Antimicrobial chemotherapy

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Antimicrobial chemotherapy

Drugs have been used for treatment of infectious diseases since the 17th. Century, e.g. quinine for malaria, emetine for amoebiasis. The chemotherapy as a science began in the first decade of the 2th. Century with the understanding of principals of selective toxicity, specific chemical relationships between microbes and drug, development of drug resistance & the role of combined therapy.

The current era of antimicrobial therapy began in 1935 with the discovery of sulfonamides. in 1940 was found that penicillin which was discovered in 1929 has an effective therapeutic activity. During the next v25 years researches on chemotherapy was concentrated on substances of microbial origin called antibiotics (penicillin, streptomycin, tetracycline, chloramphenicol & many other agents. Synthetic modification of antibiotics has been prominent in the development of new antimicrobial agents.

Mechanisms of action of antimicrobial drugs:

Antimicrobial drugs act in one of several ways.

Selective toxicity: it means that the drug is harmful to a pathogen without being harmful to the host. Selective toxicity may be a function of a specific receptor

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Required for drug attachment, or it may depend on the inhibition of biochemical events essential for pathogen. The mechanism of action of antimicrobial drugs one of the followings:

1. Inhibition of cell wall synthesis.
2. Inhibition of cell membrane functions.
3. Inhibition of protein synthesis (transcription & translation).
4. Inhibition of nucleic acid synthesis.

Inhibition of cell wall synthesis:

The cell wall maintain the shape & the size of the bacteria which has a high internal osmotic pressure. The cell wall contains a chemically complex polymers (peptidoglycan).

All B-lactam drugs are selective inhibitors of bacterial cell wall synthesis & therefore active against growing bacteria. The initial step in the drug action consist of binding of the drug to cell receptors (Penicillin binding proteins) & inhibit the transpeptidation & peptidoglycan synthesis is blocked. The next step involves removal or inactivation of an inhibitor of autolytic enzymes in the cell wall.

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The inhibition of transpeptidation enzymes by penicillins & cephalosporines may be structural similarity of these drugs to Acyl-D-Alanyl D- alanine. The remarkable loss of toxicity of B-lactam drugs to mammalian cells may be attributed to the lack of peptidoglycan layer.

