the antibiotic. Such an approach is particularly attractive because it may also result in a decrease in the onset of resistance development.

The classical example of an antibiotic-adjuvant pairing is Augmentin, which combines a β-lactam antibiotic (amoxicillin) with a β-lactamase inhibitor (clavulanic acid). The addition of clavulanic acid inhibits β-lactamase activity *in vivo* and allows amoxicillin to inhibit cell wall biosynthesis. Ultimately, this combination has allowed the continued use of amoxicillin to treat infections caused by many pathogens that are resistant to β-lactam antibiotics [48]. Besides this patients and health care professionals alike can play an important role in combating antibiotic resistance. Here are more tips to promote proper use of antibiotics.

- Take the antibiotics as prescribed.
- Do not skip doses.
- Do not save antibiotics.
- Do not take antibiotics prescribed for someone else
- Talk with your health care professional.

Antimicrobials currently in global clinical development

According to the World Health Organization and Pew Charitable Trust, there are currently 40 to 50 antibiotics in clinical development. Many of these will only bring limited benefits compared to existing treatments. And only a few targets Gram-negative bacteria, which are the most dangerous resistant bacteria and can cause severe infections like pneumonia, bloodstream infections or meningitis. The pre-clinical pipeline includes more innovative and diverse candidates-over 250 antimicrobial agents are in early-stage testing. But it will take up to 10 years for the first of these drugs to make in to market. And many promising candidates will fail along the way. For antibiotics in existing classes, on average, only one for every 15 drugs in pre-clinical development will reach patient. For new classes of antibiotics, only one for every 30 candidates [49, 50].

Table 3: List of approved antibiotics and currently in clinical development

Drug Names	Develop-ment phase	Drug class	Target	Potent indications
Nuzyra (omadacycline)	Approved Oct. 2, 2018 (U.S. FDA)	Tetracycline	30S subunit of bacterial ribosome	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections:
Xerava (eravacycline)	Approved Aug. 27, 2018 (U.S. FDA)	Tetracycline	30S subunit of bacterial ribosome	Complicated intra-abdominal infections
Baxdela (delafloxacin)	Approved June 19, 2017 (U.S. FDA)	Fluoroquino-lone	Bacterial type II topoiso-merase	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Vabomere (Meropenem + Vaborbactam)	Approved Aug. 30, 2017 (U.S. FDA)	β-lactam (carbapenem) + β-lactamase inhibitor (cyclic boronate)	PBP: β-lactamase	Complicated urinary tract infections including pyelonephritis, hospital acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia,
Zemdri (plazomicin)	Approved June 26, 2018 (U.S. FDA)	Aminoglycos-ide	30S subunit of bacterial ribosome	Complicated urinary tract infections including acute pyelonephritis, hospital acquired bacterial pneumonia/ventilator associated bacterial pneumonia, complicated intra-abdominal infections
Seysara (Sarecycline)	Approved Oct 1, 2018 (U.S. FDA)	Tetracycline	30S subunit of bacterial ribosome	Inflammatory lesions of non-nodular moderate to severe acne vulgaris
Aemcolo (Rifamycin)	Approved Nov 16, 2018 (U.S. FDA)	Ansamycin	Bacterial DNA dependent RNA polymerase	Traveler's diarrhea, Tuberculosis, leprosy
Pretomanid	Approved Aug 14, 2019 (U.S. FDA)	Nitroimidazo-oxazine	Mycolic acid synthesis	Combination with bad aquiline and linezolid, for treatment of Pulmonary extensively drug resistant or treatment intolerant or non-responsive MDR tuberculosis

