University of Jordan
Faculty of Medicine

Medical Committee
The University of Jordan

Introduction to

Microbiology

Title :

Antimicrobial drugs

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: 10

- ○ Slides
- ○ Handout
- ✓ Sheet

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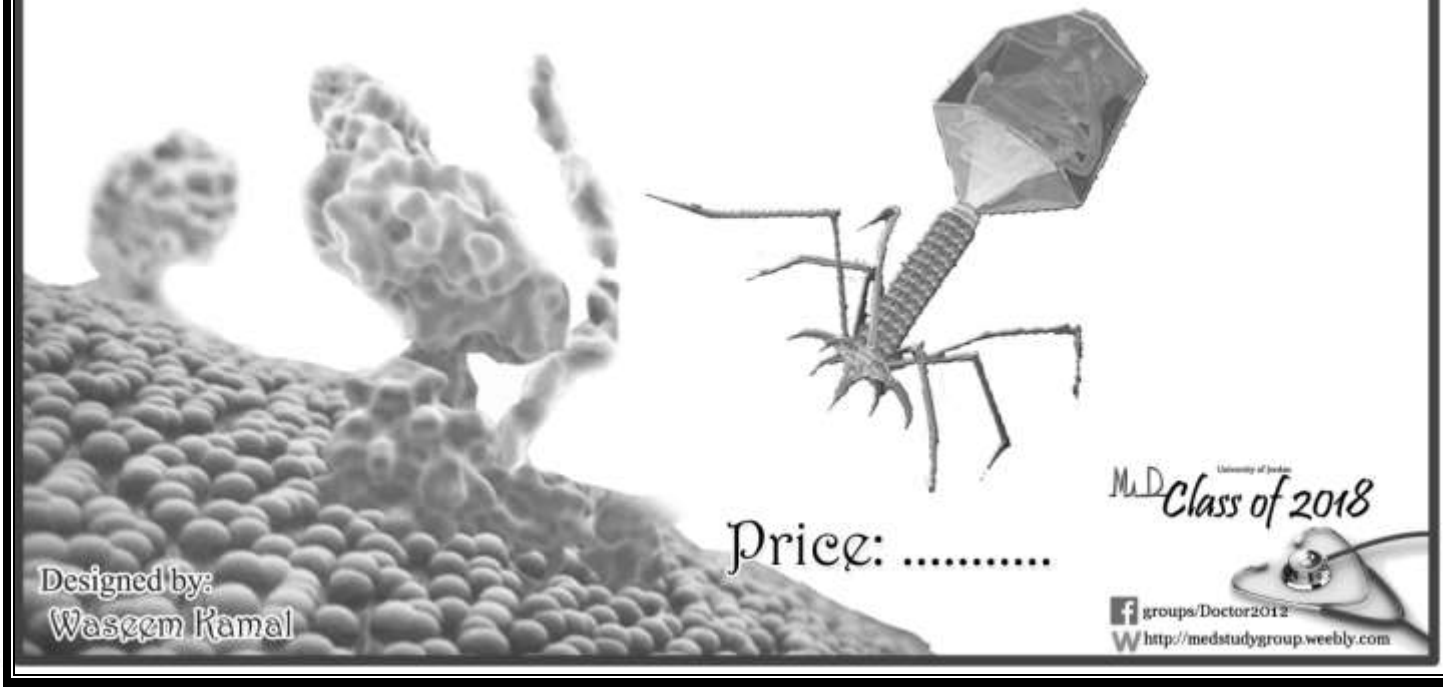

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Antimicrobial drugs:- (very important in clinical medicine)

*25-30% of drugs used to cure human diseases are antimicrobial

*in order to use the right type of antimicrobial drug that can kill the microbe with minimum side effects you need to consider three important relations:
1) host-drug

2) host-microorganism

3) drug-microorganism

-so it depends on Target , pharmacokinetics (absorption , distribution , metabolism and elimination) and pharmacodynamics (side effects)

- Antimicrobial drugs are highly effective on actively growing bacteria (vegetative) not resting cells – (no activity), no cell wall formation so difficult to target -

FACT: every antimicrobial drug has side effects but some has less than others (no 100% safe antimicrobial drug)

*difference between antimicrobial drugs and antibiotics:-

- Antimicrobial drugs: refer to all microbes: viruses, parasites, bacteria, and fungi.

