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Types of Bacterial Therapies:-

There are four types of therapies applied in antibiotic usage:

1) Prophylaxis Therapy (وقائي): This is the easiest one of the therapies, since it is used as a preventive measure before operations in -operation theatres- where the patient is susceptible to wound infections that may arise from bacteria (ex: normal flora of the skin) that may get in contact with these wounds and cause an infection.

Example: before doing a colectomy the doctor is supposed to prophylact his patients GI Tract from the Normal flora there to prevent any infection from happening there.

Always remember that prophylaxis is a hundred times better than actual treatment, and this is why we take prophylaxis measures very seriously in antibiotic usages.

2) Empirical Therapy (توقعي): It is the drug that is prescribed by a doctor depending on his suspicion of the possible bacteria that the patient might be infected with, depending on some evidences and clues that are shown on the patient.
(This type is the most important and the most difficult one)

Example: A patient came to his doctor with pneumonia therefore this patient is most probably infected by bacteria X,Y or Z (which result in pneumonia) so you give this patient either

a certain “broad spectrum drug” that is capable of acting on all of these bacteria or you can prescribe more than one drug.

This is the most important and critical step due to the fact that a lab analysis needs at least 2-3 days to give you the results of the biopsy made, and this is the biggest reason we are studying pharmacology.

3) Definite therapy: it is the drug that is given to a patient based on the results that were given from the Lab, (at this point you know exactly which microorganism caused the state of the patient)

Also we must know the result of the susceptibility test because there are many types of bacteria that were susceptible to many types of antibiotics and now they become resistant to them.

This is really not complicated since every known microorganism has a certain drug that is used to deal with it.

4) Post treatment suppression therapy: (more common in treatment of viruses)
This Therapy is not always used, it depends on the case, it is usually used when a certain patient has a high load of a certain bacteria in his body after the treatment has ended, which causes a recurrence of the infection over and over again after the actual treatment has finished.

Example: some females develop many Urinary Tract infections (3-4 times a year) which is due to the fact that she is loaded

with E.coli Bacteria for example, after regular treatment, E.coli levels are going to get back to low levels again, but the problem is that as soon as you stop the treatment E.coli levels are going to get high again, therefore we need to use the “post treatment suppression therapy”. *this is a very common practice Postpartum.

*Remember that the bacterial concentration after an infection should theoretically be low, therefore a high bacterial concentration is an abnormal condition which needs treatment by “Post treatment suppression Therapy” as stated above.

*Also remember that in Post treatment suppression therapies we use only 50% of the actual dose (used in the actual treatment) in order to not get too low levels of normal flora that might result in “disturbances resulted from low levels of normal flora”.

This is not an easy decision for a doctor because you have to balance between the fact that a patient is getting infected every few months, and the fact that low levels of normal flora will have inevitable side effects, that’s why you should always keep in mind the Benefit-Risk ratio.

Bacterial resistance mechanisms:-

Before we start talking about anything here I just want to mention that mutations among cells are very rare (only one in 10 million cells gets mutated during cell division) this is because,

the replication process is very accurate especially in bacterial cells therefore it is not that big of an issue in the development of bacterial resistance, the bigger problem is the movement of plasmids between bacteria (were a certain bacteria acquires immunity to a certain antibiotic and starts to spread this genotype to the other bacteria).

Note: bacteria don't develop mutations during treatment therapies but Cancer or viruses actually do.

There four main mechanisms of resistance in Bacteria:

1) Production of an enzyme that inactivates the drug: (B-Lactamases/ Penicillinases/ Cephalosporinases/ Extended Spectrum B-Lactamases (ESBL)).

- ESBL activity includes penicillins and some types of cephalosporines and carbapenems.
- Streptococci in general do Not produce these enzymes, so penicillins are still active against most of streptococci.

2) Mutations in the target macromolecule (Receptors): (MRSA is resistant to most antibiotics that affect the cell wall because its binding receptor has been mutated).

