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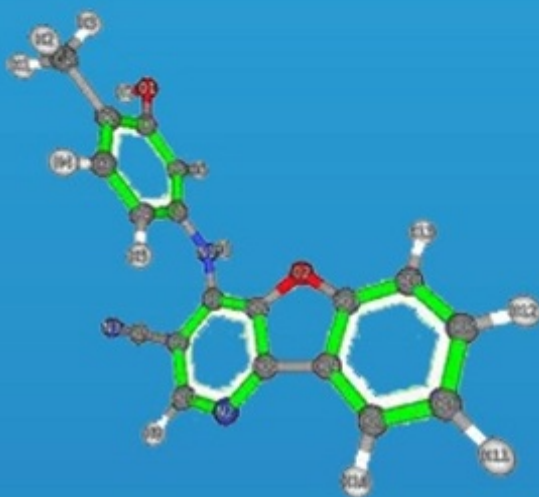
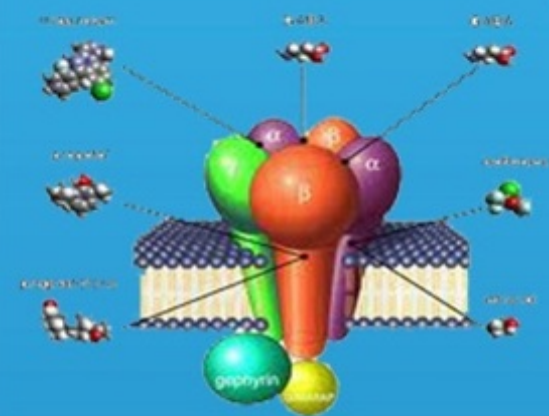
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AN- OVER REVIEW OF ANTIBIOTICS

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Abstract:

Antibiotics are the antimicrobial agent or antibacterial agent, they having both bactericidal or bacteriostatic action against microorganism. first antibiotic in 1877 when he observed that certain bacteria release substances that kill other bacteria unknowingly described by Louis Pasteur. Some of the antibiotics like sulfonamide they active against gram positive or gram negative bacterial also. and penicillin and its like derivative etc. we call broad spectrum antibiotic. and they act by alteration of protein synthesis, antimetabolite activity, inhibition of cell wall synthesis and inhibition of nucleic acid synthesis etc. they produce also resistance because of misuse of antibiotics, anomalous combinations, enhanced transmission of resistance factors, and the reservoir hypothesis.

Key Words:

Antibiotics, Penicillin, Nucleic Acid Synthesis, Resistance Factor

Introduction:

A Bacteria is unicellular prokaryotic micro-organism which does not contain chlorophyll. Bacteria are classified into several varieties dependent on their shape, arrangement like-cocci, Bacilli, Vibrio, Actinomycetes etc.

In gram(+)ve bacteria the cell wall is almost entirely made of peptidoglycan. In gram(-)ve bacteria the cell wall is almost entirely made of peptidoglycon. While in gram (-)ve bacteria It consist of alternating layer of lipoprotein and peptidoglycan⁽¹⁾.

Antibacterial agents :- These are the substances produced by micro-organism, which suppress the growth of or kill other microorganism at very low concentration. A chemical compound derived from or produced by a living organism, which is capable in small concentration of inhibiting the life processes of microorganism⁽²⁾.

Bacteriostatic agent :- These are the agent which inhibit the growth of the microorganism.

Bactericidal agent :- These are the agent which killed the microorganism.

Sulfonamide are the first antimicrobial agents (AMAs) effective against pyogenic bacterial infection. Sulphonamide are the bacteriostatic agent widely use against many gram (+)ve and gram (-)ve bacteria.

Antiseptics and disinfectants are they compounds decrease the bacterial count when applied directly to a surface and have a very low therapeutic index.

Wound infection are manily cause by the gram (+)ve bacteria⁽³⁾.

Antibiotics are mainly produced by Fungi (Penicillin) actinomycetes (streptomycin) bacteria (Polymyxins) Antibiotics differ appreciably in their physical, chemical & pharmacological properties , antibacterial spectrum and mode of action.

