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Antimicrobial agents

Abstract

The word antimicrobial was derived from the Greek words anti (against), micro (little) and bios (life) and refers to all agents that act against microbial organisms. Antimicrobial agent is a general term that is mainly concerned with antibiotics, antibacterials, antifungals, antivirals and anti*protozoans*. Antimicrobial agents are drugs, chemicals or other substances that are capable of acting by two modes either kill (*microbiocidal*) or slow the growth of microbes (*microbiostatic*). Antimicrobial medicines can be classified according to the microorganisms they act primarily against. For example, antibacterials are used against *bacteria* and antifungals are used against *fungi*.

Keywords: antimicrobial, antibacterials, antifungals, *microbiostatic*, *microbiocidal*, *bacteria*, *fungi,* antivirals, antiprotozoans, penicillium

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Introduction

Use of substances with antimicrobial properties is known to have been common practice for at least 2000 years. Ancient Egyptians and ancient Greeks used specific molds and plant extracts to treat infection. More recently, microbiologists such as Louis Pasteur and Jules Francois Joubert observed antagonism for some *bacteria* and discussed the merits of controlling these interactions in medicine. In 1928, Alexander Fleming became the first to discover a natural powerful antimicrobial fungus known as Penicillium Rubens. The substance extracted from the fungus he named Penicillin and in 1942 it was successfully used to treat a Streptococcus infections.[1,2] But nowadays, all over the world treatment of using antimicrobial agents is currently facing its own limitation, due to the development of resistance by the microbes over the period of time. *Bacteria* are involved in many aspects of ecology and health. It seems likely that all species both benefit and suffer from interactions with *bacteria*. For example we use *bacteria* for making yoghurt, curd, cheese and other fermented foods and also large number of *bacteria* lives on the skin and in the digestive tract. The human gut contains more than 1000 *bacterial species* which are beneficial.[3] Gut *bacteria* synthesize vitamins such as Folic Acid, Vitamin K and biotin and they ferment the complex, indigestible carbohydrates. Other useful *bacteria* in the gut flora include Lactobacillus species, which convert milk sugar into Lactic Acid. Also *bacteria* play very important role in the medicine such as vaccine component and in the production of antibiotics, drugs, hormones, and antibodies. On the other hand a pathogenic bacterium causes an enormous level of spoilage, suffering and death through the infection. The bacterial cells differs dramatically in structure and function compared to mammalian cells. The bacterial cytoplasm is separated from the external environment by a cytoplasmic membrane, as shown in Figure 1. The bacterial cell wall is chemically distinct from mammalian cell[4] walls and so is constructed by enzymes that often have no direct counterpart in mammalian cell construction. The following are the functions of the various parts of the bacterial cell.

Cell Wall

Protects the cell and maintains its shape, *bacteria* can be categorized according to their cell wall type:

Gram positive walls are thick with little lipid.

Gram negative walls are much thinner, with two layers. Some *bacteria* have a slimy layer of polysaccharides and polypeptides, allowing them to attach to objects and providing protection.

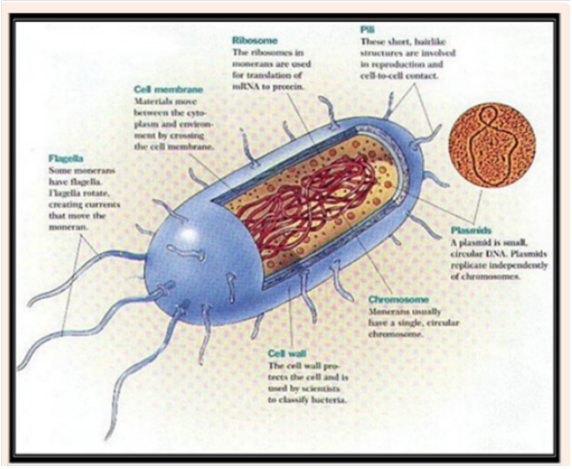

Figure 1 Bacterial Cell Structure.

70s ribosomes

These are for performing protein synthesis. They are smaller than the 80s ribosomes in eukaryotic cells. *Flagellum* another optional feature is a projection that moves around to allow the cell to move. A cell may have multiple flagella arranged around it.

