



☒ Sheet

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RECAP

During the previous lecture we have talked about the antibiotic Penicillin G. We went through the spectrum of species it covers, which are represented by Gram positive bacteria mainly streptococci; however, gram positive species such as staphylococcus Aureus have produced an enzyme (β -lactamase or Penicillinase) that inhibits the drug, in which excluded the staph out of the spectrum. It also covers some gram negative species such as Neisseria meningitides.

Penicillin G is not a good drug of choice for empirical treatment; instead it is used definitively most of the time due to its narrow spectrum. The only case that we use penicillin empirically (and can be definitively) is strep throat because it's caused only by streptococcal pharyngitis; which is covered by penicillin G. While in other cases of meningitis we can't prescribe the drug unless the cultures sent from the lab indicate that the meningitis is caused by one of the species that Penicillin G covers.

It is also used to prophylact the patient from Rheumatic fever which usually arises two weeks after streptococcus infection. The drug is combined with Benzatin to increase its half-life, so it's injected every month or 21 day to prevent the recurrence of the fever.

Now we will talk about naturally occurring penicillin (Penicillin V) that is very similar to penicillin G.

Differences between Penicillin G and Penicillin V:

1. Penicillin G cannot be given orally since it is susceptible for hydrolysis in the stomach due to the acidity, so it's not practical to inject the patient each time. The need for a new drug that can act as Penicillin G and be given orally grew, and the new drug is the acid stable Penicillin V.

The main difference between Penicillin G and V is that Penicillin V can be given orally while the other can't. (100mg of Penicillin V is given 4 times a day).

2. Another small difference is in the spectrum of species that both antibiotic cover. Penicillin G and V are actually very similar in their spectrum. Penicillin V covers most of the species Penicillin G does, in addition to **the oral anaerobes** which cause odontogenic infection. So the new Penicillin covers Streptococcus species, Neiceeria, and Oral anaerobes. Those anaerobes cause odontogenic infection, which means infection under the teeth or salivary gland or any infection near the odontogenic region (generally, infections in the mouth). Consequently, **Penicillin V is the most frequently prescribed antibiotic for oral infections caused by bacteria within the mouth.** Penicillin G is not very active against those bacteria, so Penicillin V is the best drug of choice. Another thing to point out is that the treatment of oral infection can be achieved by many drugs, but Penicillin V is used as it has the narrowest spectrum so it has minimal side effects,

and the doctor here emphasized on the importance of refraining from using broad spectrum drugs. Penicillin V is also used when Penicillin G is not available; as in our case in Jordan.

So, if we want to treat strep throat we have two choices:

1. Penicillin V through oral route.
2. Penicillin G (1.2 million units) through injection.

As we have seen before, staphylococcus species haven't been covered neither by Penicillin V nor G; rather drugs known as β -lactamase-resistant Penicillins are used. The degradation of normal Penicillins by the naturally occurring β -lactamase is a common problem; however; pharmacists used β -lactamase inhibitors like clavulanic acid and administered it with the drug and it was a successful approach. But here we want to focus on the β -lactamase-resistant Penicillins that are **intrinsically resistant** against this inhibition.

Examples of these drugs include:

1. Cloxacillin
2. Flucloxacilin
3. Oxacillin (only memorize Oxacillin)

Those drugs are well-absorbed **orally** and have similar spectrum to Penicillin G. Methicillin also belongs to this family of drugs, but it was withdrawn from the market only after a small period after its release; as it is nephrotoxic because it causes tubular necrosis, noting that Methicillin was the first drug to be introduced to the market as β -lactamase resistant Penicillin.

Staphylococcus bacteria developed throughout the time and mutated itself against the Methicillin; hence it **mutated the binding pocket for Penicillin which is the Penicillin binding protein**. This mutation produced the MRSA (Methicillin Resistant Staphylococcus Aureus) which is a very dangerous bacteria and it's known as the nightmare for many doctors. The cases of infection with MRSA increase at an alarming rate during wars, as it's mostly present in wound infections.

Clinical application:

- **Skin infection is only caused by the action of Strep and Staph.** So if I'm a doctor and I want to treat a patient with skin infection empirically can I use Penicillin V or G? The answer is no since it doesn't cover staph. I should use β -lactamase resistant Penicillins (Oxacillin/ Cloxacillin/ Flucloxacilin). Those drugs already cover the strep and we enhanced them to cover the staph. Moreover, if I receive the culture from the lab and it indicates that the skin infection is caused by Strep I should prescribe Penicillin G and it is known as **definitive therapy** because it has narrower spectrum.

Broad spectrum Penicillins:

Upper respiratory tract infections are caused by several types of infections; which are sinusitis, otitis media and tonsillitis. **Augmentin** is the drug of choice to treat upper respiratory tract infections since it covers all the causes listed formerly. It is used to treat otitis media especially in children, and also tonsillitis. Those infections are caused by 3 microorganisms which are:

1. Streptococcus pyogenes
2. Streptococcal pneumonia
3. H influenza (G-ve)

H influenza is different than Influenza A or B which causes viral infection. It is a bacteria involved in triggering all the types of infection in the upper respiratory tract in addition to meningitis. Augmentin belongs to the family of broad spectrum Penicillins, it covers H influenza within its spectrum. Augmentin also covers the Gram positive bacteria, and extra gram negative bacteria than the normal Penicillins.

