Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 26

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SHEET

SLIDES

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ANTIBIOTICS

Antibiotics are divided into 3 groups according to their target in the bacteria:

1- Antibiotics that target cell wall

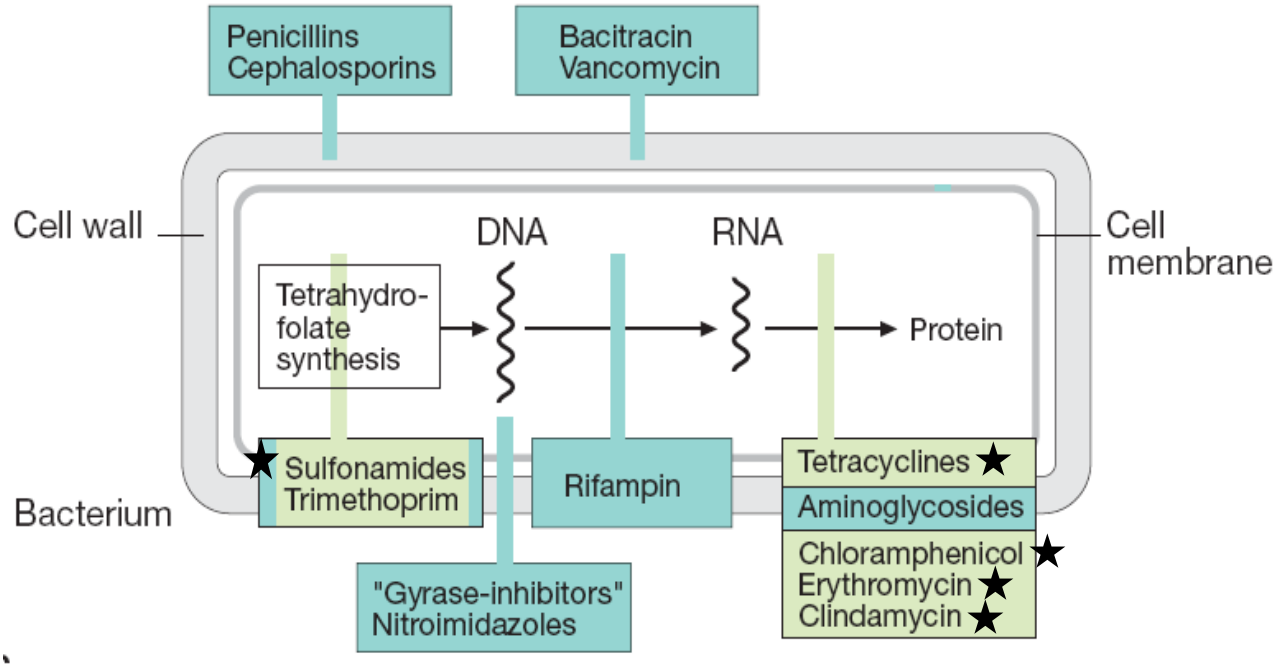
2- Antibiotics that inhibit protein synthesis

3- Antibiotics that inhibit DNA synthesis

Why do we need to know about antibiotics classification, or the way in which they target the bacteria?

Because some of them produce a bacteriostatic effect (limit growth) on the bacteria whereas others produce a bactericidal effect (kill).

*In the figure below: bacteriostatic antibiotics (in green or ★) and bactericidal antibiotics (in blue or w/out ★)



We don't only intend to stop the growth, we want to kill or destroy all the microorganisms, or what we call it in pharmacology "Eradicate".

Note: The more bactericidal the antibiotics are the better they're for life threatening conditions in most cases.

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*Now, let's talk about **bacteriostatic drugs:** it is useful to know the status of the immune system of your patient; because bacteriostatic drugs just stop the multiplication of microorganisms, but eradication of those is a function of the immune system. So patients with compromised immune systems won't be able to eradicate the microorganisms even after limiting their multiplication.