Nuclear material

A folded mass of DNA and RNA, also called the nuclear zone -containing all the genes required for vital functions. Plasmid are additional rings of genetic material that aren't essential to the cell, often contain genes for antibiotic resistance.

Mesosome

An infolding of the membrane that is the site of respiration (like a mitochondrion) - it's shape improves surface area. The existence of the mesosome is disputed and most scientists believe it is a mistake in electron microscope technique.

In addition, *bacteria* possess a crucial structure surrounding the entire cell, the Peptidoglycan (PG), which forms a sacculus around the bacterial cell, is an essential cell wall polymer since interference with its synthesis or structure leads to loss of cell shape and integrity followed by bacterial death.

The peptidoglycan[5] layer as shown in Figure 2 consists of a matrix of polysaccharide chains composed of alternating (italics) *N*-acetylmuramic acid (MurNAc) *N*-acetylglucosamine (GlcNAc) sugar moieties cross-linked through pentapeptide sidechains.

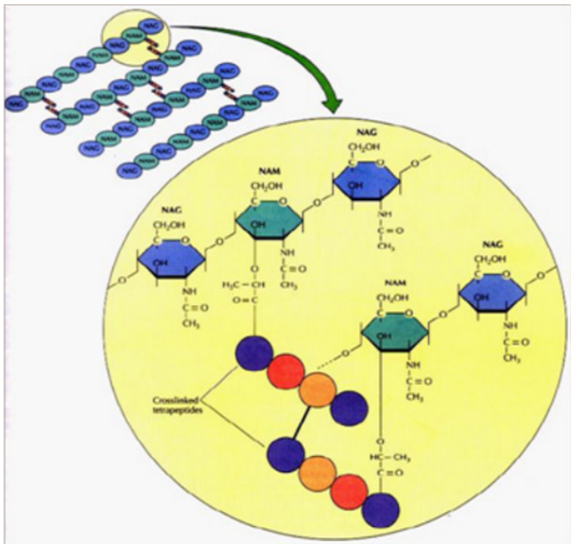

Figure 2 Peptidoglycan layer.

Classification

Hans christian gram: A Danish microbiologist, had developed the Gram stains in order to visualize *bacteria* more easily under microscope. Based upon the staining pattern pathogenic *bacteria* have been classified into two main categories viz., Gram (+) and Gram (–) *bacteria*. Schematic view of cell wall after Gram staining is shown in Figure 3.[6]

***The cell wall of gram* (+):** *Bacteria* although complex enough, is simpler than that of Gram (-) organisms. On the very outside of the cell is set of antigenic determinants which assists to adhere to particular target cell. The next barrier is the cell wall, spongy, gel-forming layer, i.e. peptidoglycan layer external to cytoplasmic membrane and accounts for 50% of the dry weight of the bacterium. Beneath this layer is the lipoidal cytoplasmic cell membrane e.g. *Staphylococci aureus, Streptococci pneumoniae, Bacillus subtilis.*[7]

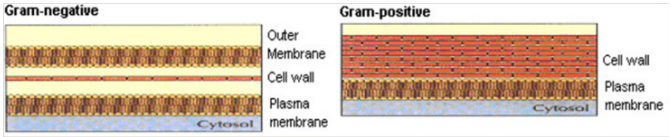

Figure 3 Gram+Ve and Gram-Ve Cell Wall.

***With the gram* (-):** *Bacteria*, the cell wall is more complex and more lipoidal. These cells usually contain an additional, outer membrane, which contains complex lipopolysaccharides that encode antigenic responses. Below this lies, less impressive, layer of peptidoglycan this is followed by a phospholipid rich cytoplasmic membrane. e.g. *Escherichia Coli, Haemophilus influenzae, Pseudomonas aeruginosa.*[7]

Microorganisms are a group of organisms which include living (ex. (b) *Bacteria*, *fungi*, *protozoans*, *algae* etc.) as well as non-living organisms (ex. (v) Virus).

