Medicinal Chemistry
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Anti-Bacterial Agents-1

Welcome back, in the past several weeks, we have looked at various aspects of drug discovery. So, we have looked at how to optimise the target drug interaction by, you know, doing structure activity relationships, we have looked at how to develop assays for testing the efficacy of a molecule. We have looked at how to generate libraries of molecule. So, for example, just recently we were looking at combinatorial chemistry which produces mixtures of compounds.

We have also looked at parallel synthesis, which gives us your material but fewer number of compounds and of course we have looked at natural products as sources of drugs. And, so all of these gives us a very strong foundation about how to carry out drug discovery. So, in the next 2 or 3 weeks, what we will focus on is to divide the drug discovery in terms of the diseases. So, the major diseases that we are going to encounter in terms of drug discovery are basically bacterial infections. So, as we are all familiar, bacterial infections are something that affects nearly everyone.

And, so there are a lot of antibiotics that are available for treating such infections. And so the 1st topic that we will take up is antibacterial agents. And then we will look at anti-viral agents and as we perhaps are familiar with, viruses are again very common and there are actually very few drugs available for viruses but we will look into these aspects of how anti-viral drugs have been discovered. Which will be followed by another major disease which affects nearly everyone, which is cancer.

So, cancer is a situation where there is, you know, uncontrolled proliferation of cells and therefore it presents a major challenge because there is a lot of similarity between cancer's and human cells. So, we look at various aspects of anti-cancer drugs. And lastly we will look at all the cholinergic and adrenergic, which are important in various diseases including cardiovascular diseases and all that. And finally we will look at quantitative structure activity relationships, which is basically one of the attempts to model a structure activity relationships, but to construct equations which show the various aspects of properties of a drug versus its activities.

Now, what we will do is we will start with antibacterial agents, so we will present the major classes of antibiotics and how they were discovered, what is the mechanism of action. So, this part of the course will be handled by Anand.

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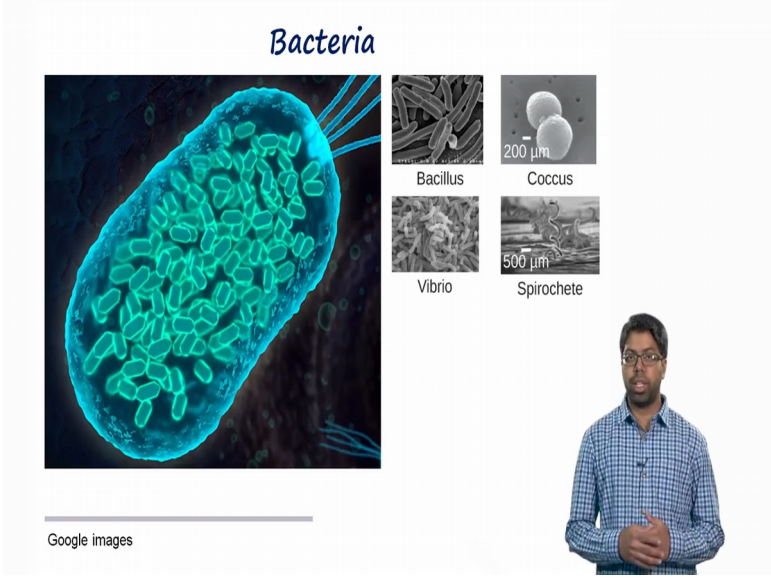

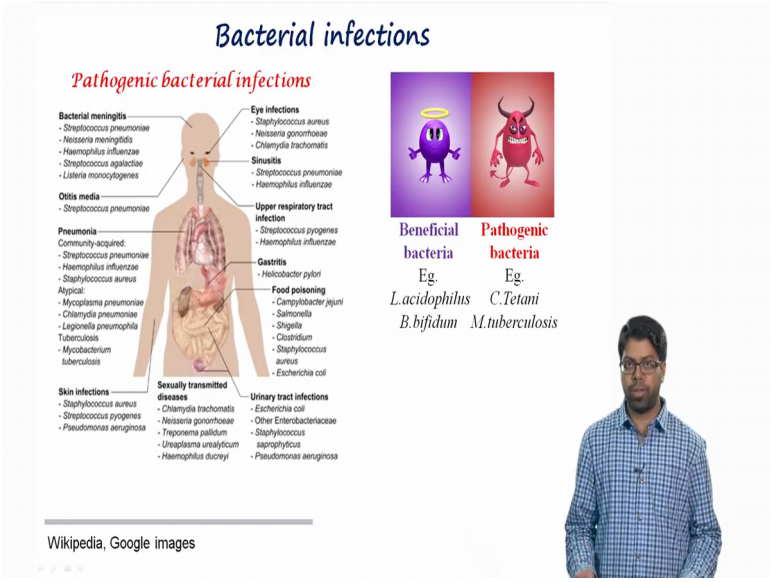

As you are now familiar with various concepts in our medicinal chemistry course, let us take it to the next level, where we are going to deal with one of the well prescribed, known class of drugs called as antibiotics that targets the bacterium. We live in a world filled with bacterium, these are so tiny organisms that we cannot see them to our naked eye. But they are there and they are literally everywhere. Actually bacteria are not all bad, there are many good bacteria which is responsible for digesting the food in your gut, there are bacteria which are helpful in making medicines, there are bacteria which are essentially for making dairy products which some of you may like to eat.