-- For example, patients who have cancer, diabetes, those with transplanted organs – all have compromised immune systems – so **bacteriostatic antibiotics won't be beneficial here and you need bactericidal types instead.**

** Also in life threatening situations like septicemia, bacteremia and many types of infection, you need bactericidal AB.

--Examples of bactericidal drugs:

1- Penicillin 2- Cephalosporin 3- Vancomycin 4- Quinolones

Quinolones: inhibit gyrase enzyme (which unwinds DNA) so the DNA of the bacteria will not be broken and replicate. (The best antibiotics are those which target the enzyme gyrase).

*There is a similar enzyme to gyrase in humans called topoisomerase 2, (the best drugs for cancer work on this enzyme).

----> Also, inhibition of RNA-polymerase (by a drug called **Rifampin**) is considered as a **bactericidal effect;** because RNA-polymerase is very important in the transcription process (copying DNA into RNA).

---->**Most bacteriostatic drugs** are used against protein synthesis (this means you are stopping the cell from producing new proteins), **except aminoglycosides** which are **bactericidal** although they are protein-synthesis inhibitors.

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*Cell wall inhibitors:

- They are **bactericidal,** they inhibit the cross-linking of peptidoglycan chains and prevent the formation of rigid cell walls (cell wall building blocks are cross-linked by transpeptidase) and this leads to osmolarity differences, which leads to lysis of the cell.

- Examples:

1) Penicillin 2) Cephalosporin 3) Monobactam

4) Vancomycin 5) Carbopenem

-Penicillin:

* Mechanism of resistance:

1) B-lactamase (penicillinase) is an enzyme produced by bacteria. When bacterial cells are attacked by antibiotics, the enzyme B-lactamase hydrolyses the antibiotic (or to be specific the enzyme targets the lactam ring in antibiotics)

Note: when the lactam ring is cut, the antibiotic won't bind to its receptor and it will not function anymore.

2) Reduction in the permeability of the outer membrane in Gram-negative bacteria.

Notes:

- Drug permeability in gram negative bacteria is less than that in gram positive bacteria.
- Gram negative bacteria have no real pores so they resist many types of penicillin.

3) Mutations to the penicillin-binding proteins.

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Natural penicillin (Benzyl penicillin):

1- Penicillin G:

- discovered by Alexander Fleming and Howard Walter Florey.
- is the oldest type of penicillin, was the first antibiotic introduced to the community.
- is poorly absorbed from GI tract and can be given IM or IV but ***Not*** orally.

A problem with penicillin is that it is broken down in the stomach because of the high acidity there, so it shouldn't be given orally.

- Its **spectrum** (range of activity):

1- Active against most gram-positive bacteria (Gram +ve = strep and staph)

When it was first introduced –during the 40s and the 50s- it was active against both strep and staph.

But now, since bacteria develop resistance with time, penicillin G is only active against strep, and ***Not*** really active against staph (99% of the staph produce penicillinase which breaks down the B-lactam ring and deactivates penicillin, so staph became resistant and not susceptible to penicillin G).

2- Not active against most gram-negative aerobic bacteria, except Neisseria Gonorrhea and Neisseria Meningitis.

-- Gram positive (strep only) is susceptible to penicillin G, while gram negative is NOT susceptible.

Note:

Streptococcus can cause:

1- Pneumonia 2- Otitis media 3- Meningitis

4-Septic arthritis: is the purulent invasion of a joint by an infectious agent which produces arthritis. If untreated, it may destroy the joint in a period of days. The infection may also spread to other parts of the body.

Clinical Uses of penicillin G:

→We use it against streptococcus infections that include:

1- Pneumonia 2- Otitis media 3- Meningitis 4-Septic arthritis

5-Pharyngitis:

- 30% of pharyngitis in children is caused by streptococcus pyogenes.

-In adults, it's only 5-10 % of the pharyngitis is caused by streptococcus.