- Antibiotics:

1) More specific for bacteria

2) Originate from living cells (bacteria/fungi)

History:-

1) Sulfonamide 1935 chemical drug, discovered by chemical analysis, not true antibiotic (not originated from living cells) *for simplicity we consider it as an antimicrobial drug*

2) Penicillin G 1940-1941 first true antibiotic (originates from penicillium fungus)

***both** targets gram +ve bacteria mainly such as staph and strep

3) Aminoglycosides 1946 true antibiotic, originates from type of Soil Bacteria called Actinomyctes

eg. Streptomycin (basic structure of Aminoglycosides), Kanamycin (modified form of streptomycin)

*targets mainly gram –ve bacteria

* Aminoglycosides were modified creating other derivatives which lead to 30-40 antimicrobial drugs used for various infections in our country (some are given orally , others by IV or IM ..) . Other countries have more, most of which are used for animal production (not only to treat infection but also to prevent it and increase the growth of animals)

NOTE:-

* Some Antimicrobial drugs can be used for animals and humans, some only for animals and some only for humans (animal Farms prefer to use human antimicrobial drugs as they are cheaper)

** Any used drug wither in animals or humans should have selective toxicity (effects at least one target of the bacterial cell). It might have more than one target

eg : Penicillin and cephalosporin drugs (β-lactame drugs)

Fluoroquinolones (antimicrobial drug) affects mainly the DNA structure but might have certain effects on the cell membrane .

Most of Antimicrobial drugs have more than one target but in order to simplify this topic we'll mention only the main target (cell wall \ cell membrane\ protein synthesis .. etc)

Classification:-

1) According to the mechanism of action:

A. Bacteriostatic : Inhibition of the growth of bacterial cell

Antimicrobial drugs: cause Inhibition of the cell wall >> inhibit the growth of the microbe preventing multiplication

The Human Body (immune system) is the one that kills the microbes.

B. Bactericidal:

Antimicrobial drugs: kill microbes

The Human Body: removes damaged cells

NOTE:

***** increasing Antimicrobial drugs concentration will turn Bacteriostatic into Bactericidal However this will be on the cost of the patient's health (hard to excrete the drug through liver and kidney and might lead to toxicity)

2) According to the Range of activity/spectrum:

A. narrow spectrum : target only gram +ve bacteria (staph) eg: vancomycin and penicillin

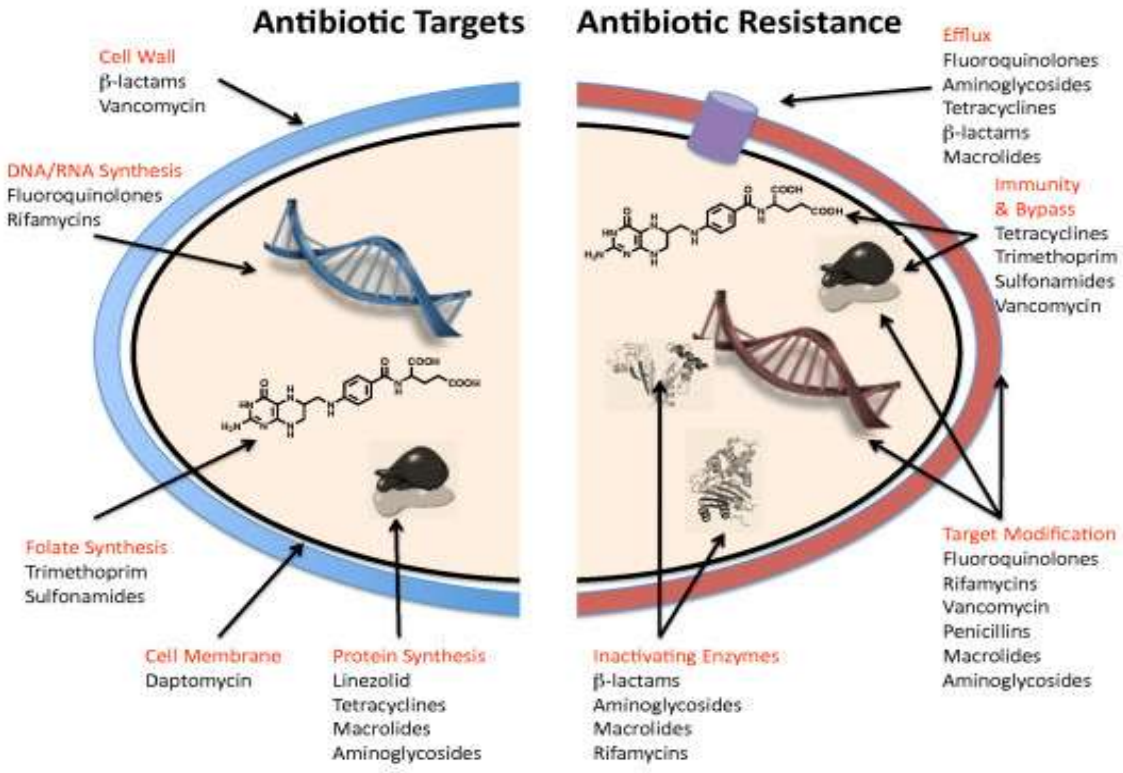
B. moderate to broad spectrum : more gram +ve and certain gram –ve (ampicillin and amoxicillin)

C. Broad spectrum –targets large number of gram +ve and-ve eg: (tetracylins, Chloramphenicol and to some extent Aminoglycosides and Fluroquinolones)

3) According to their cellular targets:

Cell wall, plasma membrane, nucleic acids, proteins synthesis.

*this picture shows a summary of the commonly used antimicrobial drugs and their classes:



Action of

Antimicrobial Drugs on Bacteria :

1) inhibiting the cell wall synthesis :

A) **Beta-Lactam Drugs**

*Contains 30-40 types of penicillin and Cephalosporins

*** * penicillin:**

-Origin: type of fungi called Penicillium nonatum (widely distributed in nature: bread, white cheese colour: blue to green)

-basic structure:

1) two rings

A. 5-Thazolidine Ring - due to the presence of sulfur -

B. Beta-Lactam ring (4 sided ring) - associated with nitrogen-

R group - amino carboxyl group >> differs from one type of penicillin to another

-Examples:

<u>1) Penicillin G</u>:

- First discovered penicillin drug.

-Introduced only by injectable roots (intramuscular or intravenous) - Beta-Lactam ring might be inhibited by the stomach acidity – that's why we don't give it orally.

-Targets mainly gram +ve bacteria, Narrow- moderate spectrum

- Susceptible to Penicillinases /ß-Lactamases actions

2) Penicillin V, Ampicillin, Amoxacillin:

- Same as Penicillin G but with a different R-group

- can be introduced orally (acid stable)

- Penicillin V targets mainly gram +ve bacteria, Narrow- moderate s**pectrum**

Ampicillin, Amoxacillin targets gram +ve and gram –ve bacteria, Broad spectrum

- Susceptible to Penicillinases /ß-Lactamases actions

Recall that >>> Gram +ve bacteria : have Multiple layers of peptidoglycans (N-acetyl glucoseamine & N-acetyl muramic acid) we have between these Peptidoglycans peptide bridges composed of penta Amino acids and these bridges are important for the rigidity of the cell wall (same in Gram –ve but the # of Peptidoglycan layers is less) .

once the cell wall comes in contact with penicillin or cephalosporin drug , these drugs bind to a specific penicillin binding proteins (PBPs)

these PBPs are found normally on the cell wall and contribute in the formation of cross bridges but the problem appears when they bind to penicillin or cephalosporins producing the complexes that inhibit the formation of cross bridges and at the same time initiate the production of lytic Enzymes called autolytic enzymes *found in the space between the wall and the cytoplasmic membrane* secreted when the bacterial cell is deprived from nutrients ! (self killing) So the End result is inhibition of growth >> Killing of the bacteria

NOTE:

- Penicillin and Cephalosporins and their derivatives have almost the same mechanism

-- Some gram +ve and –ve bacteria may lose their cell wall. They will be protected by the infected tissue however it will lose the ability to multiply.