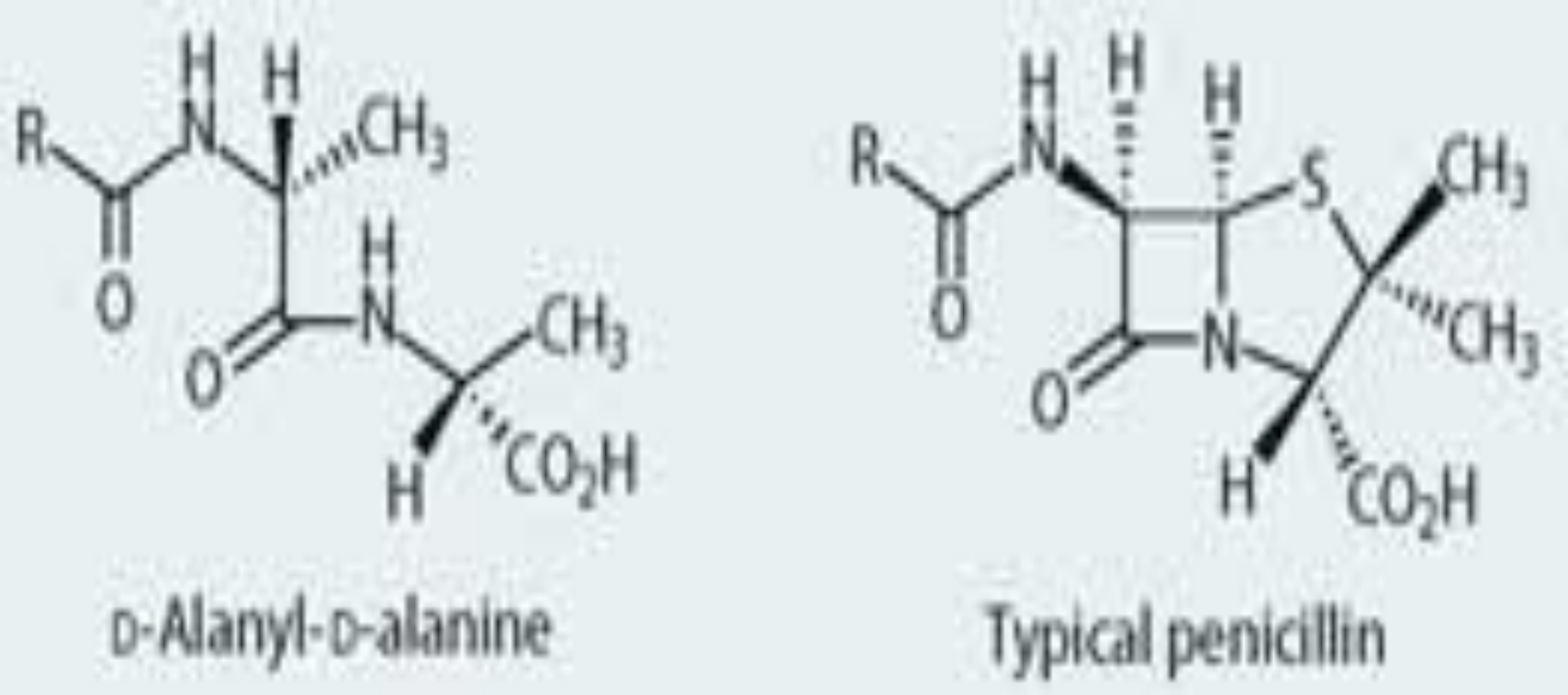
Resistance to penicillins may be determined by the production of penicillin-destroying enzymes B-lactamasees which break the B-lactam ring of penicillin & cephalosporines & delete their antimicrobial activity. B-lactamases are found in many G + & G - bacteria. B-lactamases are either plasmid mediated (*S. aureus*) or chromosomal mediated (many G- bacteria).

There is one group of B-lactamases that is found in many G- bacilli (*K. pneumoniae* & *E. coli*) these are called Extended-spectrum B-lactamases.

2. Inhibition of cell membrane function:

Detergents which contain lipophilic & hydrophilic groups, disrupt cytoplasmic membrane & kill the cell. Polymyxins, consist of detergent-like cyclic peptide that selectively damage membrane.

Similarity between D-alanine & penicillin rings



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A third class of membrane active agents are the ionohpores compounds that permit rapid diffusion of specific action's through the membrane. e.g. vancomycin specifically mediate passage of potassium ions. Daptomycin is a lipopeptide antibiotic that is rapidly bacteriocidal by binding to the cell membrane in calcium-dependent manner.

Other examples of agents acting by inhibiting cell membrane functions are amphotericin B, colisitin, & imidazole.

3. Inhibition of protein synthesis:

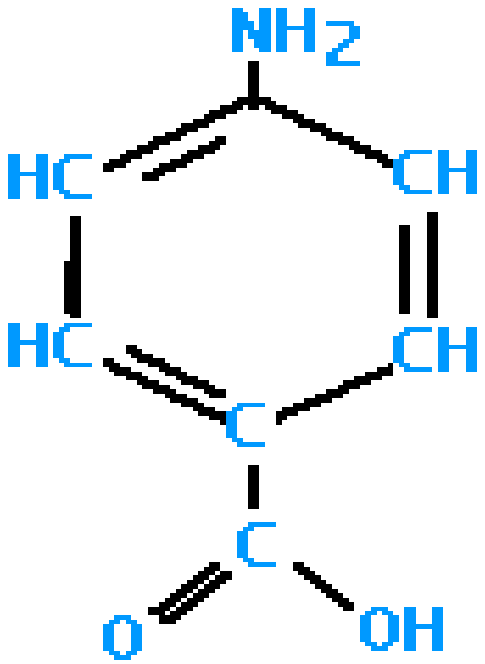
It is established that erythromycin, lincomycin, tetracycline, aminoglycocides and chloramphenicol can inhibit protein synthesis in bacteria.