Believe it or not, there are billions of good bacteria cells in our body, without which you would not be able to survive today. But there are a handful of bad bacteria as well. And they are called as pathogenic bacterium. And they are responsible for many pathogenic infections. They are more like they want to multiply by number and use your body to spread infections into an environment. So, that is basically what they do. So, there responsible for all these infections. Fortunately these pathogenic bacteria can be knocked out from your body by the so-called fantastic drugs known as antibiotics.

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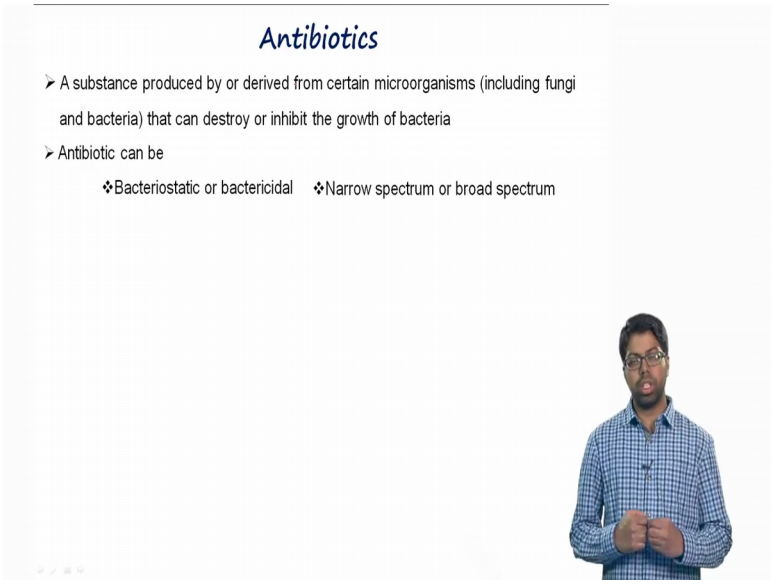

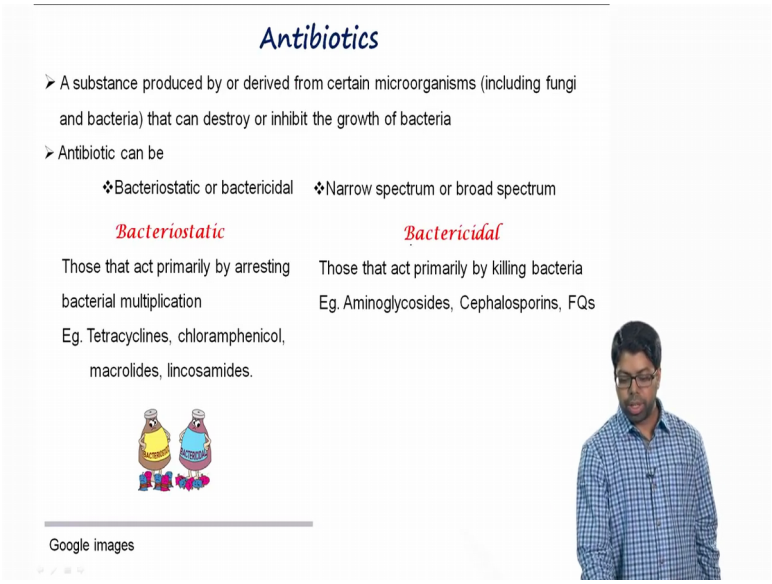

The word antibiotic literally means against life. So, the goal of the antibiotic is either to kill the bacterium or it is going to inhibit the growth of bacterium. So, these antibiotics can work in either way. So, they might be called as bacteriostatic antibiotic or bactericidal antibiotic. Here the bactericidal antibiotics are those which are going to kill the bacterium. If you see the suffix cidal means kill. There are some antibiotics which bactericidal antibiotics like aminoglycosides, cephalosporins and floropinols.

But there is another group of antibiotics called as bacteriostatic antibiotics. Here the suffix static means staying stable. So, in these bacteriostatic antibiotics, bacteria do not die, but they cannot grow or replicate either. For example tetracyclines, chloramphenicol, macrolides and

lincosamides, all these are bacteriostatic antibiotics. There is another class of antibiotic, which can be differentiated on the terms of spectrum of activity.

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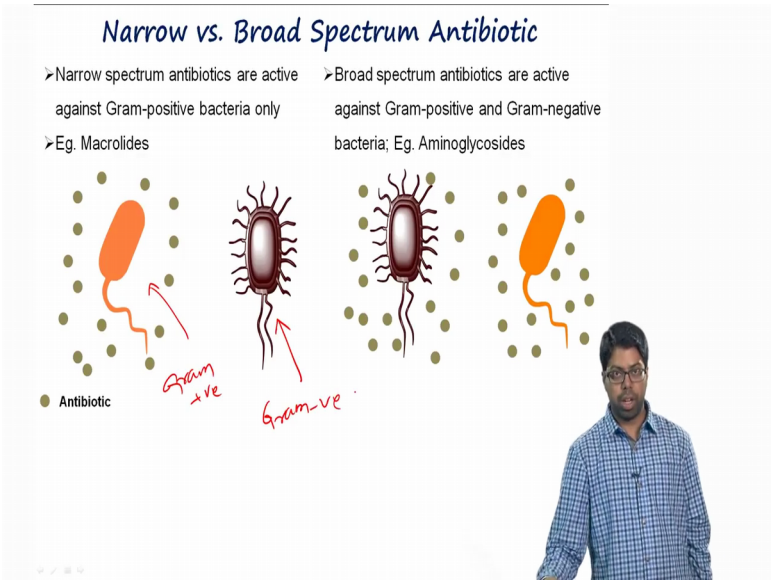