-Streptococcus pharyngitis produces antibodies within the body of the child and causes a disease called **Rheumatic fever**.

→Also, it's used against Neisseria meningitides, Clostridium tetani, Corynebacterium diphtheria, Treponema pallidum and Listeria monocytogenes.

Pneumonia can be caused by strep or staph so we need to make a culture media before we give the drug to the patient.

Listeria: infection in GI tract similar to that caused by salmonella but more lethal.

-->In America 260 death cases occur yearly because of listeria.

--- Drug prescription depends on the microorganism that causes the disease and its susceptibility to that certain drug.

Remember: 1-Different microorganisms have a different MIC (minimum inhibitory concentration) of antibiotic.

2- Resistance of bacteria differs from one patient to another according to genetic and origin variation.

--- We can't use penicillin G in empirical treatment because it covers strep only, and as mentioned before, sometimes a disease –pneumonia for example- can be caused by more than one type of bacteria which aren't all covered by that one drug, and so there is no guarantee that we're killing the causative agent. We use penicillin G only in definitive therapy, **OR** if we are sure that the causative bacteria are streptococcus.

--- Most of penicillin G applications are now gone **except** Benzathine Penicillin (penicillin G combined with benzathine), makes it like colloids. Benzathine Penicillin is given IM, and it releases low levels of penicillin within the body of the patient.

--- We give that drug as prophylaxis, only if we are afraid that patients will be attacked/ infected again by strep. (1 injection monthly for 15 years for example)

--- A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for beta–hemolytic streptococcal pharyngitis

--- Benzathine penicillin G, 2.4 million units intramuscularly once a week for 1–3 weeks, is effective in the treatment of syphilis. Here we can consider it as prophylactic.

--- So you need much more of benzathine penicillin to kill the causative agent of syphilis than that needed to kill streptococcus pneumonia, because different microorganisms need different MICs of a certain drug.

--- Also prophylactic (benzathine penicillin) which is given IM once every 3-4 weeks, it prevents re-infection.

2-Penicillin V:

-- Is given orally

-- More active than penicillin G against **anaerobes** (which are found under teeth)

-- So penicillin V has a wider spectrum than penicillin G

-- can be given to treat streptococcus pharyngitis (definitive treatment)

(The spectrum of Penicillin G + anaerobic bacteria)

-First choice in the treatment of odontogenic (related to dental "mouth of the patient") infection:

1- Post extraction infection

2- Pericoronitis

3- Salivary Gland infection.

طبيعي جدا انك ما تكون فاهم شو هدول (الحكي مو للكل طبعا); لانه الدكتور حكى مو مطلوبين منا الا كإسم لانه راح ناخدهم بالباثو بالمستقبل☺.

Other classes of penicillin, B-lactamase resistant penicillins:

1-Cloxacillin 2- Flucloxacilin 3- Oxacillin 4- dicloxacillin

5- Methicillin (not used anymore) {1-5 synthetic penicillins}

→They modify the structure of penicillin in order not to be susceptible to B-lactamase or penicillinase; so they produce B-lactamase-resistant penicillins.

→ The antibiotics above, especially methicillin were used against penicillin-resistant bacteria, with time these bacteria developed resistance against those antibiotics as well through a new type of resistance (by changing the binding pocket for penicllins). The new bacteria became resistant to penicillin G, penicillin V, Cloxa, Fluxa, Oxa and methicillin. Since methicillin was the prototype of the group, the new bacteria are called MRSA (Methicillin Resistant Staph A).