4. Inhibition of nucleic acid synthesis:

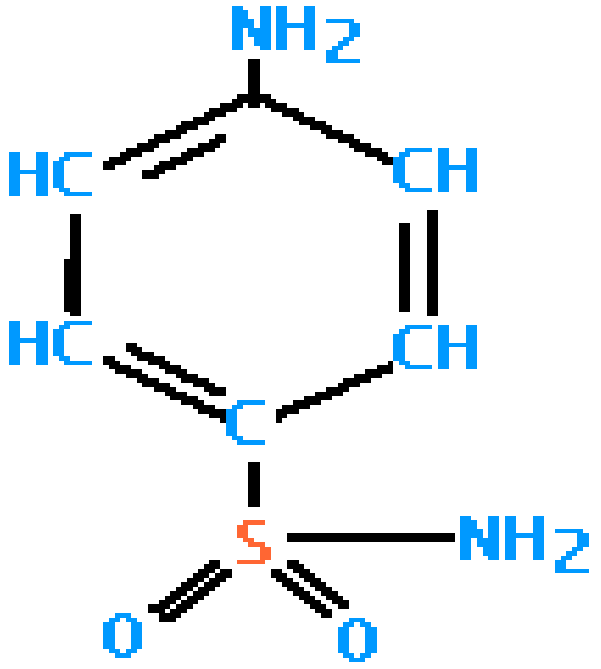
Examples of drugs acting by inhibition of DNA synthesis are quinolones, pyrimethrine, rifampicin, sulfonamides, trimethoprim. Rifadin inhibit bacterial growth by binding to DNA-dependent RNA polymerase enzyme of bacteria. All quinolones & fluroquinolones inhibit bacterial DNA synthesis by blocking DNA gyrase.

P-aminobenzoic acid is involved in the synthesis of folic acid, an important precursor to the synthesis ofDNA. Sulfonamides are structural analogue of PABA & inhibit its synthesis. Trimethoprim inhibits dihydrofolic acid reductase a stage in the synthesis of purines & then DNA.

PABA & sulfonamide structure



Para-aminobenzoic Acid (PABA)



Sulfanilamide

What is antimicrobial resistance?

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.

Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.

The use and misuse of antimicrobial drugs accelerates the emergence of drug-resistant strains. Poor infection control practices, inadequate sanitary conditions and inappropriate food-handling encourages the further spread of AMR.

There are high proportions of antibiotic resistance (ABR) in bacteria that cause common infections e.g. urinary tract infections, pneumonia, bloodstream infections in all regions of the world.

How can we defeat antimicrobial resistance

A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria.

Treatment failures due to resistance to treatments have now been reported from all countries. Some are becoming untreatable as no vaccines or new drugs are in development.

Patients with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more healthcare resources than patients infected with the same bacteria that are not resistant.

Why is antimicrobial resistance a global concern?

New resistance mechanisms emerge and spread globally threatening our ability to treat

How can we defeat antimicrobial resistance

common infectious diseases, resulting in death and disability of individuals who until recently could continue a normal course of life. Without effective anti-infective treatment, many standard medical treatments will fail or turn into very high risk procedures.