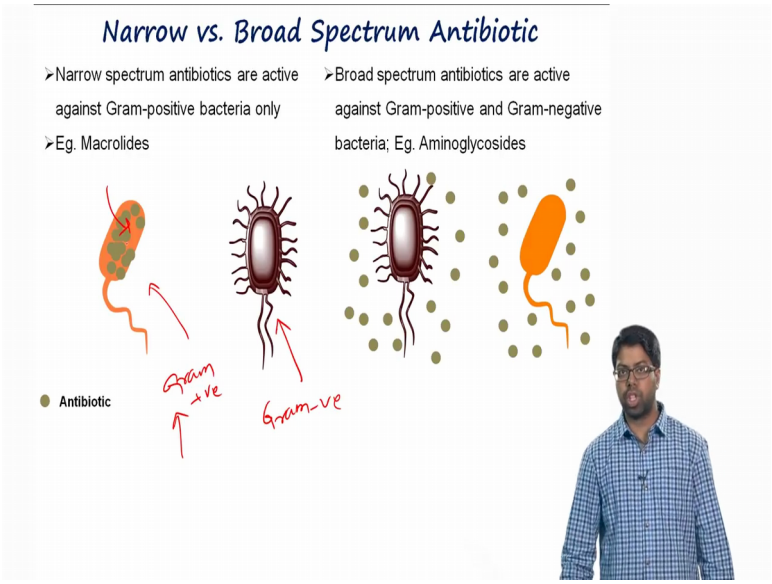

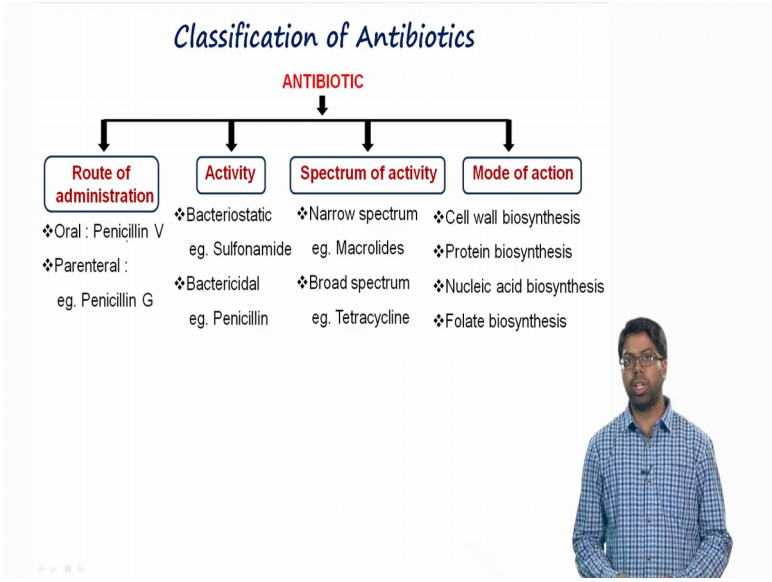

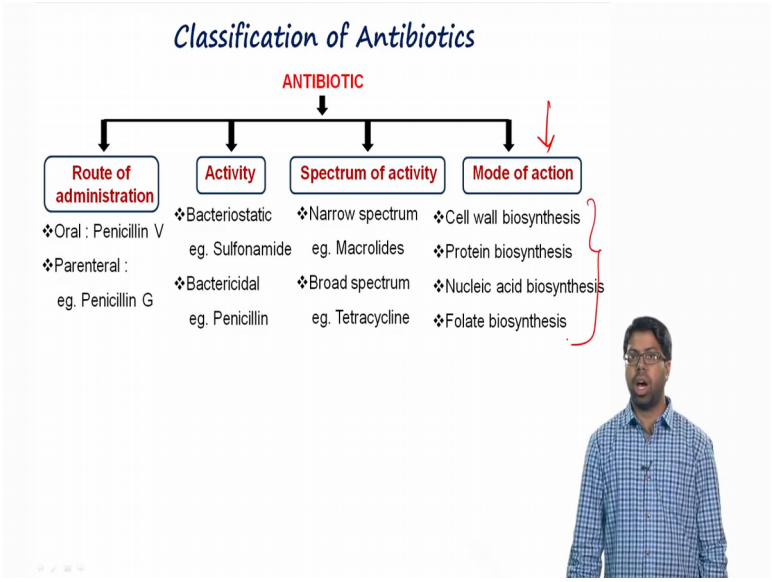

For example, they are antibiotics which are highly effective against gram positive organisms. Here, in this cartoon, this is a gram positive bacterium and this is an example of gram negative bacterium. Do not bother about the terms of gram positive and gram negative for the time being, we will discuss in detail in the next couple of minutes, but for the time being, please do remember there are some antibiotics which are highly effective against these gram positive organisms, because they have very simpler cell wall structure.

