Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 27

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SHEET

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Revision:

*Let's have the general big picture of the battle between us human kind and the little microorganisms:

1- FIRST (Narrow) came Penicillin V and Penicillin G to fight against the gram-positive bacteria ,Anaerobic and Gram negative cocci bacteria (At first, we never reveal our most powerful guns against the enemy)

2- NEXT (Moderate) came Methicillins, Flucloxicillin, Oxacillin to fight against penicillinase/B-lactamase resistant bacteria. (The bacteria here became stronger)

3- THEN (Broad) came Ampicillin and Amoxicillin to fight against the tough bacteria → Gram-negative bacteria.

4- FINALLY (Extended) came Pipercillin, Ticacillin (pronounced as "TIGER-cillin"), & Carbenicillin to fight against gram-positive & gram-negative bacteria, pseudomonas (one of the powerful weapons bacteria use against us), and anaerobes.

**IMPORTANT trends to notice here:

1- The more powerful our drugs (weapons) become, the **wider spectrum** it can fight against.

2- As our drugs are having wider and wider spectrums of activity, we **lose the drug's ability to fight B-lactamases/penicillinases**. So, what do we do now? This is exactly where the idea of "formulations" came from. A formulation is combining two chemicals together to achieve a better activity against bacterial infections. For example, the very famous drug Augmentin that is a combo of Amoxicillin and clavulanic acid. Would you expect amoxicillin ALONE to be effective against B-lactamases? No.

1- Penicillin G and Penicillin V:

They are many differences between them. They share so much of the spectrum: mainly gram-positives such as Clostridium Tetani.

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Penicillin V is used orally to treat any infection in the oral cavity. It is the most prescribed drug in dental uses. Ospen, the trade name for penicillin V, is commonly used for children to treat infections in the oral cavity that are caused by Streptococcus Pharyngitis. Obviously, we CANNOT give a child multiple injections of a drug as this is tiring and painful for the little ones, so giving Penicillin G is NOT possible in treating children with pharyngitis. In the case of Ospen, we give 500 mg of the drug 4 times a day for 5-7 days. (Dosing amount and intervals are not required of you to memorize; the doctor just gave an example here)

2- Second generation of penicillins: against B-lactamases.

Unfortunately, we aren't the only ones playing the battle here. Bacteria are becoming resistant to the penicillin drugs. How? By producing penicillinases/B-lactamases. This problem can be solved by introducing B-lactamase Resistant Penicillins: **cloxacillin, Flucloxacillin, Methicillin, and oxacillin** that are well absorbed orally.

We don't fully trust Methicillin here because many bacteria have become resistant to it, like MRSA (Methicillin Resistant Staphylococcus Aureus).

*the bacterial spectrum for methicillin is the same as penicillin G but less potent

3- Third generation of penicillins: against Gram-negatives. (Broad spectrum)

All the above drugs work perfectly against gram-positive bacteria. It's the gram-negative bacteria's turn now. To fight the gram-negative bacteria, we add amide groups to Penicillin to produce a new drug called **aminophylline: amoxicillin & ampicillin.**

Amoxicillin: It is given orally. It is used to treat upper respiratory tract infections. Those drugs are active against Staphylococci, Streptococci and H.influenza. REMEMBER: (SSI) those 3 bacteria are the main cause of **upper respiratory tract infections** such as sinusitis, pharyngitis, tonsillitis, otitis media.

Ampicillin: It is given as injections. Always remember that we give a drug intravenously whenever we have a serious infection. High doses of

Ampicillin can be used to treat **endocarditis**, which is caused by Enterococci. Ampicillin covers many gram-positives such as staphylococci, streptococci, Neisseria, enterococci (like in the case of endocarditis), and Gram negatives such as H.influenza , Neisseria .

Aminopenicillins
(ampicillin, amoxicillin)

Developed to increase activity against gram-negative aerobes

Gram-positive	Gram-negative
pen-susc *S. aureus*	*Proteus mirabilis*
Pen-susc streptococci	*Salmonella,*
viridans streptococci	some *E. coli*
Enterococcus sp.	βL- *H. influenzae*
Listeria monocytogenes	

P.S: Augmentin can also be used to treat upper respiratory infections, which is just a formulation of amoxicillin and clavulanic acid.

In many situations, we use Augmentin to cover bacteria that produce B-lactamases in upper respiratory tract infections, BUT not for children. We don't want to give a child a broad-spectrum drug. We give a narrow spectrum drug. Penicillin V(Ospen) is the drug of choice for children with upper respiratory tract infection. REMEMBER, Narrow*est* is always the b*est*.