3) Induction of mechanisms to reduce accumulation of the drug: (Tetracycline: and this is because most of the bacteria have evolved a "pump like structure "that resembles P-glycoprotein which removes the tetracycline as soon as it enters the bacteria).

4) Multiple drug resistance involving all these mechanisms: (uses more than one of the mechanisms illustrated above) Example: Pseudomonas bacteria release Extended Spectrum B-lactamase + it has the “pump like structure” which pumps out some types of antibiotics (this is why Pseudomonas is considered very strong bacteria).

Note: we consider a bacteria as “multi drug resistant” when it shows resistance against 2 or three drugs from different drug groups (cell wall acting antibiotics/ protein synthesis acting antibiotics/ cell membrane acting antibiotics…)

Antibacterial chemotherapy:

The ways that antibiotics interfere with the microorganism’s growth and the life:-

1) External integrity of the bacterial cell (cell wall inhibitors” penicillin/ Cephalosporin”)
2) Protein Synthesis (Tetracyclines, Aminoglycosides, Macrolides)
3) Perturbation of nucleic acid synthesis

a. Inhibition of the synthesis and function of folic acid (Sulphonamides, Trimethoprim)
b. Inhibition of DNA gyrase (Fluoroquinolones, Nalidixic acid)

*DNA gyrase in bacteria resembles topoisomerase in humans.
c. Inhibition of RNA polymerase (Rifampicin)

-Antibiotics can also be classified into Bacteriostatic or bactericidal, and this depends on the structure or the way that the antibiotic acts on.

1) For example antibiotics that act on the cell wall (penicillin, cephalosporin, bacitracin, and vancomycin) are considered bactericidal.

2) While antibiotics that act on protein synthesis (tetracycline, chloramphenicol, erythromycin, clindamycin) are considered bacteriostatic. (The bacteria enters a static phase where it lives normally but cannot undergo replication, therefore the immune system has enough time to act on the bacteria).

*It is forbidden to use a bacteriostatic drug on an immunosuppressant patient or a patient that has a “life threatening condition”, (cancer patients/AIDS patients).

3) Antimetabolite antibiotics which work on the folic acid and DNA precursors (Sulphonamides, trimethoprim) are also considered bacteriostatic.

4) Quinolones antibiotics which inhibit DNA gyrase (Topoisomerase) “which unwinds the DNA and then rewinds it again” therefore if I inhibit it, this will result in the death of the cell that’s why it is considered bactericidal.

There is an Exception to the rules above which is: Aminoglycoside (it is a protein synthesis inhibitor but it is bactericidal not bacteriostatic) Why?

This is because Aminoglycoside is not a pure protein synthesis inhibitor(it has a dual effect), meaning that it first binds to the cell wall, then enters the membrane of the microorganism which results in a decrease in the membrane fidelity (membrane patterns are changed) therefore this results in making the membrane too lose and unstable.

Dual effect means that it has both an effect in protein synthesis inhibition and cell wall/membrane disruption, and this is what makes this drug so effective until now (with little resistance against it).

Side note: the bactericidal effect of the aminoglycoside is from the cell wall/membrane disruption.

Aminoglycoside is a very nephrotoxic drug (if used more than one week, it will cause acute kidney failure)

Antibiotic brands:-

There are hundreds of antibiotics all over the place but we should be able as doctors to differentiate between them and not get confused.

Now we are going to talk about each class of antibiotic depending on its action as stated above.

First of all: Antibiotics that affect the cell wall of Bacteria:

-Effect: bactericidal.

-Species range: Gram +ve Bacteria (because it's easier to penetrate and disrupt the membrane of gram +ve bacteria than the two membranes of gram –ve bacteria).

*Random question from the doctor: why is Pseudomonas Bacteria more resistance than other gram –ve bacteria? This is because it doesn't have pores which prevent the entry of antibiotics to the inside.

Way of action: These antibiotics attach onto their corresponding receptors on the cell (penicillin binding protein/transpeptidase enzyme) which causes the inhibition of the end stage cross over of peptidoglycan that in turn causes the disruption of the cell wall structure which leads to osmolality instability therefore causing cell burst.