So, these antibiotics can easily get inside the gram positive bacteria look. For example, macrolides is an spectrum antibiotic, which is only effective against gram positive organisms. There are some antibiotics which can kill both gram positive as well as gram negative organisms, for example aminoglycosides. Other than these classifications, there is another major classification of antibiotic based on the route of administration. For example there are

some antibiotics which cannot be taken via oral route, the reason is they are susceptible to acid that is present in the stomach.

And therefore these antibiotics will undergo degradation. So, in such cases these antibiotics must be entered through intravenous route of administration, where you can interact the given antibiotic directly inside the vein so that it can reach inside the bloodstream. Penicillin V is one of the example of orally active antibiotic, that means you can given the form of a tablet and it can be a can via oral route. Penicillin G must be given via intravenous route of administration, because it is highly susceptible to stomach acid.

And now you are familiar with the classification of antibiotics based on bacteriostatic or bactericidal antibiotics. Again these antibiotics can have either narrow spectrum of activity, that is they are highly effective only against gram positive organisms and other one is broad-spectrum acrobatics, where they are effective against both, gram positive and gram negative organisms. But basically each antibiotics have their unique mode of action. Ultimately the job of the antibiotic is to kill the bacteria or it is going to inhibit the growth of bacteria.

And this can be done via these different mode of action. Some antibiotics are going to inhibit the cell wall biosynthesis, some are going to target nucleic acid biosynthesis, some are going to target protein biosynthesis and some are going to affect the metabolic pathways of the bacteria. In this lecture we will be mostly focused on how these antibiotics are going to kill the bacteria or inhibit the growth of bacteria by these unique mode of actions.

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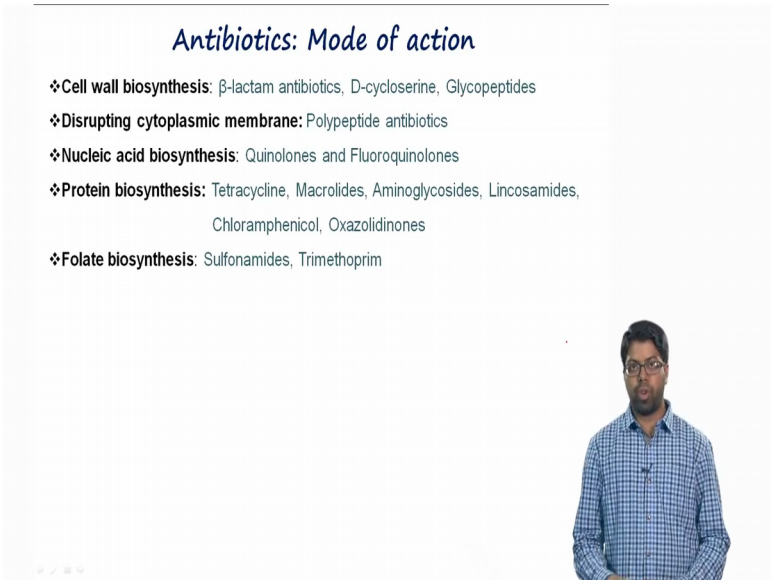
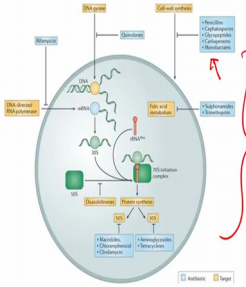


Antibiotics: Mode of action

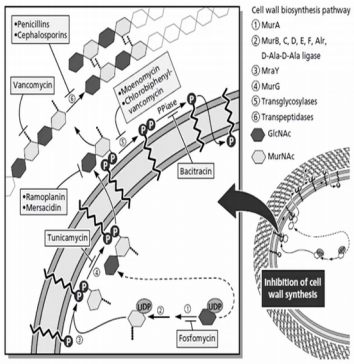
- **Cell wall biosynthesis**: β-lactam antibiotics, D-cycloserine, Glycopeptides
- **Disrupting cytoplasmic membrane:** Polypeptide antibiotics
- **Nucleic acid biosynthesis**: Quinolones and Fluoroquinolones
- **Protein biosynthesis:** Tetracycline, Macrolides, Aminoglycosides, Lincosamides, Chloramphenicol, Oxazolidinones
- **Folate biosynthesis**: Sulfonamides, Trimethoprim



Lewis, K. *Nat. Rev. Drug Discov.* **2013**, *12*, 371–387

Kill bacteria (or) growth of bacteria

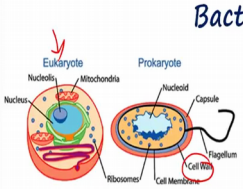
Antibiotics targeting cell wall biosynthesis



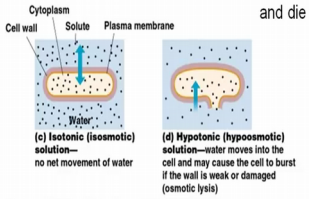
Cell wall biosynthesis pathway
① MurA
② MurB, C, D, E, F, Alr, D-Ala-D-Ala ligase
③ MraY
④ MurG
⑤ Transglycosylases
⑥ Transpeptidases
GlcNAc
MurNAc

Walsh, C. *Antibiotics: Actions, origins, resistance*, 2003; p 22.