Those broad-spectrum drugs are widely used in treatment of upper respiratory tract infection (sinusitis, pharyngitis, tonsillitis, and otitis media) and ALSO in SOME lower respiratory tract infections (pneumonia). Those drugs include Chloram, Germentin (a derivative of

amoxicillin), Augmentin, amoxicillin and ampicillin. They are prescribed empirically.

Can these drugs be active against all lower respiratory tract infections? Of course not. Those drugs are not active against the spectrum of bacteria that cause the lower respiratory tract infections (mainly pneumonia), such as chlamydia, mycoplasma, legionella, and klebsiella.

So when do we prescribe these drugs against lower respiratory tract infections? There's only one case when you can use those drugs (mainly Augmentin) against LOWER respiratory tract infection (pneumonia): in a child less than 4 years of age who does not go to school or to gardens and open spaces. A child that stays at home is not susceptible to getting a lower respiratory tract infection from Legionella, Klebsiella and mycoplasma since these bacteria are acquired in closed spaces such as classes in schools. Now, amoxicillin and Augmentin can be used empirically to treat community acquired pneumonia that is NOT caused by Legionella, Chlamydia, and Klebsiella.

As a summary, Aminophylline (Amoxicillin/Ampicillin) & Augmentin are used against:
1- upper respiratory tract infections
2- Endocarditis
3- some cases of Community Acquired Pneumonia (CAP)

Writer's Note: Obviously, Augmentin and aminophylline are very different in many ways. So, putting augmentin and aminophyllines under the same headline does NOT mean they are the same. This is done only to show you where the roles of augmentin and aminophylline intersect.

Dosing and Resistance:

In treatment against otitis media or upper respiratory tract infections, we don't give a dose of 375 mg/ml of Augmentin like it used to be before. Nowadays due to the new era we live in where bacteria have become very resistant, we give either 650 mg/ml of Augmentin 3 times a day OR 800 mg/ml of Augmentin twice a day. Streptococcus Pneumonia is the main cause of otitis media. We give a larger dose to kill resistant Streptococcus Pneumonia. Augmentin is always the right drug of choice against otitis media no matter how resistant streptococcus pneumonia might get; we just have to increase the dose whenever there is resistance. Let's just hope the bacteria don't become resistant enough to be able to work its way against Augmentin.

Clinical uses of Amoxicillin, Augmentin, & Ampicillin:

Those 3 drugs work on almost the same spectrum[2] (Augmentin is the only one to have an effect against B-lactamases/Penicillinases), so when do we prefer a drug over the other?

Dental Use: In dental cases where we have a patient with endocarditis caused by enterococci, we need to protect him/her from wound infection. So, we prophylact him/her. We give him the narrowest active oral drugs- Amoxacillin and Augmentin (2 grams of drug 2hours prior to surgery).

Hospital/Emergency Use: A patient is admitted to the hospital with endocarditis. Since the case here is very serious and needs to be treated as fast as possible, the drug of choice will be Ampicillin that is given parenteral (injectable) to reach the steady state quickly and save the patient's life.

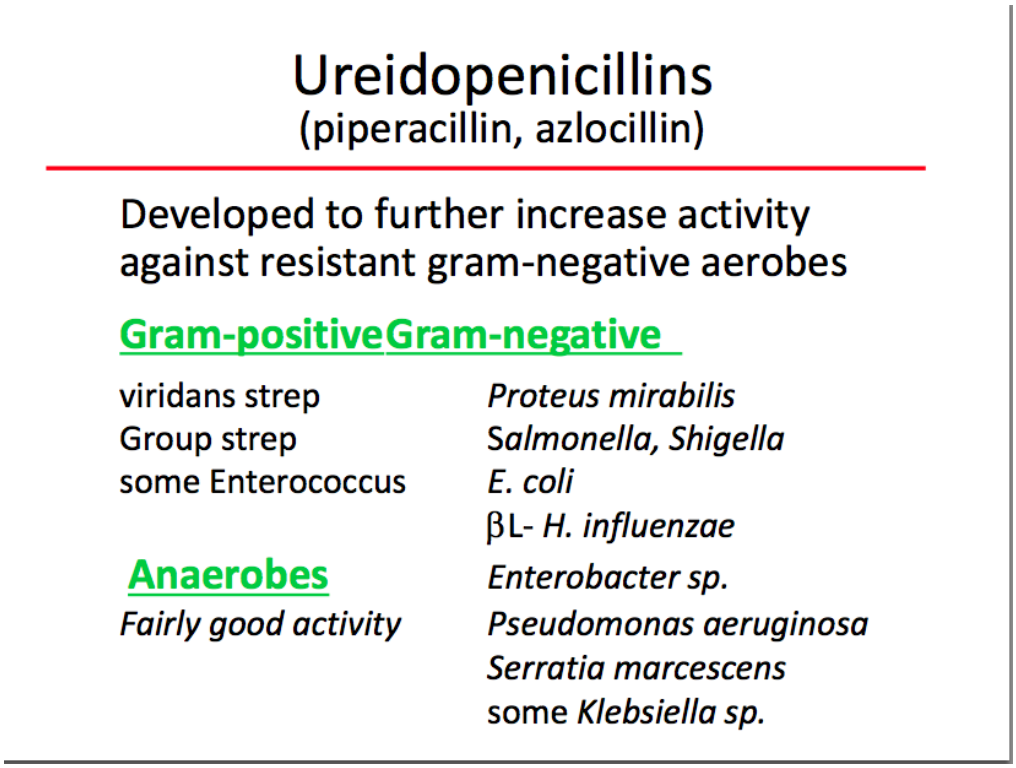
The Extended Spectrum: against Gram-negatives, Pseudomonas & Anaerobes.