Sulfapyridine was the first sulfonamide to be marketed in 1938 The phenomenon of Antibiosis was demonstrated by pasteur in 1877.

Fleming (1929) Found that a diffusible substance was elaborated by penecillium mould which could destroy staphylcoccus on the culture plate⁽⁴⁾.

In the 1940s waksman and his colleagues undertake a systematic search of actinomycetes as source of antibiotics and discovered streptomycin in 1944.

Penicillin was the first antibiotics to be used clinically in 1941⁽¹⁾.

Urgent Need for Antibiotics Reflected in Resistance Data

Focus Technologies of Herndon, Va., maintains a database that includes results from 65 million antimicrobial susceptibility tests—or 2.6% of all isolates tested per year—on cultures ordered by clinicians in various locations throughout the United States. Only 27 bacterial taxa account for 95% of clinically encountered organisms, and *Staphylococcus aureus* accounts for 16% of all clinical isolates. Almost 40% of clinical isolates include those with potential for multiple drug resistance, and 20% of clinical isolates are, in fact, multiply resistant (see table). Meanwhile, the frequency of multidrug-

resistant isolates from blood cultures is also increasing.

Table 1. Prevalence of resistant pathogens

Pathogen	Overall %	% Multiresistant ^a
<i>S. aureus</i>	16.2	8.5
CoNeg staphylococci	9.4	8.6
<i>Enterococcus faecium</i>	0.9	0.6
<i>Enterobacteriaceae</i> ^b	3.4	1.7
<i>Pseudomonas</i> , <i>Acinetobacter</i> , <i>Stenotrophomonas</i> , and <i>Burkholderia</i> spp.	8.9	5.0
Total	38.8	20.4

^aResistant to more than two antibiotics (usually of differing classes) to which a species is typically susceptible.
^bIncludes *K. pneumoniae*, *S. pneumoniae*, *E. cloacae*, and other members of the *Enterobacteriaceae*.

For many of these pathogens, especially gramnegative bacteria, options for therapy are becoming extremely limited. Therefore, the need for better treatments for these infections, particularly in hospitals where resistance is immediately life threatening, is growing more urgent.

Historically, the pharmaceutical industry owes much to the discovery that some microbial secondary metabolites can serve as antibiotics. Identifying these life-saving compounds and subsequently developing related analogs provided benefits to humankind and the pharmaceutical industry. Among the early compounds from the golden age of antibiotics are sulfonamides, penicillin, and streptomycin. Soon after this first wave came the tetracyclines, isoniazid, macrolides, glycopeptides, cephalosporins, nalidixic

acid, and a variety of other molecular classes. Progress was so heady that, by the late 1960s, some experts considered infectious diseases nearly conquered. Since then, however, new cycles of discovery, development, and marketing of antibacterial compounds continue to occur—albeit irregularly. For example, the cephalosporins became the rage during the 1970s, with multiple second- and third-generation compounds entering the marketplace by the mid-1980s.

Then, despite an emerging epidemic of multiply-resistant *S. aureus* infections in U.S. hospitals and similarly resistant *Streptococcus pneumoniae* infections in U.S. communities, the pharmaceutical industry began pulling back on their discovery efforts in antibacterial drugs.

History:

- Louis Pasteur unknowingly described the first antibiotic in 1877 when he observed that certain bacteria release substances that kill other bacteria.
- In 1909, Paul Ehrlich discovered arsphenamine (Salvarsan), an arsenic compound that kills *Treponema palladium*, the bacterium causing the sexually transmitted disease, syphilis.