Bacterial cell wall



- Cell walls make good targets for Antibiotics
- Bacterial cell walls are rigid structures that form a protective layer around the bacterial cell and help them to resist the effects of osmosis
- Without an intact cell wall, bacteria would burst and die



(c) Isotonic (isosmotic) solution— no net movement of water

(d) Hypotonic (hypoosmotic) solution—water moves into the cell and may cause the cell to burst if the wall is weak or damaged (osmotic lysis)

Google images

This is again a broad classification of all the antibiotics according to their mode of action. As I already mentioned to you, there are some antibiotics which target the cell wall biosynthesis, for example the beta-lactam antibiotics and like glycopeptide antibiotics. Polypeptide antibiotics is an example that disrupts the cytoplasmic membrane. Quinolones and fluoroquinolones is another class of antibiotics that target the new click acid biosynthesis of the bacteria.

Majority of the antibiotics are going to target protein biosynthesis, such as tetracycline, macrolides, aminoglycosides, chloramphenicol, etc. Very few antibiotics target the metabolic pathways, such as folate biosynthesis. So, this is a graphical abstract which tells how each antibiotics have their unique mode of action and ultimately they are going to either kill the bacterium or inhibit the growth of bacterium. Now let us continue with the topic on the antibiotic that target the cell wall biosynthesis.

So cell walls are very good targets for antibiotics, because bacteria need them for their survival and our cells do not even have them. So, let us briefly review what these bacteria cell walls are. So, bacteria cell walls are very tough and rigid structures that form the protective outer layer on the bacteria cell and it helps them to resist the effects of osmosis. Remember the term osmosis is the tendency of water to flow across the membrane in such a way to balance out the number of Salute molecules on either side.

Without this bacteria cell wall, cell loses its rigidity and bacteria would burst and die due to osmotic stress. Different bacteria have different cell wall structures, just like the outside of buildings can have many different designs but still fulfill the same purpose. That is keeping the outside separate from the inside and protecting the inhabitants from an environment that is sometimes hostile.

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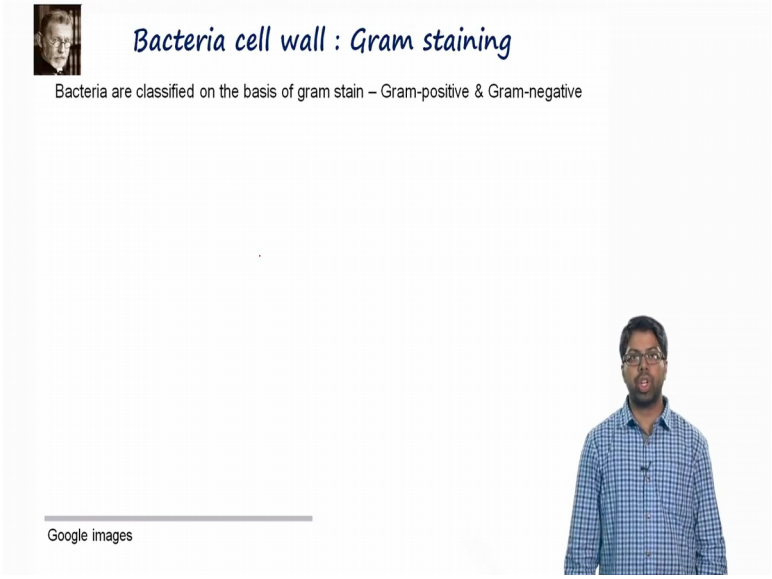

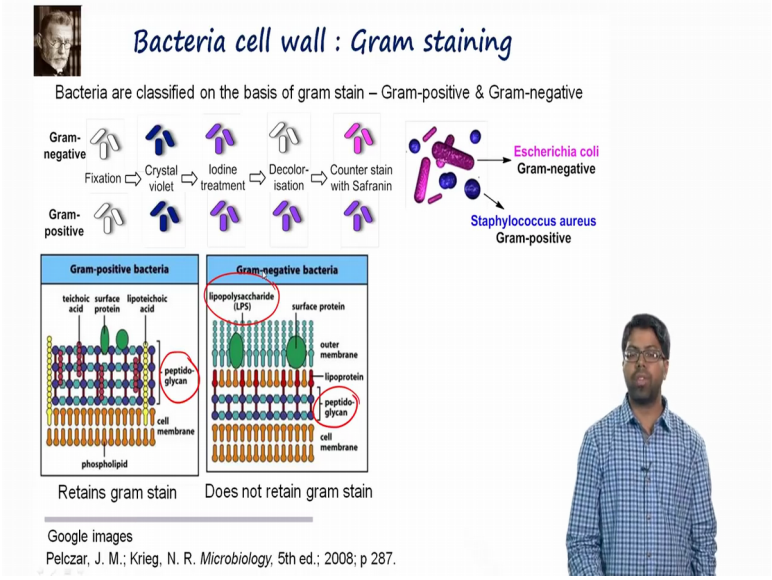

Danish scientist Hans Christian Gram developed a strategy to differentiate the different types of bacteria based on their structural differences in the cell wall. In this test, the gram positive bacteria retains this crystal violet die and that is why they are going to appear in the microscope as violet colour. One such example of gram positive bacteria is Staphylococcus aureus. In contrast, gram negative bacteria do not retain the crystal violet die, instead they are stained by the counter stain called their saffranin red and that is the reason why they appeared in pink colour in the microscope.