Bacteria: *Bacteria* are unicellular organisms found in nature on all living and non-living things at temperature range from below zero (psychrophiles) to up to 1000C (thermophilic). *Bacteria* are classified according to the shape of cell, on temperature in which they grow, on the basis of group of cells, depending on patogenecity and on staining. On the ground of staining they are further classified as *Gram positive* (*Gram+ve*) and *Gram negative* (*Gram-ve*). *Gram positive bacteria* shows violet color and *Gram negative bacteria* shows pink colour in a procedure called Gram Staining developed by C. Gram. Based on pathogenicity, the classification is pathogenic disease/ infection causing i.e. infectious and non-pathogenic-non infectious. In medicinal chemistry, this classification is important.

Fungi: *Fungi* are universal in distribution. Many are terrestrial and thrive best in soil. Some live in tissues of plants and animals while the remainder is found in aquatic places. Many *fungi* grow on food stuffs such as bread, jams, pickles, fruits, and vegetables. *Fungi* are *saprophytic* and parasitic in nature. *Saprophytes* grow on dead organic matter, while parasites live on living bodies of other animals. Parasitic *fungi* include *Candida albicans* which is the causative agent of Candiditis.

Protozoans: Protozoa are minute and acellular animalcules without tissues and organs having one or more nuclei. They are free living or they remain in association with animals and plants. Some *protozoans* which are parasitic in nature include *Amoeba* causing amoebiasis and *Plasmodium* causing Malaria.

Viruses: Viruses are acellular, micro-organisms which are intracellular obligate parasites. They occupy position in between living and non-living. Viruses are host specific and depend on hosts like plants, animals and *bacteria* for their survival. Viruses are inherent intracellular parasites of living cells. ex. *M. poliomyelitis* causes Poliomyelitis, *HIV* causes AIDS.

Infections by pathogenic microbes: Many microorganisms or microbes are pathogenic to plants, animals and human life causing various diseases resulting in extensive mortality and morbidity. Pathogenic microbes are microorganisms that cause infectious diseases. These organisms involved include pathogenic *bacteria*, causing diseases such as plague, tuberculosis, and anthrax; protozoa, causing diseases such as malaria, sleeping sickness and toxoplasmosis; and also *fungi* causing diseases such as ringworm, candidiatis or histoplasmosis. However, other diseases such as influenza, yellow fever or AIDS are caused by pathogenic viruses, which are not living organisms. Pathogenic *bacteria* contribute to other globally important diseases such as pneumonia caused by *Streptococcus* and *Pseudomonas* and food borne illnesses, which can be caused by *bacteria* such as *Shigella*, *Campylobacter* and *Salmonella*. Pathogenic *bacteria* also cause infections such as tetanus, typhoid fever, diphtheria, syphilis and leprosy.[8] Each parasitic species has a characteristic interaction with their hosts. Microorganisms like *Staphylococcus* or *Streptococcus species* which cause skin infections pneumonia, meningitis and other forms of surface infections. On the other hand, many organisms are part of normal flora of human body that exist on skin, nose, urinary tract, intestine etc. without causing disease. But sometimes these became opportunistic parasite and led to infections.[9] Obligate intracellular parasites such as, Rickettesia and Chlamydia are able to grow and reproduce only within host cells. Some species such as *Pseudomonas aeruginosa, Burkholderia cenocepacia* and *Mycobacterium avium* are parasitic when individual suffering from immune suppression or cystic fibrosis cells.[10] Development of new therapeutic agents to treat or to fight these infection/infectious microorganism is a continuous process in

the clinical medicine. With the advent of antibiotic resistant strains, synthesis of new drugs has become one of the main objectives of researchers across globe.