Xanleta (Lefamulin)	Approved Aug 19, 2019 (U.S. FDA)	pleuromutilin	50S ribosomal subunit at the peptidyl transferase center	Community acquired bacterial pneumonia, acute bacterial skin and skin-structure infections.
Fetroja (Cefiderocol)	Approved Nov 14, 2019 (US FDA)	Siderophore-β-lactam i.e., cephalosporin	Penicillin Binding Proteins (PBP)	Complicated urinary tract infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, bloodstream infections, and sepsis
Imipenem/ cilastatin + relebactam	Approved Jul 16, 2019 (U.S. FDA)	β-lactam (carbapenem)/ dehydropepti-dase inhibitor + β-lactamase inhibitor (diazabicyclo-octane)	PBP + β-lactamase	Complicated urinary tract infections including pyelonephritis, complicated intra-abdominal infections, and hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia
Lascufloxacin	NDA submitted (Japan PMDA)	Fluoroquinol-one	Bacterial type II topoisomer-ase	Community-acquired bacterial pneumonia
Cefepime + AAI101	Phase 3	β-lactam (cephalosporin) + β-lactamase inhibitor (β-lactam)	PBP + β-lactamase	Complicated urinary tract infections including pyelonephritis, complicated intraabdominal infections, and hospital-acquired bacterial pneumonia / ventilator-associated bacterial pneumonia
Cefilavancin	Phase 3	Glycopeptide-β-lactam (cephalosporin) hybrid	PG chain elongation + PBP	Acute bacterial skin and skin structure infections
Contezolid & contezolid acefosamil	Phase 3	Oxazolidinone	50S subunit of bacterial ribosome	Acute bacterial skin and skin structure infections
Murepavadin	Phase 3	Antimicrobial peptide mimetic	LptD	Hospital-acquired / ventilator-associated bacterial pneumonia, acute bacterial skin and skin structure infection, bloodstream infection, and complicated intraabdominal infection
Ridinilazole	Phase 3	Bis-benzimidazole	Inhibition of cell division and reduction of toxin production	*C. difficile* infections
Iclaprim	Phase 3	2,4-diamino pyrimidine	Dihydro-folate reductase	Acute bacterial skin and skin structure infections and hospital-acquired bacterial pneumonia
Finafloxacin	Phase 2	Fluoroquinol-one	Bacterial type II topoisomer-ase	Acute bacterial skin and skin structure infections, complicated intra-abdominal infections, complicated urinary tract infections including pyelonephritis, and uncomplicated urinary tract infections
Nafithromycin	Phase 2	Macrolide	50S subunit of bacterial ribosome	Community-acquired bacterial pneumonia
Taigexyn	Phase 2	Quinolone	Bacterial type II topoisomer-ase	Community-acquired bacterial pneumonia, diabetic foot infection, and acute bacterial skin and skin structure

				infections
TNP-2092	Phase 2	Rifamycin-quinolone hybrid	RNA polymerase, DNA gyrase, DNA topoisomer-ase IV	Acute bacterial skin and skin structure infections
Gepotidacin	Phase 2	Triazacenapht-hylene	Bacterial type II topoisomer-ase (novel A subunit site)	Complicated urinary tract infections, uncomplicated urinary tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gonorrhea, and community-acquired bacterial pneumonia
BOS-228	Phase 2	β-lactam (monobactam)	PBP	Complicated urinary tract infections and complicated intraabdominal infections
Delpazolid	Phase 1	Oxazolidinone	50S subunit of bacterial ribosome	Gram-positive bacterial infections
KBP-7072	Phase 1	Tetracycline	30S subunit of bacterial ribosome	Community-acquired bacterial pneumonia and hospital-acquired bacterial pneumonia / ventilator-associated bacterial pneumonia
Meropenem + nacubactam	Phase 1	β-lactam (carbapenem) + β-lactamase inhibitor (diazabicyclo-octane)	PBP + β-lactamase/ PBP2	Complicated urinary tract infections, complicated intraabdominal infections, and hospital-acquired bacterial pneumonia / ventilator-associated bacterial pneumonia
SPR206	Phase 1	Polymyxin	Cell membrane	Complicated urinary tract infections and hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia
TP-271	Phase 1	Tetracycline	30S subunit of bacterial ribosome	Community-acquired bacterial pneumonia
CRS3123	Phase 1	Diaryldiamine	Methionyl-tRNA synthetase	*C. difficile* infections

Conclusion

Antimicrobials are vast category of medicines. Forms of resistance to antimicrobials have been advanced in several ways and these patterns of resistance have been progressed alongside different modes of action of respective drug molecules. Thus, there is need to find newer drugs which can combat resistance. We can conclude that this review will help researchers further to design and synthesis new drugs with promising antimicrobial activities.

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