E. coli is one such example of this gram negative bacteria. Now, what is the basic difference between this gram positive and gram negative bacteria? The only difference is on the basis of this cell wall structure. So, in case of gram positive bacteria, they have a very thick layer of

peptidoglycan, which is again a molecule that is made up of sugars and polypeptides, which farms are very rigid mesh like structure that protects the bacterial cell. Gram negative bacteria also has a peptidoglycan layer but this is very thin layer, that is sandwiched between 2 membranes.

In addition, the outer membrane of the gram negative bacteria contents are component called as lipopolysaccharide, which further adds to the complexity of the gram negative bacteria cell wall. Due to the presence of this additional complex barrier, it is very challenging for the antibiotics to target the gram negative bacteria. Now, if you recall I mentioned about 2 terms of antibiotics, which is nano spectrum antibiotic and broad-spectrum antibiotics. I told you that nano spectrum antibiotics are highly effective against gram positive organisms because the cell wall structure is very simpler, so the antibiotic can easily get inside the gram positive bacterial cell.

But in case of gram negative bacteria, because of the presence of the lipopolysaccharide, many antibiotics are unable to penetrate the gram negative bacteria and there were the antibiotic which can target both gram positive and gram negative bacteria, they are called as broad-spectrum antibiotics. As you are familiar that the cell walls are the perfect target for the antibiotic, now what do these gram positive and gram negative bacteria cell walls have in common? It is peptidoglycan. So, let us look at the structure and biosynthesis of peptidoglycan.

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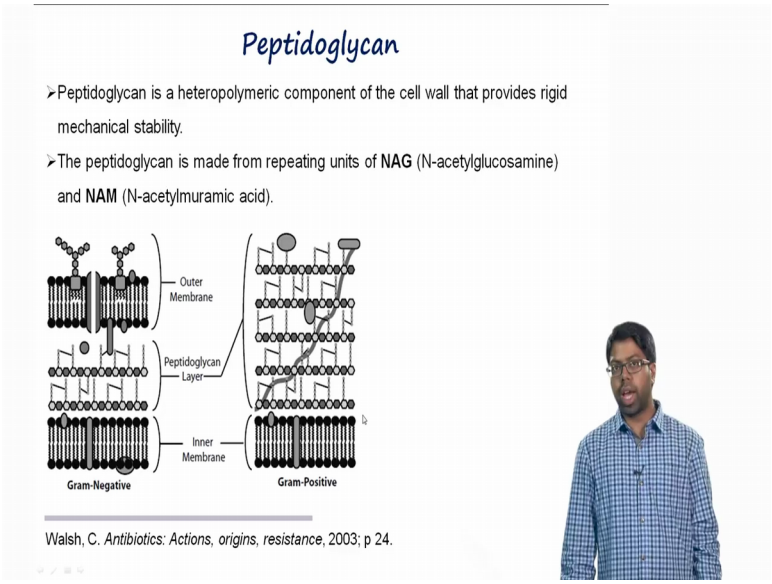

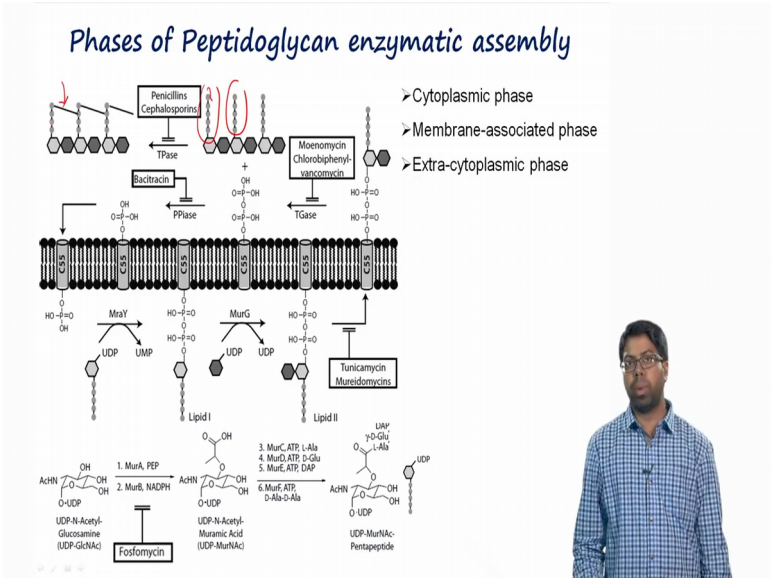

But before that, let me remind you that peptidoglycan is made up of of repeating units of N acetylglucosamine, which is abbreviated as NAG and N acetylmuramic acid or NAM for short. Let us quickly look at the biosynthesis of peptidoglycan. Peptidoglycan is Bio synthesised in 3 phases. The 1st phase is called cytoplasmic face. So, here is the cytoplasmic phase, then these components, must be about synthesised in the cytoplasm, that are located from the cytoplasmic side to the periplasmic side and this is called as the membrane associated phase.