Antifungal Agents: An antifungal agent is a drug, chemicals or other substances that selectively eliminates fungal *pathogens* from a host with minimal toxicity to the host, which is most commonly found on the skin, hair and nails. The fungus is a eukaryotic organism which is classified as a separate kingdom from plants, animals and *bacteria*. *Fungi* contain unicellular, multinucleate and multicellular forms they are classified on the basis of their reproductive spores and the nature of hyphae. They divide sexually or asexually or by both ways. *Fungi* are almost entirely multicellular with exception of yeast *Saccharomyces cerviseae* which is prominent unicellular fungus. *Fungi* are heterotrophic, deriving their energy from another organism, whether alive or dead. *Fungi* are eukaryotic protista differing from bacteria in many ways, as they posses rigid cell wall containing chitin, mannan, other polysaccharides and their cytoplasmic membrane contains sterol. The major difference between fungal cells and plant cell is that fungal cell walls contain chitin, while plants contain cellulose.[11-13]

The antifungal agents are classified according to their mode of interfering with:

a. Cell wall synthesis,

b. Plasma membrane integrity,

c. Nucleic acid synthesis,

d. Ribosomal function (Figure 4).

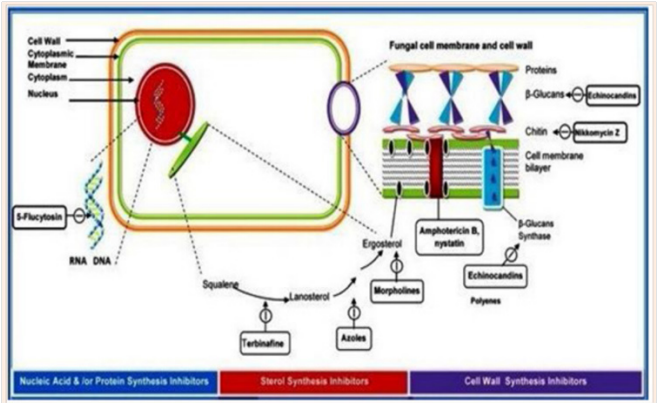

Figure 4 Classification of antifungal agents by their mode of action.

The classification of antifungal drugs are made upon their mode of action, viz,

A. Systemic antifungal drugs:

a. **Polyenes antibiotics:** Amphotericin B.

b. **Azole derivatives:** (Imidazole: Ketoconazole, Miconazole; Triazole: Fluconazole, Itraconazole, Voriconazole, Posaconazole, Ravuconazole).

c. **Echinocandin:** Capsofungin, Anidulafungin, Micafungin.

d. **Antimetabolite:** Flucytosine (5-FC).

e. Nikkomycin.

B. Topical antifungal drugs:

a. **Polyene antibiotics:** Amphotericin B, Nystatin, Hamycin, Natamycin, Rimocidin, Hitachimycin, Filipin.

b. **Azoles:** Clotrimazole, Ketoconazole, Miconazole, Econazole, Butaconazole, Oxiconazole, Sulconazole, Fenticonazole, Isoconazole, Bifonazole, Terconazole.

c. **Others:** Tolnaftate, Undecyclinic acid, Povidone iodine, Triacetin, Gentian violet, Sodium thiosulphate, Cicloporoxolamine, Benzoic acid, Quinidochlor.

C. Systemic antifungal drugs for superficial infections:

a. **Heterocyclic benzofurans:** Corticofunvin, Griseofulvin.

b. **Allylamine:** Terbinafine, Butenafine, Naftifine.

Mycology: The discipline of biology which is devoted to the study of *fungi* is known as mycology. Mycology is concerned with the systematic study of *fungi*, including their genetic and biochemical properties. Mycoses affecting humans can be divided into four groups based on the level of penetration into the body tissues as.[14,15]

a. **Superficial mycoses: C**aused by *fungi* growing only on the outermost surface of the skin or hair. An example of a fungal infection is Tinea Versicolor, a fungus infection that commonly affects the skin of young people, especially the chest, back, upper arms and legs.

b. **Cutaneous mycoses or dermatomycoses:** Caused by *fungi* growing only in the superficial layers of skin, nails, and hair causing infections commonly known as athlete's foot, jock itch and ringworm.

c. **Subcutaneous mycoses**: Caused by *fungi* penetrating below the skin in the subcutaneous, connective, and bone tissue. The most common is sporotrichosis, occurring amongst gardeners and farmers who come in direct contact with soil.

d. **Systemic or deep mycoses:** Are caused by primary pathogenic and opportunistic fungal pathogens. The primary pathogenic *fungi* cause infection in a normal host; whereas, opportunistic pathogens require immune depressant host in order to establish infection (e.g., cancer, surgery and AIDS). The primary pathogens usually gain access to the host via the respiratory tract and include *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. The opportunistic *fungi* invade via the respiratory and alimentary tract, and include *Cryptococcus neoformans, Candida spp., Aspergillus spp., Penicillium marneffei, Zygomycetes, Trichosporon beigelii* and *Fusarium spp*.