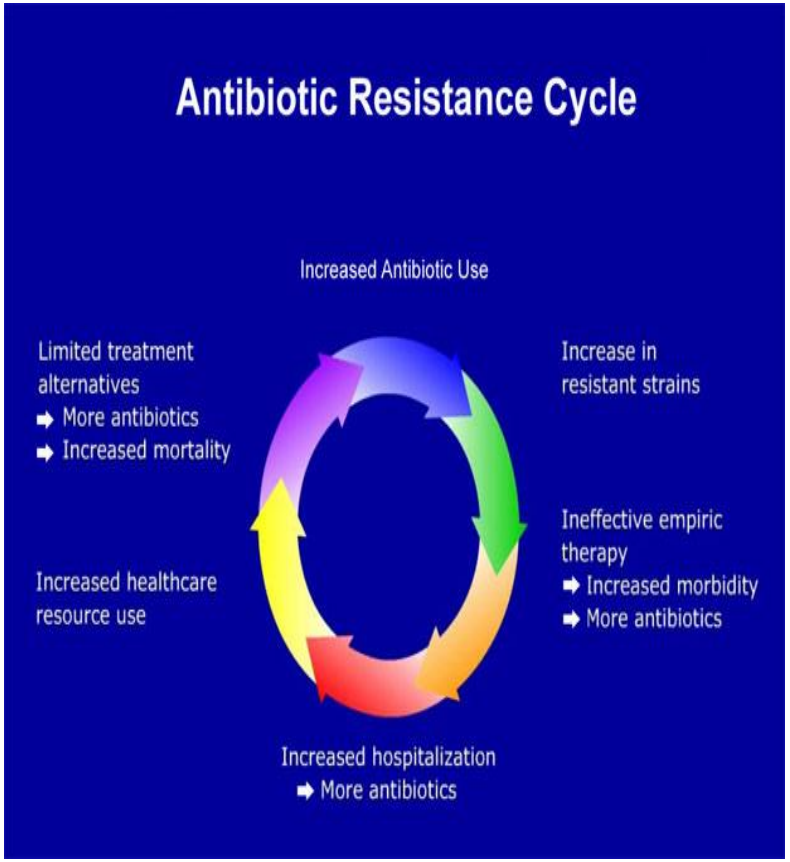
1. AMR kills

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death. For example, people with MRSA , is a common source of severe infections in the community and in hospitals, are estimated to be 64% more likely to die than people with a non-resistant form of the infection.

2. AMR hampers the control of infectious diseases

AMR reduces the effectiveness of treatment; thus patients remain infectious for a longer time, increasing the risk of spreading resistant microorganisms to others.

How can we defeat antimicrobial resistance



3. AMR increases the costs of health care

When infections become resistant to first-line drugs, more expensive therapies must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies.

4. AMR jeopardizes health care gains to society

The achievements of modern medicine are put at risk by AMR. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised.

5. AMR has the potential to threaten health security, and damage trade and economies

The growth of global trade and travel allows resistant microorganisms to be spread rapidly to distant countries and continents through humans and food.

How can we defeat antimicrobial resistance

Estimates show that AMR may give rise to losses in Gross Domestic Product of more than 1% .

How can we defeat antimicrobial resistance

AMR is a complex problem driven by many interconnected factors. Coordinated action is required to minimize emergence and spread of AMR.

1. Patients: can help tackle resistance by:

1. using antibiotics only when they are prescribed by a certified health professional;

2. completing the full treatment course, even if they feel better;

3. never sharing antibiotics with others or using leftover prescriptions.

2. Health workers and pharmacists:

1. enhancing infection prevention and control;

2. prescribing and dispensing antibiotics only when they are truly needed;

How can we defeat antimicrobial resistance

3. prescribing and dispensing the right antibiotic(Antibiotic susceptibility test) to treat the illness.

