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Antimicrobial Drug Resistance (AMR)

This lecture will shed light about the following questions:

-What is antimicrobial resistance?

-How do bacteria become resistant????

-What are the mechanisms of antimicrobial drug resistance?

-What accelerates the emergence and spread of antimicrobial resistance?

*** (Be Linked to Lec-1 also)**

Antibiotic Resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic.

--Penicillin G: first introduced, only 3% of bacteria resistant. Now, over 90% are resistant.

- Resistance of pathogens to antibacterial and other chemotherapeutic agent may be the result of a natural resistance or may be acquired. In either case, it occurs through mutation, adaptation, or gene transfer.
- As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others.

Key Facts

- Antimicrobial resistance (AMR) threatens the effective treatment of infections caused by bacteria, parasites, viruses and fungi.
- Without effective antibiotics, the success of major surgery and cancer chemotherapy would be compromised.
- The cost of health care for patients with resistant infections is high.

- **Reasons for bacterial resistance:**

1. Uncontrolled and improper use of antibiotics.
2. Poor hand hygiene.
3. Failure of infection control measures.
4. Antibiotics in livestock, other animals and agriculture.

Antimicrobial Drug Resistance Mechanisms

1- Inactivation of the antibiotic…..bacteria produce enzyme that inactivate the drug….. e.g. **β-lactamase, Chloramphenicol Acetyl Transferase.**

2- Alteration of metabolic pathway….e.g. **Sulfonamides.**

3- Mutation in the target site…..bacteria synthesized modified targets against which the drug has no effect….e.g. **Penicillin binding proteins (penicillin's).**

4-Reduced drug accumulation: …..by

1. Decreasing drug permeability…e.g.**(TMP / SMX)**
2. Increasing active efflux… (Pumping out) of the drugs across the cell surface…e.g. **quinolone.**

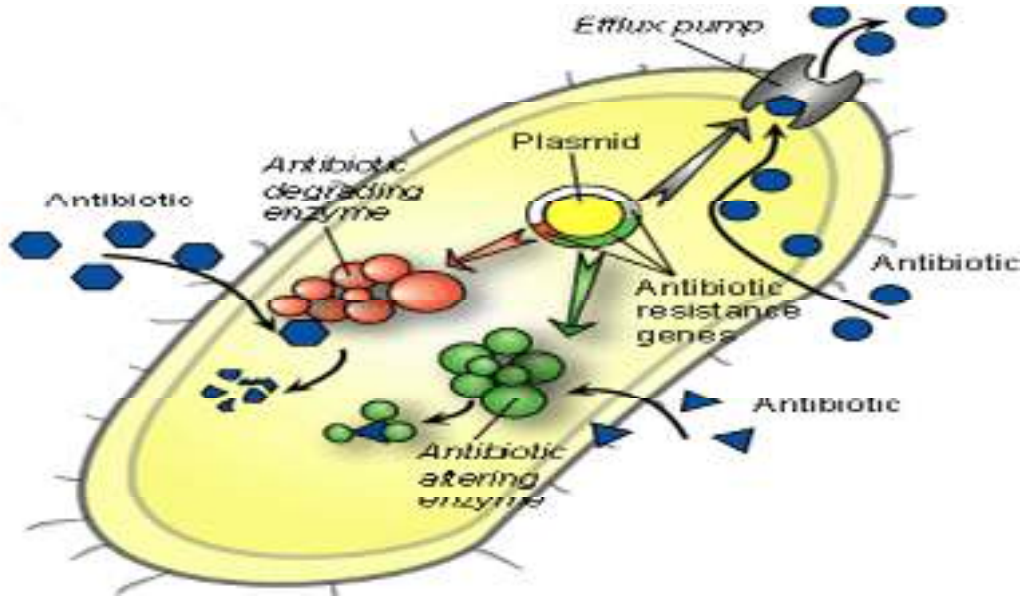

Fig1- **Mechanisms of antibiotic resistance in bacteria**

Examples

- Resistance to penicillins falls into several categories:

1. Production of β-lactamases by staphylococci, Gram negative bacteria.

2. Lack of PBPs or altered PBPs (eg, pneumococci, enterococci) or inaccessibility of receptors because of permeability barriers of bacterial outer membranes.

3. Failure of activation of autolytic enzymes in cell wall, which can result in inhibition without killing bacteria (eg, tolerance of some staphylococci).

4. Failure to synthesize peptidoglycans, such as in mycoplasmas, L forms, or metabolically inactive bacteria.

- Resistance to polymyxins is also associated with a change in permeability to the drugs.
- Erythromycin-resistant organisms have an altered receptor on the 50S subunit of the ribosome.

How do bacteria become resistant?

Bacteria can gain resistance over time through:

- Intrinsic resistance
- Acquired resistance
  1- Vertical gene transfer
  2- Horizontal gene transfer