Mycology-pathogenic *fungi*: The study of pathogenic *fungi* is referred to as medical mycology. Pathogenic *fungi* cause disease in humans or other organisms. The commonly observed pathogenic *fungi* are enlisted below,

Candida: Candida species are important human pathogens causing opportunist infections in immune compromised hosts (AIDS sufferers, cancer patients and transplant patients). The infections caused by the Candida species are difficult to treat and could be fatal. Candida species alone account to 30-40% death cases caused by the systemic infections. Fungal species of the genus Candida generally live communally on and in the human body. There is increase in development of drug resistance by Candida species to current therapies, motivating researchers to understand their genetics and discover new therapeutic targets.

***Aspergillus*:** The aerosolized *Aspergillus* spores are found almost everywhere around human being and generally does not possess

health issues. But still *Aspergillus* is capable of causing disease in three major ways: by the production of mycotoxins; by the induction of allergenic responses; and lastly by the localized or systemic infections. *Aspergillus flavus* produces mycotoxins, aflatoxin which can act as both toxin and a carcinogen, having ability to contaminate foodstuff such as nuts.

***Cryptococcus*:** The majorities of *Cryptococcus species* are found in the soil and generally do not cause disease in humans. Exception is *Cryptococcus neoformans* which cause disease in immune depressant patients like AIDS, causing a severe form of meningitis and meningo-encephalitis.

Histoplasma: Histoplasma capsulatum can cause histoplasmosis in humans, dogs and cats. The infection is usually due to inhaling the contaminated air and is prevalent.

***Pneumocystis*:** *Pneumocystis jirovecii* can cause a form of pneumonia in people with weakened immune systems, such as the elderly, AIDS patients and premature born children.

***Stachybotrys*:** *Stachybotrys chartarum* can cause respiratory damage and severe headaches, in houses that are persistently damp.

Fungal infection prominent in particular diseases: The association of most commonly occurring *fungi* along with the patient suffering from the particular disease is enlisted below,

a. *Candida species, Aspergillus species, Phycomyces species*: Leucopenia.

b. *Zygomycetes*, *Rhizopus, Mucor, Absidia*: Diabetes.

c. *Candida, Cryptococcus, Histoplasma*: Malignancies and Hodgkin's disease.

d. *Candida, Cryptococcus, Histoplasma*: AIDS.

Clinically significant *fungi* and the site they affect: The pathogenicity and virulence of *fungi* causing infections, in humans is major concern in clinical world which focuses on the major causative agents of disease, particularly Candida, *Cryptococcus* and *Aspergillus* spp. The large diversity of potentially harmful *fungi* existing outside these groups, though rare may still posses potential to be more important than the common clinical fungi. The site affected by the clinically significant *fungi* are enlisted as below,

a. *Malassezia furfur and Exophiala werneckii*: Superficial skin.

b. *Piedraia hortae and Trichosporon beigelii*: Hair.

c. *Microsporum species*: Skin and hair.

d. *Epidermophyton species*: Skin and nails.

e. *Trichophyton species*: Skin, hair and nails.

f. *Sporothrix schenckii, Cladosporium species*: Chromoblastomycosis.

g. *Histoplasma capsulatum, Penicillium species*: Systemic respiratory.

h. *Blastomyces dermatitidis*: Subcutaneous/respiratory.

i. *Cryptococcus neoformans*: Respiratory/CNS.

Antifungal resistance: The development of drug resistance in *fungi* is a broad concept, which describes failure of current antifungal therapy to overcome the fungal infection. The antifungal therapies are designed to eradicate fungal infection by various mechanisms of action, like by disrupting their reproductive capabilities, destroying the cell walls or by modifying the fungal DNA and altering the cell functioning. Antifungal resistance has been traditionally classified as three types

a. Primary (intrinsic),

b. Secondary (acquired),

c. Clinical resistance.