--- You can find bacteria with no cell wall - outer membrane or part of the cytoplasmic membrane – but it won't have the ability to multiply

NOTE:

*due to the fact that Penicillin is widely used, bacteria developed resistance towards it by producing an enzyme called Penicillinase or B-lactamase - mutation in the bacterial chromosomes producing these enzymes which attack the structure of Penicillin or Cephalosporins – (attack the β-lactame ring)

3)Penicillinase –R Drugs (drugs that inhibit the action of penicillinase that cause resistance to the bacterial cell) *where ever you find R it stands for Resistance *

a- Oxacillin, flucloxacillin,Methicillin: (Pencillinase resistance drugs)

- Penicillin drug that can overcome β-lactamase (not susceptible or sensitive to β-lactamase)

-only used against Gram +ve bacteria

b- **Clavulinic Acid:**

- a chemical compound used with a Penicillin drug susceptible to Penicillinase

- have no anti-bacterial activity only anti-β-lactamase – affect only enzymes not cell walls -

- eg: Amoxacillin+Clavulinic Acid= augmentin (low characteristic due to the presence of Clavulinic Acid), Broad Spectrum

c- **Carbencillin, Piperacillin , Ticarcillin:**

-Modified Penicillin – different side chain (carboxyl penicillin group) - to have narrow spectrum and specific targets

- Targets mainly gram –ve bacteria, particularly bacteria causing infection in hospitals such as Pseudomonas

d- Monobactam:

-more modified (more carboxylic groups)

-associated with an extra cyclic compound in the Beta-Lactam ring

-developed for two purposes:

1. Escape the action of Penicillinase produced by Gr –ve bacteria

2. To be more effective against gram –ve bacteria especially enteric bacteria (but again the bacteria managed to develop extended spectrum β-lactamases) means they produce a type of penicillases with wide spectrum against penicillin drugs !

e- Carbapenem: Last modified penicillin drug

-Developed because enteric bacteria produce extended spectrum B-lactamase –a type of Penicillinase with a wide spectrum against many types of drugs –

- represented by imipenem & meropenem drugs

-managed to inhibit 70-80% of extended spectrum B-lactamase bacteria

- Broad spectrum antimicrobial drug

-targets gram +ve and –ve bacteria (but gram –ve more) resists to some extent a large # of pencillinases (but some bacteria also managed to find a way to resist them -_-)

- Usage is restricted in hospitals. Cure some severe infections caused by many types of bacteria such as Acinetobacter , Pseudomonas aeruginosa and certain klebsiella species

Note : there have been more than 60 types of penicillinases !

****Cephalosporins:**

-Origin: type of fungus (cephalosporin)

-Basic structure:

1. Beta-Lactam ring - same as penicillin -

2. 6-Dihydrothiazine Ring - differ in the number of carbons -

- divided into four generations

1) Cephalexin, Cephradine:

-have similar spectrum of activity to Ampicillin, Amoxacillin

-developed for two reasons

1. Penicillin might produce hyper sensitivity in humans –to avoid killing the patient by anaphylactic shock-

2. To resist action of Penicillinase

FACT: although it is less associated with allergies in some cases it will cause hyper sensitivity to people with Penicillin allergy

<u>2) Cefoxitin, Cefuroxime:</u>

-both gram +ve and –ve (wide spectrum)

<u>3) Ceftriaxone, Cefotaxime</u>

-rarely used

- Targets both gram +ve and –ve but more effective on gram -ve

<u>4) Cefepime</u>

- Used only in hospitals to treat gram –ve infections

These Drugs (penicillin and cephalosporins) are used to treat upper respiratory tract infection ,renal tract infection , blood sepsis .. etc

-despite the usage of Penillinases drugs , sometimes the bacteria manage to find another way of resistance ! related to a mutation in the bacterial chromosome or a resistance plasmid transfer (carry a gene called MecA gene related to Methicillin drug) here the penicillin binding proteins have changed their configuration so the penicillin can't interact with them anymore .