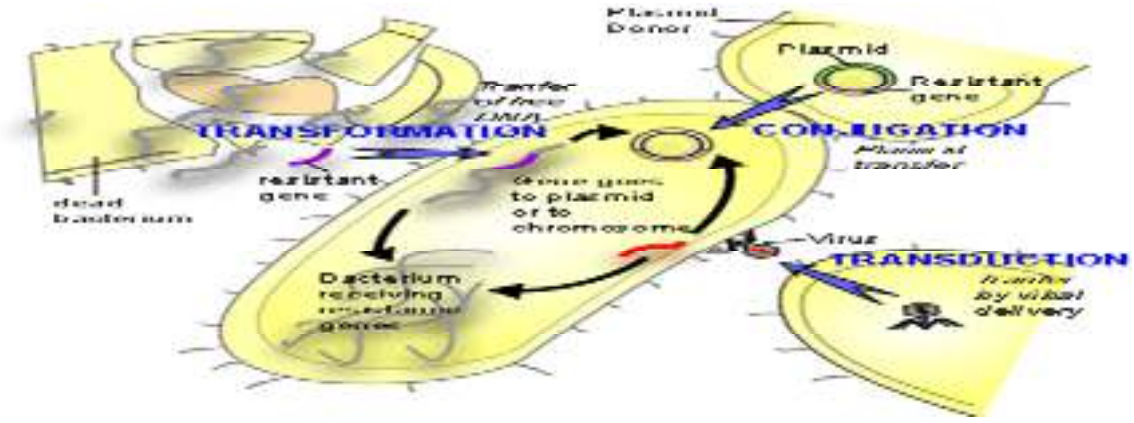

Fig-2 Mechanisms of horizontal gene transfer in bacteria

Origin of Drug Resistance

A- Nongenetic Origin of Drug Resistance

1. Microorganisms that are metabolically inactive (non multiplying) or in resting state…. e.g. ***Mycobacterium tuberculosis***
2. Microorganisms may lose the specific target structure for a drug.
3. Microorganisms may infect the host at sites where antimicrobials are excluded or are not active. ***Examples:*** **Aminoglycosides** such as gentamicin are not effective in treating ***Salmonella typhi*** (enteric fever)…..why??

B- Genetic Origin of Drug Resistance

1. **Chromosomal Resistance** ….This develops as a result of spontaneous mutation in a locus that controls susceptibility to a given antimicrobial drug. e.g. **rifampin.**
2. **Extrachromosomal Resistance**
   a- Plasmid-mediated resistance

- **It is very important because;**

1. Occur in many species especially G-ve.
2. Mediate resistance to multiple drugs.
3. Have a high rate of transfer from one cell to another, by conjugation.

- **Resistance plasmid (Resistance factor, R factor)**
  It is carry the gene for a variety of enzymes that can degrade antibiotics and modify membrane transport system.

b-Transposone-mediated resistance

Notice: ***(Most drug-resistant microbes emerge as a result of genetic change)***

Resistant pathogens

1- MRSA (methicillin-resistant *Staphylococcus aureus*)…

- First detected in Britain in 1961.
- It is a bacterium that is resistant to many antibiotics.
- Staph and MRSA can cause a variety of problems ranging from skin infections and sepsis to pneumonia to bloodstream infections.
- Strains of the bacterium that are resistant to the action of methicillin, and related beta-lactam antibiotics (e.g. penicillin and cephalosporin).
- ***S. aureus*** can develop into two types of MRSA:
  1-HA is hospital acquired. 2 - CA is community acquired.

- People with MRSA are estimated to be 64% more likely to die than people with a non-resistant form of the infection.

2- VRSA (Vancomycin-resistant *Staph. aureus*)…….(Current)

3-VRE (Vancomycin Resistant Enterococci)

4- *Mycobacterium tuberculosis*: (INH, rifampin), WHO estimates that, in 2014, there were about 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB), a form of tuberculosis that is resistant to the 2 most powerful anti-TB drugs.

5- ESBL Extended-Spectrum beta-lactamase - producing Gram-negative bacteria: are plasmid-associated beta lactamases that have recently been found in the *Enterobacteriaceae*. ESBLs are capable of hydrolyzing penicillins, many narrow spectrum cephalosporins, many extended-spectrum cephalosporins, and monobactams.

- Resistance in *Klebsiella pneumoniae* to a last resort treatment (carbapenem antibiotics) has spread to all regions of the world. *K. pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients.
- Resistance in *E. coli* to the treatment of urinary tract infections (fluoroquinolone antibiotics) is very widespread.
- Resistance to colistin (last resort treatment for life-threatening infections) has recently been detected in several countries and regions, making infections caused by such bacteria untreatable.

Multi-resistance (superbugs)

It is generally results from a combination of different independent mechanisms of resistance.

- ***Pseudomonas aeruginosa*** (natural resistance).
- **(MRSA)** have become resistant to most antibiotics (acquired).
- Multi- resistant ***Mycobacterium tuberculosis*** (future problem)

Cross-Resistance

Microorganisms resistant to a certain drug may also be resistant to other drugs that share a mechanism of action. Such relationships exist mainly between agents that are closely related chemically or that have a similar mode of binding or action.

- **Key Prevention Strategies**

1. Prevent infection.
2. Diagnose and treat infection effectively.
3. Use antimicrobials wisely.
4. Prevent transmission.

- **The Future of Chemotherapeutic Agents**

1. **Antimicrobial peptides**
   Broad spectrum antibiotics from plants and animals. e.g. Squalamine (sharks).
2. **Antisense agents**
   Complementary DNA or peptide nucleic acids that binds to a pathogen's virulence gene(s) and prevents transcription.
3. **Probiotics**
4. **Phage therapy**

Study of Antimicrobials Activity

1- *In Vitro* (See Practical Lab4)

2- *In Vivo*: The activity involves not only the drug and parasite but also a third factor, the host.

A. Drug-Pathogen Relationships…… which include:

1- Environment
2- State of Metabolic Activity
3- Distribution of Drug
4- Location of Organisms
5- Concentration
6- Absorption

B. Host-Pathogen Relationships ……. It may be altered by antimicrobial drugs in several ways:

1- Alteration of Tissue Response
2- Alteration of Immune Response
3- Alteration of Microbial Flora

Questions?

1- Define antimicrobial drugs?
2- Mention the properties of ideal antimicrobial drugs?
3- Explain the mechanism of action for antimicrobial drugs?
4- Give an example for first, second, third and fourth generation cephalosporin's antibiotics?
5- Mention the mechanism of action for penicillins?

- **Note: All figures and pictures are available freely in web during preparation of this lectures**