

***Title of Lecture: Antibacterial Agents***

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***Refer to slide no. : 25-49***

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**Revision:**

* B-lactamase breaks up the B-lactam ring of the penicillin. Once this happens, it will not be able to bind to penicillin binding proteins and produce its effect.
* To counteract the effect of B-lactamase, we have B-lactamase inhibitors which include clavulanicacid and sulbactam.
* B-lactamase inhibitors are not antibiotics but are added to antibiotics. For example: Amoxicillin alone is sensitive to the B-lactamase (will be destroyed). However, if we add clavulanic acid to Amoxicillin it will inactivate the B-lactamase and stop it from breaking the B-lactam ring.

Some antibiotics (for example: Cephalosporins) are resistant to B-lactamases . Other bacteria including E.coli and some of the gram negative bacteria have an extended Spectrum B-lactamase and have the ability to destroy the Cephalosporins.

**Note:** As the cephalosporins evolve (1st generation to 2nd to 3rd to 4th..), the generations become more resistant to B-lactamase. So the advantages of cephalosporins include :

 1) More resistant to B-lactamase and are hence used in cases of bacteria which produce B-lactamase.

2) Broader range of action and they are active against gram –ve bacteria.

Some bacteria can produce extended spectrum B-lactamases which destroy all B-lactam rings and in these cases all what we can use are Carbapenems . Carbapenems are the last resort used in cases of extended spectrum B-lactamases. Nevertheless, studies in India have discovered the presence of bacteria which produces Carbapenemases which in turn destroys Carbapenems.

These bacteria can (structurally) change the penicillin binding proteins. HOW? Changing the structure of the enzymes responsible for the bridging of the peptidoglycan. In this case we can’t use any of the B-lactams. An example on that is the penicillin resistant staphylococcus aureus. In this case, we resort to the use of other antibiotics which work on the cell wall as well but at a different stage.

**Stages of Peptidoglycans on which antibiotics can work:**

1. B-lactam ring
2. Attacking the formation of the bridges formed by peptidoglycans (by the use of other anitibiotics).

Both stages are acted upon in Methicillin resistant staphylococcus aureus and in vancomycin. These are used only in special occasions and restricted to the use in hospitals and by professionals.

Others that work on the cell wall:

1. Bacitracin: not used extensively. May be used topically in some creams because it is toxic.
2. Isoniazid, Ethionamide, Ethambutol and cycloserine : Agents that work on certain content of certain cell walls of bacteria. Mycobacteria causing TB (Tuberculosis) and Leprae causing Leprosy have a lot of lipid in their wall known as mycolic acid. These antibiotics interfere with the lipolic acid synthesis and can kill the bacteria. Mainly used for the treatment of TB.

**Note:** All the above were inhibitors of cell wall synthesis. The following are inhibitors of cell membrane.

**Inhibitors of cell memberane Function.**

1. Polymyxins: very toxic to human cells and hence never really used.
2. Imidazole and polyenes: antifungal agents. Given orally or parenterally (might cause some side effects). We resort to these in cases of fungemia (fungus in the blood).
3. Daptomycin: A drug acting on the cell membrane in cases of skin infections and bloodstream infections. Not supposed to be used in cases of pneumonia because it has no activity in the lung. It actually inactivates the surfactants in the lungs (those which keep the alveoli open).

**Inhibitors of protein sysnthesis (work on ribosomes):**

How? Mainly by stopping protein production, or by allowing only part of the protein to be released –which will be ineffective-.

Result: stop growing/eventually dies (depending on antibiotic used)

Antibiotics attach to ribosome. If this attachment is reversible, they are bacteriostatic. If the attachment is irreversible, they are bactericidal.

1. **Aminoglycosides:**

- Ribosome is made of two components (30S and 50S) these attach to the 30S and their attachment is irreversible so they are bactericidal.

-Active against Gram –ve.

-1st discovered was the streptomycin. Others include neomycin, kanamycin (all those ending with ”cin” are members of the aminoglycosides).

-Most of them are given parenterally (IM or IV) because they are not absorbed in the intestinal tract.

-Can be toxic to the 8th nerve; one might become deaf or lose their balance.

- Aminoglycosides are excreted by the kidney. Hence, in cases of renal deficiency; less doses of netilmicin are given (to avoid the accumulation and toxicity).

-Streptococci and anaerobbesa are resistant to aminoglycosides because they are aerobic.

\*\*Resistance to aminoglycosides develops if:

- the antibiotic is destroyed

-prohibited from entering

- site of action changed

-Expelled using an active pump

-mutation of ribosome (if it cannot bind then it won’t be active)

-since they are oxygen dependent; decreased uptake of the antibiotic

- modified antibiotic (change within the cell/bacteria)

1. **Tetracyclines:**

-broad spectrum but their attachment to 30S ribosome is reversible so they are bacteriostatic.

- stain teeth and bones resulting in green or brown teeth. Therefore shouldn’t be given to pregnant women (contraindication) or growing children.