Klebsiella Pneumoniae carbanemase -R is resistant to all available antibodies .

Some side effects of penicillin drugs >> Penicillin allergy , fever ,serum sickness, Nephritis and more dangerous anaphylactic shock that usually kill the person within few hours .

B) Glycopeptides Drugs

Another group of Drugs that affect the cell wall surfaces but in another form (not related to PBPs but to the formation of cross bridging –the last item that contribute In the rigidity of the bacterial cell wall- so the end result is inhibition and killing effect

We have two types of GLycopeptides >>> Vancomycin & Teicoplanin

*we don't have to memorize the structure but to have a general idea about it *

***If you have a large structure of a drug with many carboxylic groups or hydroxyl groups >>this drug can't be easily absorbed from the intestine , and the liver can't easily do the detoxification of that drug and it might accumulate in kidney and cause kidney failure .

And as an example the Vancomycin , Aminogycosides And tetracycline (Large polycyclic peptides)

Vancomycin >> effective in treating Gr+ve Bacteria Especially Methicillin resistant Staph (Multi resistant Gr+bacteria) NOT Gr-ve !

There is still no resistance from Staph against Vancomycin :D but there is a resistance against Enterococcus (might develop resistance at future)

The problem with Vancomycin that it should be given only in Hospitals . y? it's highly Toxic and given intravenously

Teicoplanin >> has a similar function and structure to Vancomycin but very expensive in comparison to Vancomycin and we use the cheaper one .

2) Drugs that affect the cell membrane

-cell membrane of the bacteria is not easily disturbed

-for any drug to be affective it must react with specific glycoproteins within the cell membrane of the bacteria

1-Colistin \Polymixen E Drugs : similar to vancomycin and very complex (isolated from Bacteria)

Colistin is used mainly for treating infections caused by Gram –ve bacteria but the side effects were very harmful so they stopped using it and returned back to using it after modifying it .

Used for infections that can't be covered by Penicillin and cephalosporin drugs.esp those caused by Pseudomonas and Acinetobacter .

Why it was used ?

1)Colistin is almost 100% effective against the multi resistance microorganisms

2) these drugs are the only last resort to treat the patient otherwise there is no useful drug for treating him. But on the other hand it's always associated with side effects *No other Choice*

2-polypeptides : similar to vancomycin called Bacitracin (can't be given by IV and produce a damage to the cell membrane >>interacts with the membrane phospholipids and allow minerals to leak out of the cell causing side effects)

Bacitracin is Only used in topical Form (Powder ..)to treat infections in the skin but never for systemic use (Highly toxic)

3) Drugs that affect protein synthesis :
Same mechanism in relation to bacterial ribosomes >> inhibit the amino acids transfer to the ribosomes OR prevent the attachment of bacterial polymerase OR cause a damage to the sequence of RNA resulting in Preventing protein synthesis >> affect growth of bacteria (Bactericidal Dugs)
-Have Wide Spectrum (might cover More Gr-ve than +ve)

-Aminoglycosides >> first introduced was Streptomycin (very useful in the treatment of tuberculosis TB)
-Not given orally (only IV)

- then they developed Neomycin,Amikacin,Gentamicin,Tobramicin & Netilmicin
Mostly used >> Strepto,Amika,Genta

Mainly used against Gr-ve . Y? we can kill Gr+ve by less toxic drugs .

Side effects : Ototoxicity , Nephrotoxicity, Ototoxycity (affecting 8th Cranial nerve >.hearing loss)

-Bacteria might be resistant to these drugs following the wide use of the drugs by producing Accetylate ,Phosphorylate& adenylate Enzymes

*Structure of Aminogycosides >>
3 sugar Rings attaches to amino , hydroxyl groups (can't be easily absorbed due to the large size)

*Structure of Tetracycline
(as the name indicates : 4 fused rings with different groups attached to them)

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