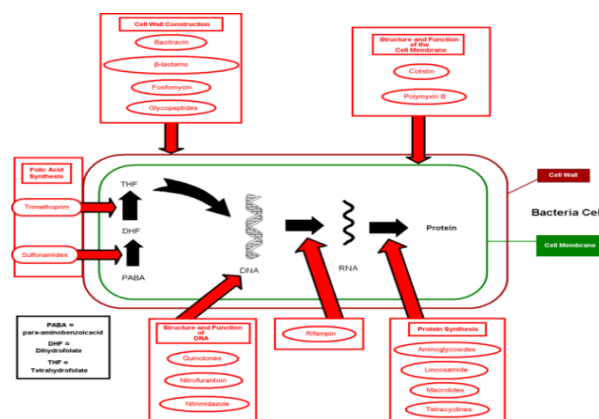
- In 1928 Alexander Fleming discovered that a mold inhibited the growth of staphylococcal bacteria and named the substance it produced “penicillin” (possibly Pasteur’s unknown substance).
- It was not until 1940 that Howard Florey and Ernst Chain isolated the active ingredient in Fleming’s mold.
- With wide-scale production of penicillin, the use of antibiotics increased, leading to an average eight-year increase in human life span between 1944 and 1972. Unfortunately, many bacterial species continued to survive penicillin treatment due to their resistance mechanisms.

Mechanism of action

Five Basic Mechanisms of Antibiotic Action against Bacterial Cells²⁻¹⁰:

- Inhibition of Cell Wall Synthesis (most common mechanism)
- Inhibition of Protein Synthesis (Translation) (second largest class)
- Alteration of Cell Membranes
- Inhibition of Nucleic Acid Synthesis
- Antimetabolite Activity

[Fig: site of action of antibiotics]



Inhibition of Cell Wall Synthesis

Beta-Lactams → Inhibition of peptidoglycan synthesis (bactericidal)

Resistance →

- (1) fails to cross membrane (gram negatives)
- (2) fails to bind to altered PBP's
- (3) hydrolysis by beta-lactamases

Vancomycin → Disrupts peptidoglycan cross-linkage

Resistance →

- (1) fails to cross gram negative outer membrane (too large)
- (2) some intrinsically resistant (pentapeptide terminus)

Bacitracin → Disrupts movement of peptidoglycan precursors (topical use)

Resistance → fails to penetrate into cell

Antimycobacterial agents → Disrupt mycolic acid or arabinoglycan synthesis (bactericidal)

Resistance →

(1) reduced uptake

(2) alteration of target sites

Inhibition of Protein Synthesis (Translation)

30S Ribosome site

Aminoglycosides → Irreversibly bind 30S ribosomal proteins (bactericidal)

Resistance →

(1) mutation of ribosomal binding site

(2) decreased uptake

(3) enzymatic modification of antibiotic

Tetracyclines → Block tRNA binding to 30S ribosome-mRNA complex (b-static)

Resistance →

(1) decreased penetration

(2) active efflux of antibiotic out of cell

(3) protection of 30S ribosome

50S Ribosome site

Chloramphenicol → Binds peptidyl transferase component of 50S ribosome, blocking peptide elongation (bacteriostatic)

Resistance →

(1) plasmid-encoded chloramphenicol transferase

(2) altered outer membrane (chromosomal mutations)

Macrolides → Reversibly bind 50S ribosome, block peptide elongation (b-static)

Resistance →

(1) methylation of 23S ribosomal RNA subunit

(2) enzymatic cleavage (erythromycin esterase)

(3) active efflux

Clindamycin → Binds 50S ribosome, blocks peptide elongation; Inhibits peptidyl transferase by interfering with binding of amino acid-acyl-tRNA complex

Resistance → methylation of 23S ribosomal RNA subunit¹³

Alteration of Cell Membranes

Polymyxins (topical) → Cationic detergent-like activity (topical use)

Resistance → inability to penetrate outer membrane

Bacitracin (topical) → Disrupt cytoplasmic membranes

Resistance → inability to penetrate outer membrane

Inhibition of Nucleic Acid Synthesis

DNA Effects

Quinolones → Inhibit DNA gyrase or topoisomerases required for supercoiling of DNA; bind to alpha subunit

Resistance →

(1) alteration of alpha subunit of DNA gyrase (chromosomal)

(2) decreased uptake by alteration of porins (chromosomal)

Metronidazole → Metabolic cytotoxic byproducts disrupt DNA

Resistance →

(1) decreased uptake

(2) elimination of toxic compounds before they interact¹³

RNA Effects (Transcription)

Rifampin → Binds to DNA-dependent RNA polymerase inhibiting initiation & Rifabutin of RNA synthesis

Resistance →

(1) altered of beta subunit of RNA polymerase (chromosomal)