\*\*Resistance develops if:

* Decreased penetration (porins in the bacterial cell wall)
* Active efflux (requires an active pump)
* Mutation of chromosomal gene encoding the outer membrane porin protein.
1. **Chloramphenicol**
* Broad spectrum
* Binds to the 50S ribosome
* Bacteriostatic
* Disrupts the protein synthesis
* Very useful antibiotic. Restricted because it has side effects including aplastic anemia (not a gross side effect but- like hypersensitivity-some patients are sensitive to it (1 in 25000)).
* Used however in some eye drops
* Used previously for typhoid fever, salmonella, meningitis and flu.

\*\*Resistance develops if:

* Chloramphenicol itself is altered and hence cannot bind to the 50S unit
* Porin proteins decrease the permeability of the cell
1. **Macrolides (erythromycin):**
* Broad spectrum
* Effective against gram +ve bacteria
* Often used as a substitute for penicillin (especially those allergic to penicillin)

**Note:** if patient is allergic to penicillin, patient should not be given any of the other B-lactam drugs because it may result in an anaphylactic shock. Others say that there is a 10% chance that if one is sensitive to penicillin, one may undergo an allergic reaction if given Cephalosporins (cross-reactivity/sensitivity).

Hence Cephalosporins are not given unless it’s the only drug available.

* Erythromycin is given if a patient with tonsillitis (caused b y streptococcus) is allergic to penicillin.

\*\*Resistance develops if:

* Change occurs in action site of the antibiotic (in this case ribosome)
* Active efflux pump
* the structure is destroyed (which makes it ineffective).
1. **Clindmycin and lincomycin:**
* Usually given by dentists
* Work on 50S ribosome
* Inactive against aerobic gram –ve bacteria
* Have a serious side effect; can produce pseudomembranous colitis which kills the normal flora in the GI tract and allows a bacteria called clostridium difficile to grow and produce toxins. The toxins produced damage the membranes of the colon resulting in bloody diarrhea while other toxins affect the systems of the body and may cause death.
* If you develop pseudomembranous colitis, you should stop taking the antibiotic and take Vancomycin. However clindmycin and lincomycin are not the only ones which cause this; instead, any broad range antibiotic may cause it. Why broad? They kill all/most the normal flora in the GI tract and allow clostridium difficile to grow.
* **Note:** not everyone who takes clindmycin will experience pseudomembranous colitis.

**Inhibitors of Nucleic acid synthesis**

Work on the DNA synthesis or RNA synthesis by interfering with the enzymes responsible for the duplication of DNA .

1. **Quinolones**

-broad range

-Very effective

-Chromosomal resistance may develop (which is responsible for the duplication of the DNA so duplication is no longer valid).

- RNA synthesis interference by rifampicin (used in the treatment of TB).

1. **Metronidazole:**
* Not active against aerobes
* Used for clostridium difficile
* Not given to pregnant women because it may affect the development of the fetus.
* Metronidazole is commonly known as fagyl.
1. **Antimetabolites:**
* Interfere with metabolism of folic acid synthesis
* One of the needs of bacteria is folic acid; humans as well need folic acid.
* Difference between both is that human cells do not produce folic acid but attain it from the diet, while the bacteria synthesize the folic acid they need.
1. Sulfonamides are the first antibiotics used and they actually interfere with metabolism of folic acid and prevent folic acid from being produced.

B) Trimethoprim inhibits the production of tetrahydrofolic acid and works the same way as the sulfonamide but at a different stage in the production of folic acid.

* Each on their own is bacteriostatic but together they become bacteriocidal.
* Synergism of both involves 5 parts of sulfonamide and 1 part of trimethoprim. These form co-trimoxazole which causes a bacteriocidal effect.
* **Note:** thymidine is a pyrimidine not a purine.

**Measuring Antimicrobial Sensitivity: Disk Diffusion**

A patient with tonsillitis caused by streptococcus pyogenes is given penicillin. This is a relatively easy decision to make. Sometimes however, in patients with urinary tract infection or meningitis we need to know specifically which bacteria is causing the infection and then determine the best antibiotic to be used. To do so, a sample is taken, bacteria is isolated and differentiated. A solution of the bacteria is poured into a petri dish and left to grow. The result is uniform growth/confluent growth of a pure culture.

To determine the antibiotic to be used, a ring (similar to filter paper in texture) with circular discs is impregnated into the petri dish where each disc contains a different antibiotic. The Petri dish is incubated for 24 hours.

Clear areas are observed; these contain no growth. The bigger the clear area the more effective the antibiotic is to the bacteria. The diameter of the clear zone is measured and will be an indication of the effectiveness of the antibiotic. Manufacturers will have detailed data concerning the relation of the diameter to the effectiveness of the antibiotic. Effectiveness is indicated as S for sensitive, M for sensitive and R for resistant.

**Note:** if the petri dish has no clear areas then the bacteria is resistant to all antibiotics impregnated.