Once these components are cars located to the periplasm, they are added to the precursor of cell wall components and that is how they are going to assemble the cell wall structure. And this is called as the extra cytoplasmic phase. In case of the cytoplasmic phase, if you recall, I already mentioned you that peptidoglycan is made up of N acetylglucosamine and N acetylmuramic acid. So, obviously this UDP N acetylglucosamine is converted to A UDP N acetylmuramic acid by a presence of enzyme called as mode A enzyme.

Once the UDP N acetylmuramic acid is being formed, the penta peptide chain is added to this and this leads to the formation of UDP N acetylmuramic acid Penta peptide. And this is just a cartoon representation of that Penta peptide chain. This whole process is carried out by a series of enzymes, which belongs to mode family, from mode A to mode F, so this is the cytoplasmic phase. Now, here if you see, it has a UDP component added has a sugar molecule attached to it, because of which it is highly polar and hydrophilic.

Now, the thing is it has to be task located from the cytoplasmic side to the periplasmic side and which cannot be done without the help of any lipid. So, here in this case, the lipid which

helps in cars locating this component from the cytoplasmic side to the periplasmic side is C 55 lipid phosphate. So, what actually happens is the C 55 lipid phosphate attacks on the pyrophosphate linkage of this UDP N acetylmuramic acid Penta peptide in the presence of an enzyme called as MRAY, believing this UMP and forming a new pyrophosphate bond between the C 55 lipid phosphate and the UDP N acetylmuramic Penta peptide.

This is the 1st lipid intermediate that is being formed that this is called as lipid 1. Then this is followed by addiction of UDP N acetylglucosamine component to this lipid. This results in the formation of another liquid intermediate called as lipid 2. This processor is carried out by an enzyme called as mode G. Now, once this lipid 2 is formed, it is staff located from the cytoplasmic side to the periplasmic side and this is carried out by an enzyme called as translocase enzyme.

No definitive evidence for this enzyme is yet available, once it is being translocated to the periplasmic side, then it becomes a subject for many membrane-bound enzymes such as trans glycosylase, trans peptidase, etc.. So, here this trans glycosylase cleaves this bond and releases this C 55 lipid pyrophosphate and peptidoglycan component. If this cycle is to happen again, this C 55 lipid pyrophosphate must be converted to C 55 lipid phosphate. This pyrophosphate bond is cleaved in the presence of an enzyme called pyrophosphatase.

Then again the C 55 Leopard phosphate is recycled, so that this process can happen again and again. Here, whatever the Penta peptide chains are there, so the Penta peptide chains are extensively cross-linked by an enzyme called as trans peptidase enzyme. This process of excessive cross-linking continues until it forms a very rigid mesh like structure of cell wall. This is the whole process how the peptidoglycan components are being my synthesised and transported from the cytoplasmic side to the periplasmic side.

Antibiotics inhibit the cell wall synthesis by targeting any of these steps. For example, phosphomycine is an antibiotic which inhibits this cytoplasmic phase by inhibiting the conversion of UDP N acetylglucosamine to N acetylmuramic acid. There are some other antibiotics like tunicamycin and muridamycin, that are going to inhibit the translocation enzyme. Majority of the antibiotics that inhibit the cell wall synthesis either target the trans glycosylase or trans peptidase enzyme. For example beta-lactam antibiotic like penicillin, cephalosporin, there are going to target the trans peptidase enzyme.

There is another class of antibiotic called as basicrasin which targets this pyrophosphatase. As you are familiar with the biosynthetic pathway of the peptidoglycan component, let us look at the molecular structure of peptidoglycan.

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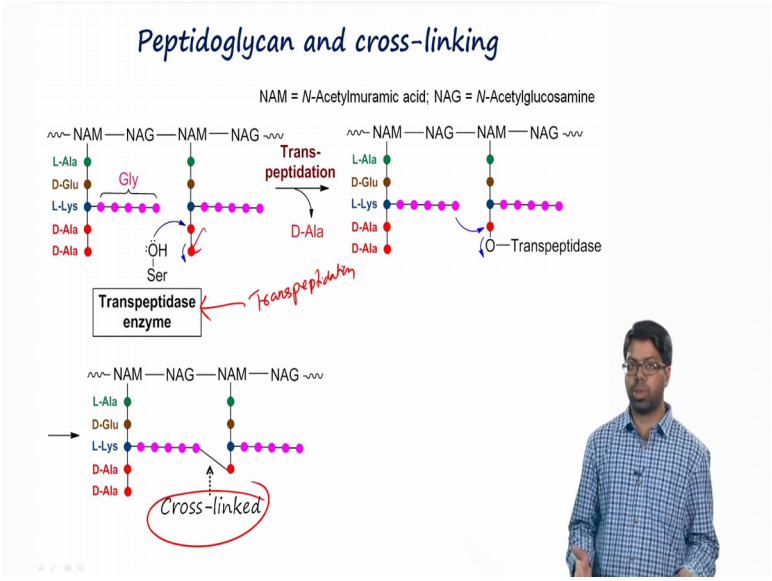

So peptidoglycan is made from N acetylglucosamine and N acetylmuramic acid but it has a Penta peptide unit chain attached to it. And this Penta peptide contains amino acids such as L aluminum, D glutamic acid, L Lysin, D alanine and D alanine, this is the composition of peptidoglycan component in gram positive bacteria. For example, Staphylococcus aureus. But in case of gram negative bacteria, acid of this L lysin, they will have mesodiamino pymelic acid.