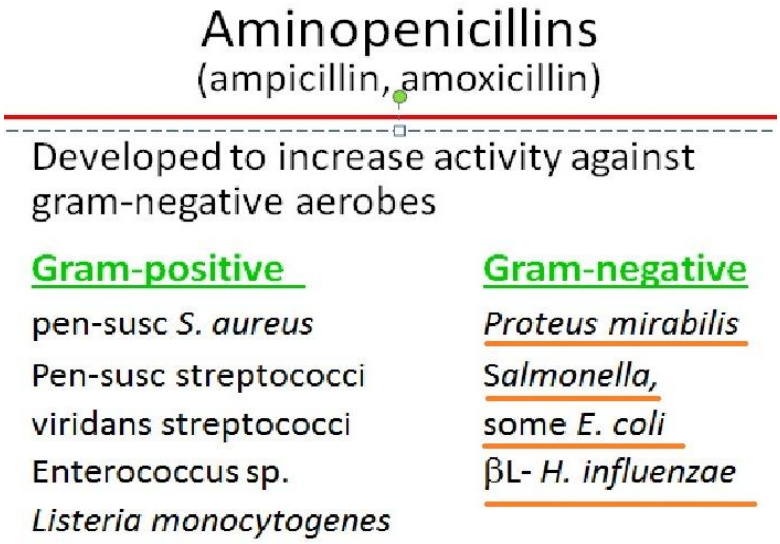
Aminopenicillin:

- used against gram negative bacteria

-contain 2 types:

1- Ampicillin 2- Amoxicillin

→How do they differ from G and V? They have an amine group which allows them to penetrate cell walls and membranes of gram negative bacteria more effectively.



Modified penicillins (Aminopenicillins) are active against these gram negative bacteria in addition to listed gram positive bacteria.

** According to spectrum variability, Aminopenicillin (especially amoxicillin) are used for RTI but it doesn't cover staph, so we use Augmentin instead (Amoxicillin + B-lactamase inhibitor- clavulanic acid-).

--- Ampicillin and amoxicillin are among the most useful antibiotics for treating children suffering from infections caused by sensitive gram-negative aerobic bacteria, enterococci, and B-lactamase-negative H. influenza.

--- Nowadays, H. Influenza produces B-lactamase (even when they are gram –ve bacteria which usually don't produce B-lactamase) due to the misuse of antibiotics.

--- As a result, Ampicillin is not used against B-lactamase-producing bacteria.

NOTE: correct the titles: ** in slides # 28, 31, 32 changes ~~extended~~ to broad. ** in slide # 34 change ~~broad~~ to extended.

--- Broad spectrum penicillin is widely used in RTI.

--- Also, it is given orally to treat sinusitis, otitis, and lower respiratory tract infections.

--- Amoxicillin is the favored drug for the treatment of acute otitis. Empirical in children (Increase the dose to 80-90 mg/kg/day), in the past we used to give (40-50 mg/kg/day) and now we need to give a larger dose again because of the misuse of antibiotics in our community. YOU GUYS AS FUTURE DOCTORS HAVE TO STOP THIS PHENOMENON!!

--- remember: we wait 2 days before prescribing antibiotics for otitis media patients because they may improve without antibiotics.

---Leading cause of CAP (Community Acquired Pneumonia), meningitis, otitis media in the US.

---Excessive antibiotics use for ARIs (Acute Respiratory tract Infections) is fueling an epidemic of community antibiotic-resistant bacteria.

---Major risk factor for carriage & spread of resistant S. pneumonia is prior antibiotic use.

These are studying in some country:

---JAMA 1998:

→Prior to 1980, 99% of all S. pneumonia cases were susceptible to penicillin.

→In the past decade, 40% of isolates have intermediates to high penicillin resistance.

---Dagan 1998:

→19 of 120 children had a new pneumococcal isolate colonizing their nasopharynx within 3-4 days of treatment.

→In 16 of the 19 children, the isolate was resistant to the antibiotic the child was taking.

---Ampicillin is the same as amoxicillin but one is injectable (Ampicillin) and the other is given orally (amoxicillin).

---As a result we use ampicillin against enterococci which cause endocarditis (inflammation in the heart) because that is a life-threatening condition so we need to use injectable bactericidal antibiotics to reach steady state very fast.