3. Policymakers (Political will):

1. strengthening resistance tracking and laboratory capacity;

2. strengthening infection control and prevention;

3. regulating and promoting appropriate use of medicines;

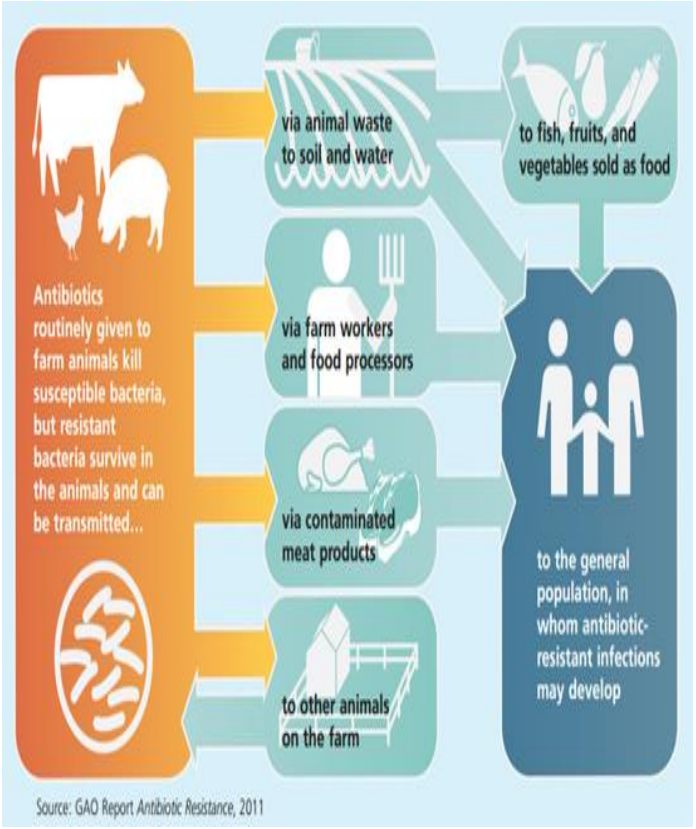
4. promoting cooperation and information sharing among all stakeholders.

5. Regulation & legislation:

Some institutions, such as hospitals, have '**Antibiotic Policy**' guidelines and antibiotic review committees, to ensure that antibiotic use is rational and does not compound the antibiotic resistance problem.

6. Governmental oversight of antibiotics varies widely from country to country. In some countries, antibiotics can be purchased 'over-the-counter,' that is, without a prescription from a doctor. Other countries require a doctor's prescription before a patient is allowed to purchase an antibiotic.

How can we defeat antimicrobial resistance



Antibiotics have also been sold over the Internet, with little governmental oversight that reaches across national borders.

7. Furthermore, food animals are often given long-term, low-levels of antibiotics to promote growth. This antibiotic use represents a large fraction of the total antibiotic use in the industrialized world. A few governments restrict which antibiotics can be used for food animals, with the goal of preserving the most powerful antibiotics for treating human disease.

4. Policymakers, scientists and industry:

1. fostering innovation and research and development of new vaccines, diagnostics, infection treatment options and other tools.

5. Community:

1. Use good hygiene! By washing your hands often and thoroughly with soap and water, you are helping to prevent disease - and therefore the need for antibiotics. Additionally, cooking food thoroughly and handling food hygienically will help to prevent food-borne illnesses. Also, you should take antibiotics only when necessary.

2. Health education:

How can we defeat antimicrobial resistance

6. international action on the antibiotic resistance issue:

The World Health Organization (WHO) has become quite concerned about the rising levels of resistant bacteria in all areas of the world. Experts agree that a global system for tracking antibiotic resistance is needed. It would serve as an indicator for recognizing "hot-spots" of resistance and measuring trends that can tell us if our educational programs or other solutions are having positive effects.