Now lets get into the area where we find the dangerous, very resistant bacteria.. the hospital! Going towards the hospital, we find more Gram-negative bacteria; we call them green pus (pseudomonas aureginosa). Can we treat Pseudomonas with Penicillin V, Penicillin G, fluclaxocillin, amoxacillin, nifacillin, ampicillin, and amoxacillin? No, because its not within the spectrum. We need a more powerful drug to fight pseudomonas. Here's where the role of **ticarcillin, carbencillin, and pipercillin** come .These drugs cover gram-positive bacteria, gram-negative bacteria, pseudomonas, and also anaerobes (found in the mouth and intraperitoneal cavity, like Bacteriodes fragilis). These are considered extended spectrum drug due to the large spectrum of bacteria that can be worked on by these drugs. They are not given orally ,because the gut poorly absorbs them. Surprisingly, they do not work against staphylococci that produce B-lactamases. How can we solve this problem? By giving formulations. We combine pipercillin with tazobactam (a suicide inhibitor for Beta-lactamase) to produce tazocin. Problem solved! Now, tazocin will be the best drug to be used against

Gram-negative bacteria, Pseudomonas, anaerobes AND ALSO B-lactamases.

When do we use extended spectrum of drugs? In hospitals where we have nosocomial infections, the main causes of these bad infections are gram-negative bacteria. Where exactly in the hospital? In the ICU (Intensive Care Unit) and CCU (Critical Care Unit, a term used in the UK that has the same meaning as ICU); it is an area of heavy antibiotic use. So, all the resistant bacteria and gram-negative bacteria predominate there. In these special rooms, we are always dealing with life-threatening situations. So, we always give an empirical treatment of extended spectrum of drugs, like pipercillin.

The extended spectrum of bacteria that pipercillin works against are Streptococcus Viridans, Streptococcus Pyogenes, Streptococcus Pneumonia, some Enterococci, some anaerobes, and Pseudomonas Aeruginosa.



Side effects of Penicillin:

1- **Allergy** (or hypersensitivity): 10% of people in Jordan are allergic to penicillin. Mechanism of action: Part of the penicillin will cut and bind to immune cells to produce a hapten that is immunogenic. Our immune cells will then identify any penicillin as something foreign and produce

anaphylaxis along with bronchospasm and hypotension Drug of choice against anaphylaxis is epinephrine.

2- Alterations in the normal flora in the gut that are associated with **Gastrointestinal disturbances** such as diarrhea.
Q) Which one of those drugs -Pencillin G, Pencillin V, Amoxacillin, Floxacillin, Pipercillin- are able to produce GI disturbances (Diarrhea)? The more extended the spectrum is, the more GI disturbance it will cause, like diarrhea. The answer here is "Pipercillin" because the more extended the spectrum is the more the chance to effect the normal flora .

3- all oral penicillin are best given on an empty stomach to avoid **delay of absorption** this will cause a delay to reach steady state because of drug-food interaction. EXCEPTION amoxicillin. For example, you can take Augmentin whenever you want; on the other hand, Penicillin V must be taken only before a meal -on an empty stomach.

*Other side effects that the doctor did not discuss:

-All penicillins, particularly Methicillin, have the potential to cause acute nephritis. (Though Methicillin is not used anymore)

-Neurotoxicity

-Antipseudomental Penicillins (Carbenicillin, ticarcillin & pipercillin) may decrease agglutination.