The broad spectrum family includes Ampicillin which is poorly absorbed orally (should be given intravenously or intramuscularly), and also Amoxicillin which is very well absorbed and can be given orally (Both of them are known as Aminopenicillins). Amoxicillin is a prodrug for ampicillin; therefore whenever it's administered it becomes Ampicillin, so eventually they are the same drug. Their antibacterial spectrum is the same as for Penicillin G plus some Gram-negative bacteria as they have an enhanced ability to penetrate the G-ve outer membrane. The spectrum consists of:

1. Gram positive:

- I. Penicillin-susceptible Staphylococcus Aureus (pen-susc S. aureus): This represents only 1-3% of the species since most of the staph species are resistant to Penicillins.

Note: susceptible mean that they don't produce β -lactamases.

- II. Pen-susc streptococci which represents most of the Streptococcus species since Penicillin covers most of them.
- III. Viridans streptococci
- IV. Enterococcus sp.

2. Gram Negative:

- I. H Influenza

The Penicillin that covers all the species of bacteria mentioned above is used to treat upper respiratory tract infections. Augmentin is the most prescribed antibiotic in the world, as it covers all the species mentioned above so can be used in every case of respiratory infection (sinusitis, otitis media, Tonsillitis, and also lower respiratory tract infections). This treatment is classified as empirical as it covers all the causes. Doctors initially (empirically) prescribe Augmentin for upper respiratory tract infections, and if they receive the culture from the lab and it indicates that the infection is caused by streptococcus they stop Augmentin and prescribe Penicillin V or G (definitive therapy). This is the ideal scenario that should take place, but doctors usually use Augmentin alone in such cases without referring to the culture.

Staphylococcus Aureus plays a very minimal role in the upper respiratory tract infections, as it causes only 1-3% of the cases. Doctors usually prefer to cover all the causes without any exception, so they favor using Augmentin (Amoxicillin is not given alone as it's not resistant against the staph; instead it is given with a suicidal inhibitor for penicillinase known as clavulanic acid (suicidal inhibitor for penicillinase) and this is known as Augmentin). Theoretically, Augmentin can be used to treat skin infections, but they are not the drug of choice (β -lactamase-resistant Penicillins should be used).

- What is the difference between Augmentin and Amoxicillin?
Augmentin is Amoxicillin with clavulanic acid to inhibit Penicillinase and β -lactamase produced by Staphylococcus Aureus.
- What is the difference between Amoxicillin and Ampicillin?
Ampicillin is poorly absorbed orally so it should be given IV or IM, while Amoxicillin can be given orally. Besides, Amoxicillin is the prodrug for Ampicillin.

In general, Enterococci (gram positive) cause endocarditis which is an inflammation within the walls of heart and is manifested by abnormal heart valves. Another cause of endocarditis is the Staphylococcus Aureus. The treatment of endocarditis (empirically and prophylactically) is achieved using broad spectrum Penicillins (Aminopenicillins). Endocarditis is a life threatening situation so we should inject the patient with Ampicillin rather than giving it orally since it's faster. If we are scared of the presence of staphylococcus Aureus, we can inject Ampicillin with tazobactam which is an inhibitor for the Penicillinase because clavunlic acid cannot be injected while tazobactam can.

We are currently living in the era of dangerous Streptococcal Pneumonia (cause upper respiratory tract infection and it's the main cause of otitis media) resistance. The bacterium is not completely resistant against the Aminopenicillins, but it has developed "Mid resistance" as

the doctor mentioned. The solution in this case is to increase the dose, so if the MIC (Minimum inhibitory concentration) for Augmentin was 10mg; we should increase it to 15 or 20. If the new MIC is 60 or 70 this means that Streptococcal Pneumonia is very resistant in this case. By increasing the dose we kill more microorganisms, so if we kept the dose constant and Streptococcal Pneumonia mutated itself then the treatment is **sub-therapeutic**. Another solution for this resistance is to give Augmentin more frequently with lower doses in order to establish a steady state, but this is not the chosen approach in most of the times since it takes a longer time.

Extended spectrum Penicillins:

All the drugs we have mentioned before (Penicillin V and G, β -lactamase resistant Penicillins, Aminopenicillins) are community drugs which mean that they are used by individuals. Hospitals are special environments where we need drugs different than the community drugs to deal with special species present there. The drugs to be used are known as extended spectrum Penicillins such as Ticarcillin. The main two species that cause problems in the hospitals are MRSA (G+ve) and pseudomonads. Extended spectrum Penicillins can help minimizing the threat by covering pseudomonads but not MRSA.

The antibacterial spectrum for the extended spectrum Penicillins is the same as broad spectrum Penicillins plus pseudomonads. The spectrum includes most Gram positive; strep, staph if clavulanic acid is added (if they produce β -lactamase), enterococci and anaerobes. It also covers Gram negative bacteria; most importantly pseudomonads and H influenza. MRSA is not covered by the extended spectrum Penicillins which forms an additional challenge for the doctors.

The End