Now we are going to talk about a few antibiotics specifically:

But before let us understand how to classify each type of bacteria:

Gram +ve bacteria: streptococcus + Staphylococcus

Gram –ve bacteria: (we didn't take these yet)

a)E.coli

b) Pseudomonas

c) Enterobacteriaceae (salmonella shigella, Proteus, serratia, Neisseria)

1) Penicillin G (benzylpenicillin) :-

Spectrum: a) gram +ve bacteria except penicillinase producing Staphylococcus Aureus (covers all other streptococcus bacteria though)

b) Neisseria species (ex: Neisseria meningitidis)

Introduction method: Injection (because it is hydrolysed by stomach acidity)

Inhibition by: beta-lactamase

Obvious Toxicity: no, except some allergic reactions in some adults.

*commonly used for: treatment of beta–hemolytic streptococcal pharyngitis (upper respiratory tract infection most common in children" strep throat")

*Remember that we always use the narrowest spectrum antibiotics when we are sure of the microorganism responsible of the infection (after lab tests).

*Penicillin G is considered the narrowest spectrum antibiotic for strep throat.

*but we can't use Penicillin G if we are not sure of the microorganism that caused the condition. (We only use it if we are sure of the microorganism that caused the condition (after the lab test), and the microorganism should be in the spectrum

range of Penicillin G), this is a very important concept and applies on all narrow range Antibiotics so take extra care when understanding it.

Examples that will help you understand: there are 2 case scenarios:-

1) A certain patient came to your clinic with strep throat, the first thing you should be thinking about is all the potential microorganisms that may cause this condition, luckily strep throat is only caused my Streptococcal pharyngitis which is treated by Penicillin G (in this clinical case scenario we use the Penicillin G as an Empirical Therapy and Definite therapy since there are no other microorganisms that cause this condition)

2) A certain patient came to your clinic with meningitis, same technique as before “what are the microorganisms that cause this condition?” Answer: a) streptococcus pneumonia b) Neisseria meningitidis c) H-influenza, second question would be now: “does penicillin G cover all of these microorganisms?” Answer: No, question three “is penicillin G a good Empirical treatment for Meningitis?” Answer is obviously No, why? Because Penicillin G doesn’t cover all the microorganisms.

- Although in this second case Penicillin G wasn’t a good Empirical treatment but it could be the drug of choice as a (definitive therapy) if the lab tests showed that the meningitis was caused by one of the microorganisms covered by the

spectrum of Penicillin G(Neisseria meningitidis or Streptococcal pneumonia).

This is the most important point of the lecture and you should be able to understand how did we reach those conclusions –Dr Malek emphasised on this- and he even said that he might be giving us the spectrum of the drug in the exam but we should be able to understand the steps that we followed to deduce the drug of choice.

In addition, penicillin G is effective against Clostridium tetani (causes tetanus), and Corynebacterium diphtheriae (causes diphtheria), Treponema pallidum (causes syphilis) , and Listeria monocytogenes (causes listeriosis). (Expect a question in the exam about these since dr malek said احفظوهم زي اسمكم) (Those drugs are simply treated only by Penicillin G)

- Usually in clinics or Hospitals you are going to find a Needle called “Benzathine penicillin”, Benzatine is a chemical compound that binds to Penicillin G and results in colloids (which is a homogenous gel like substance) This gel like substance is then administered to the body by an intramuscular injection which is released over a long period of time (21 days approximately.) this is important because this way your extending the half-life of the drug.

Now you may ask why would I need such a treatment?

The answer is simple, usually 2 weeks after streptococcus infections a condition called Rheumatic Fever arises which Is a very critical situation, (if the patients gets infected right after rheumatic fever he will probably die), therefore I prophylact him every 21 days with an injection of this Benzathine penicillin compound to prevent the reoccurrence of rheumatic fever.

This Benzathine penicillin injection could also be used sometimes after the treatment of Strep throat recurrences.
Last note : Penicillin V differs from Penicillin G in that it can be given orally.