(2) intrinsic resistance in gram negatives (decreased uptake)

Bacitracin (topical) → Inhibits RNA transcription

Resistance → inability to penetrate outer membrane¹⁵

Antimetabolite Activity

Sulfonamides & Dapsone → Compete with *p*-aminobenzoic acid (PABA) preventing synthesis of folic acid

Resistance → permeability barriers (*e.g.*, *Pseudomonas*)

Trimethoprim → Inhibit dihydrofolate reductase preventing synthesis of folic acid

Resistance →

(1) decreased affinity of dihydrofolate reductase

(2) intrinsic resistance if use exogenous thymidine

Trimethoprim-Sulfamethoxazole
synergism¹⁵

Causes of antibiotic resistance

For many years it was believed that antibiotic resistance was only caused by the failure of prescribed drug regimens. It is now accepted that human errors also contribute to the development of antibiotic-resistant bacteria.

- 1 **Misuse of antibiotics** occurs in medicine, agriculture, and household products. Common examples include erroneous antibiotic prescriptions for nonbacterial infections and the addition of antibiotics to livestock feed and cleaning agents, which have helped create a reservoir of antibiotic-resistant bacteria.
- 2 **Anomalous combinations** have perpetuated drug-resistant microbes. For example, one study on Rhesus monkeys reports that mercury in dental amalgam fillings fostered a 61% increase in antibiotic-resistant bacteria. Upon removal of the amalgam fillings,

drug-resistant bacteria dropped 58%. In another example, *S. aureus* was shown to acquire vancomycin resistance genes through cohabitation with the vancomycin-resistant bacteria, *Enterococcus faecalis*, in the wound of a hospitalized patient. Through mechanisms of genetic exchange between bacterial species, the mere coexistence of these two particular bacteria helped to bring about drug resistance in *S. aureus*

- 3 **Enhanced transmission of resistance factors**, or the increased efficiency with which resistance genes are exchanged, is another important way that antibiotic resistance is perpetuated. Factors that contribute to enhanced transmission include the survival of patients with chronic disease, an increased number of immunosuppressed individuals, substandard hospital hygiene, more international travel, and budget cuts in health care administration.
- 4 **The reservoir hypothesis** suggests that antibiotic-resistant bacteria have evolved because of the selective pressures applied by antibiotic drugs; moreover, the hypothesis states that each

antibiotic has a threshold level that is required to induce and maintain antibiotic resistance. After a decline in the populations of susceptible bacteria from antibiotic treatment, naturally resistant bacteria begin to thrive, creating a reservoir of antibiotic-resistant bacteria¹⁶.

Conclusion:

Antibacterial agents are the challenging drugs for the different type of disease in the world . Now a day various type of Antibiotics are developed to decrease the side effect and increase the therapeutic effect of low concentration of the drug.

Lipophilic drugs are use for longer effect and they penetrate the blood brain barrier. Antibiotics are the harmful drugs at over or high doses they should be taken under supervision they have faster action.

Antibiotics have the interaction to the another drugs and produces the dangerous side effects antibacterial agent are taken in therapeutics range

Now a day few bacteria are resistant from the Antibiotics so in research institute the new drugs are create for the resistant bacteria.

For the effective treatment combined therapy are widely use they have high therapeutic index.

Antibiotics are uses condition of patient the drugs the drugs can be changes according to the patients.

Antibiotic resistance is a continually evolving and dangerous problem that requires immediate attention as well as future planning to impede a global health crisis. Is it not time too seriously consider other methods for which current antibiotic therapies are ineffective and therefore prolong sickness, treatment, an even sometimes result in mortality? Many feel these new alternatives, such as those discussed in this article, are not mainstream. I would agree, but since the efficacy of current therapies is waning and conventional antibiotics are a temporary fix to bacterial multi-drug resistance, society must look elsewhere. If the reservoir hypothesis is true, as most scientists agree, then curbing drug usage to prevent resistant bacteria should be key. Although this viewpoint is highly debated, it holds some merit. Bacteria thrive on mutations and removal of selective pressures should slow mutational rates. Indeed, the alternative methods mentioned have begun to target the pathogen and not the organism.

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