Cephalosporin:

Introduction:

Cephalosporins come in 4 generations. The 5th generation is also present but still not in Jordan. Cephalosporins are bactericidal and have a very similar activity to Penicillins. It is a **bicyclic dihydrothiaizine ring structure** that includes the beta-lactam ring as one of the cyclic structure and a 6 membered sulfur-containing dihydrothiazine ring. Changes in the R side chains will give changes in spectrum activity. You can notice high heterogeneity within the generations of cephalosporins as not all drugs within the same generation have the same spectrum activity i.e you can have 2 or more cephalosporins from any generation with different spectrum activity. One works against Gram-negative, for

example, and the other does not..
**(Very Important) note: ALL cephalosporin generations are NOT active against enterococci (the main bacteria that cause endocarditis). EXCEPTION: the 5th generation of Cephalosporins (which are not in Jordan yet). Those DO work on enterococci.

Resistance against Cephalosporins is done by extended spectrum B-lactamases , changes in the permeability of the bacterial cell wall toward cephalosporins or by mutation of the target protein (which is the binding site on the cell wall of the bacteria)

1st Generation: Cefazolin & Cephalexin

The most important ones we will discuss are Cefazolin & Cephalexin. Both have the same spectrum activity. They work against methicillin resistant S.aureus ,Staphylococcus Aureus and Streptococcus Pyogenes.
*[If you have noticed, 1st generation cephalosporins are very similar in action to penicillin G EXCEPT that cefazolin and cephalexin are B-lactamase resistant.]

Usages:

I- By dermatologists: Streptococci and Staphylococci are the main causes of skin infections, such as epidermatitis & dermatitis. We have to use an oral drug here so the drug of choice here is cephalexin .

II- II- By surgeons: making a cut doesn't just mean your hurting your patient; you are also making him/her more susceptible to getting an infection from his/her own skin normal flora. How? The human skin is FULL of normal flora, such as staphylococci and streptococci. Making a cut in the skin will increase the chances of any of these bacteria to get into the blood stream to eventually cause an infection (REMEMBER, translocation of Normal flora from its original position to another will cause an infection). That is why hygiene is very crucial for surgeons. The drug of choice here is Cefazolin (1g of it) that is given parenteral. We cannot give oral drug here – cephalexin- because you can't give an oral drug to an anesthetized patient, although both drugs serve the same function.

Why cant we give penicillin V and Augmentin to treat such skin or surgical problems? Pencillin V is not effective against B-lacatamases or

Penicillinase. Augmentin works on broad spectrums of bacteria, and as we know, we always try to avoid such drugs because they disrupts the normal flora homeostasis in the body .

2nd Generation: Cefuroxime/Cefoxitin/Cefotetan

They have greater activity against three additional Gram negative bacteria :H.influenza , Neisseria ,Enterbactor erogenes It is divided into groups (A & B):

A. Cefuroxime: Close brother to Augmentin. It is active against Streptococci, staphylococci, and H.influenza. This drug can be used to fight off upper respiratory tract infection like sinusitis, tonsillitis, pharyngitis and otitis media .

Cefuroxime is used to treat community acquired Pneumonia because its active against B-lactamase producing H.influenza , K.pneumonia ,streptococci pneumonia .

Can we give cefuroxime to treat endocarditis that is caused by enterococci? No, because ALL 4 generations of cephalosporins do NOT work against enterococci.

B. Cefoxitin and Cefotetan: work against streptococci, staphylococci, H.influenza AND Bacteroides Fragilis (anaerobic bacteria found intraperitoneally).

In intra abdominal surgeries, we have to be careful of the anaerobic bacteria (B. Fragilis). To prophylact a patient during colorectal surgery for example, we give 2nd generation of cephalosporins (cefoxitin/cefotetan) to prophylact the patient against skin normal flora (streptococci and staphylococci) AND ALSO against anaerobes that are found intraperitoneally (B. Fragilis). We don't give 1st generation of cephalosporins (cefazolin) as a prophylactic before Abdominal surgery because they are NOT active against Anaerobes.
examples about intraperitoneal infections include peritonitis and diverticulitis .

P.S the drugs given prior to surgery for prophylactic purposes are administered **intramuscularly**.

Student Question : do we use cefuroxime to treat Urinary tract infection ?

We did use it 10 years ago but we stopped using it now because E-coli has developed resistant against them .

By your colleague, Dana Khlayfat
Your feedback would be highly appreciated.

Best of Luck!