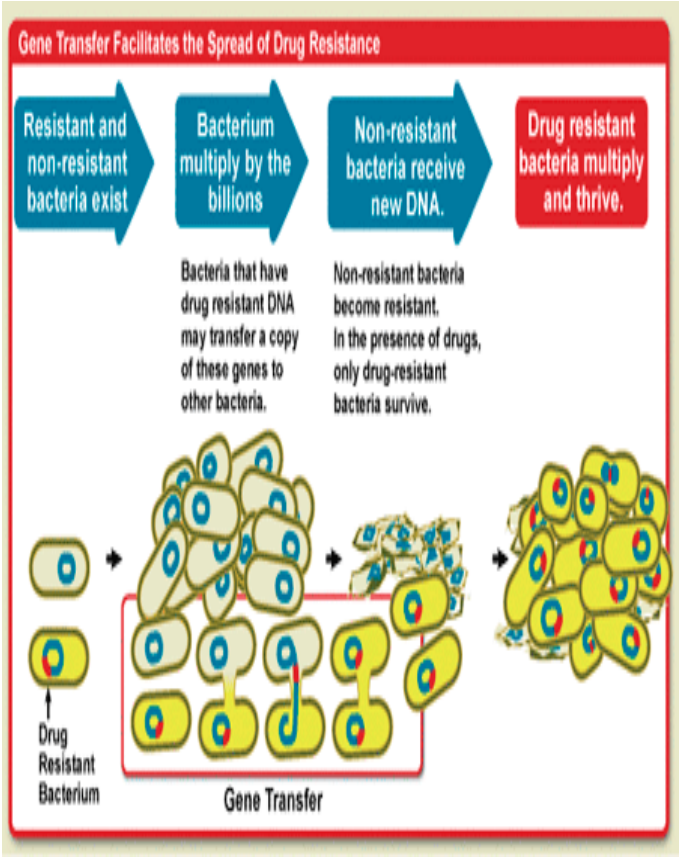
Can new antibiotics be developed:

The process of producing a new antibiotic, however, is long and expensive, Nonetheless, scientists are still searching for new antibiotics.

One approach taken by scientists to combat antibiotic resistance is to strengthen the action of existing antibiotics by modifying them so the bacterial enzymes that cause resistance cannot attack them.

An alternative approach to the antibiotic resistance problem is to interfere with the mechanisms that promote resistance, rather than to attempt to kill the bacteria.

How can we defeat antimicrobial resistance



Resistance to antimicrobial agents

Resistance to antimicrobial agents:

The ability of bacteria to become resistant to antibacterial agents is an important factor in their control. Bacterial genes for resistance are either chromosomal or plasmid bearing.

There are many different mechanisms by which microorganisms develop resistance to antimicrobial drugs:

1. Microorganisms produce enzymes that destroy the active drug. e.g. *S. aureus* resist penicillin by producing B-lactamase.
2. Microorganisms change their permeability to drug. e.g. tetracycline accumulate in susceptible bacteria but not in resistant bacteria.
3. Microorganisms develop an altered structural target for the drug. e.g. erythromycin-resistant microorganisms have an altered receptor.
4. Microorganisms develop an altered metabolic pathway that bypass the reaction inhibited by the drug. e.g. sulfonamide.
5. Microorganisms develop an altered enzyme that can still perform its metabolic function but it is much less affected by the drug. e.g. trimethoprim.

Origin of drug resistance

Origin of drug resistance:

1. Non-genetic origin of drug resistance:

a. Microorganisms that are metabolically inactive (non multiplying). e.g. *M. tuberculosis*, Brucellae.

b. Microorganisms may loss the specific target structure for a drug for several generations and thus be resistant. e.g. Penicillin-susceptible bacteria may change to cell-wall deficient L form during penicillin administration.

c. Microorganisms may infect the host at sites where antimicrobials are excluded or not active. e.g. Gentamicin is not effective in treating salmonella enteric fever because the salmonella are intracellular & the gentamicin do not enter the cell.

2. Genetic origin of drug resistance:

Most drug resistant microbes emerge as a result of genetic changes.

a. Chromosomal resistance:

This develop as a result of spontaneous mutation in the locus that control susceptibility to a given antimicrobial drug. E.g. chromosomal resistant mutants to rifampicin occur with high frequency (about 10^{-7} to 10^{-5}).

b. Extrachromosomal resistance:

Bacteria often contain extrachromosomal genetic elements called plasmids. Some plasmid carry genes for resistance to one or more than one antimicrobial drugs.