In the last decade, microorganisms are becoming drug resistant at a much faster rate than the rate of discovery of new drugs. The drug resistance of *fungi* is importunately observed in patients with weak immune system suffering from diseases like AIDS and cancer. The researchers thus face a major challenge to develop new, safe and more effective antifungals taking into account the increase in opportunistic infections in the immune compromised host. This can be overcome by the discovery of new drugs acting by novel mechanisms of action.[16-18]

Historic perspective: In 1903, de Beurmann and Gougerot were the first to discuss the use of potassium iodide to treat *sporotrichosis*. Whitfield in 1907 treated superficial fungal infections by using ointment. In the mid 1940s sulfonamides were used to treat *paracoccidioido mycosis* though they had limited efficacy towards fungistatic properties and required longer times for treatment with high relapse rate. This was followed by the commercial use of penicillin in the 1940s. In rapid succession, came the discovery and development of *streptomycin* in 1944 and Benzimidazole the first azole to have notable antifungal activity was discovered in 1944. It was followed by the discoveries of Chloramphenicol in 1947 and chlortetracycline in 1948. In 1948 Hydroxystilbamidine, an antiprotozoal agent having antifungal action was used to treat *blastomycosis*. In 1951 Hazen and Brown, discovered the first polyene antibiotic called nystatin, commonly used topical and oral polyene. In 1952 substituted benzimidazole compounds were found to have antifungal properties. The macrolides were developed in 1952 having bacteriostatic properties. In 1956 Gold et al. reported the antifungal properties of the polyene amphotericin B, which was the first significantly effective systemic antifungal. It became the standard and soon it replaced hydroxy stilbamidine. Amphotericin B enjoyed the prime status of only antifungal agent available to treat systemic mycoses for nearly decade against which newer therapies for systemic mycoses were compared. In 1957 Flucytosine, was developed as an antifungal agent who had failed to provide favorable results for the use as cytostatic agent. The use offlucytosine as a monodrug often developed fungal resistance which led to use in combination with Amphotericin B to overcome the resistance. The first significant oral antifungal agent *Griseofulvin* was developed in 1958, which became available for the treatment of superficial mycoses. Before *Griseofulvin*, the treatment of superficial Dermatophytoses was only by the topical drugs which were not especially effective against Tinea capitis and Onychomycosis. The semi-synthetic Penicillin's, Cephalosporin's and Glycopeptides were developed from 1958 onwards. The development of Chlormidazole as a 5% cream in 1958, was beneficial over wide range of cutaneous Mycoses. In the 1960s, Thiabendazole and Mebendazole were reported to have antifungal and antihelminthic properties. In 1969 the imidazoles, clotrimazole and miconazole were introduced, which was soon followed by econazole in 1974. The allylamines discovered in 1974 are the other classes of antifungal drugs that have a significant impact on antifungal therapy especially for superficial *dermatomycoses*, including Onychomycosis. Ketoconazole was developed in 1977 and since has become the standard among the azoles. In the mid-1980s two broad-spectrum, orally available triazoles, Fluconazole (1982) and Itraconazole (1984) were discovered. Intensive research began between 1990-1999 to

develop new antifungal agents and resulted into introduction of three azoles Voriconazole (2000), Posaconazole (2005)-Schering-Plough, Ravuconazole (2007) and three new echinocandins (Caspofungin (2002) Anidulafungin (2004), Micafungin (2006) for theirclinical use.[19,20]

Conclusion

Antimicrobial agents act against bacterial infection either by killing the microbes or by arresting its growth. They do this by targeting DNA and its associated processes, attacking metabolic processes including protein synthesis, or interfering with cell wall synthesis and function. Antimicrobialdrugs are important class of chemotherapeutic drugs. Compounds are organized according to their target, which helps the reader understand the mechanism of action of these drugs and how resistance can arise.

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Conflicts of Interest

The authors do not have any financial interests.

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None.

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