This is the only difference between the peptidoglycan component of gram positive bacteria with respect to gram negative bacteria. It is interesting to note the presence of D amino acids in this chain. In human biochemistry, there are only L amino acids, but in bacterium, there is an enzyme called (())(17:22) which can convert the L amino acid into the D amino acid. In the final step of cell wall biosynthesis, the 2 peptide chains are cross-linked and this occurs due to the displacement of one of the D alanine unit from the chain by the glycine unit of the other chain.

And this whole process is called as trans peptidation reaction. And this is carried out by an enzyme called as trans peptidase enzyme. Due to presence of this transported in enzyme, there is extensive cross-linking between the peptide units of the peptidoglycan components and that is how it forms a rigid, mesh like structure on the bacterial cell. And it helps them to

resist the effects of osmosis. Let us try to understand the mechanism of trust peptidase enzyme.

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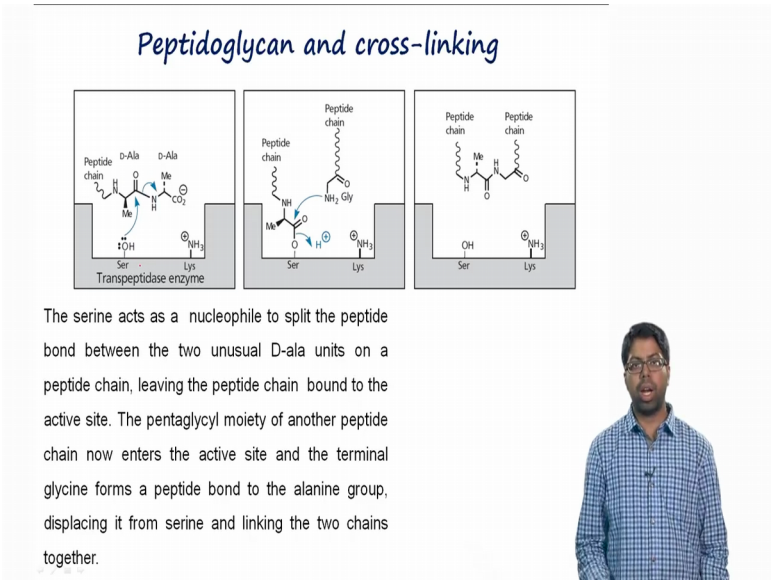

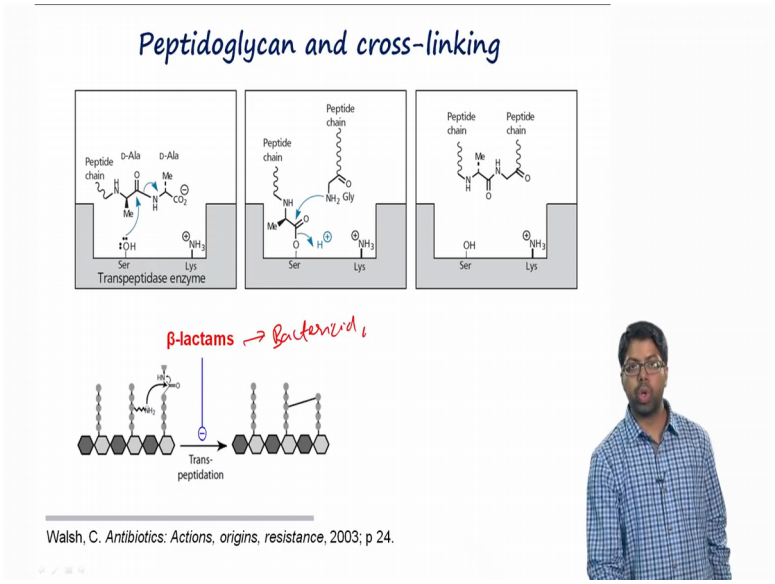

Here is the transcript today's enzyme is an enzyme that is bound on the outer surface of the cell membrane and it contains a residue in the active side of the this enzyme. This is very much similar to the family of enzymes called as the serine proteases. So named because it contains a serine residue and they are involved in the hydrolysis of the peptide bond. Here in this case, the serine residue of the car peptidase enzyme acts as a nucleophile and its splits the peptide bond between the 2 unusual D alanine units on the peptide chain.

And in this way the terminal D alanine unit departs the active side, leaving the peptide chain bound to the active side. Next the penta glycine moiety of another peptide chain enters the

active side and the terminal glycine forms the peptide bond, displacing it from the serine and this is how the 2 chains are cross-linked with each other. And this process continues until it forms a very rigid mesh like structure on the bacterial cell. The trans peptidase enzyme is a specific target for beta-lactam antibiotics, which is one of the widely prescribed class of cell wall biosynthetic inhibitor.

These beta-lactams include drugs such as penicillin and cephalosporin and they are going to inhibit these trans peptidase enzyme. They are going to bind to this enzyme and irreversibly inhibit these enzymes and that is how it is going to inhibit the peptidoglycan biosynthesis. Because of that reason, cell wall becomes very fragile and eventually osmotic pressure builds up that the bacterium would burst and die. As a result these beta-lactam antibiotics are bactericidal in nature. Because they are going to directly kill the bacteria by inhibiting these peptidoglycan biosynthesis.

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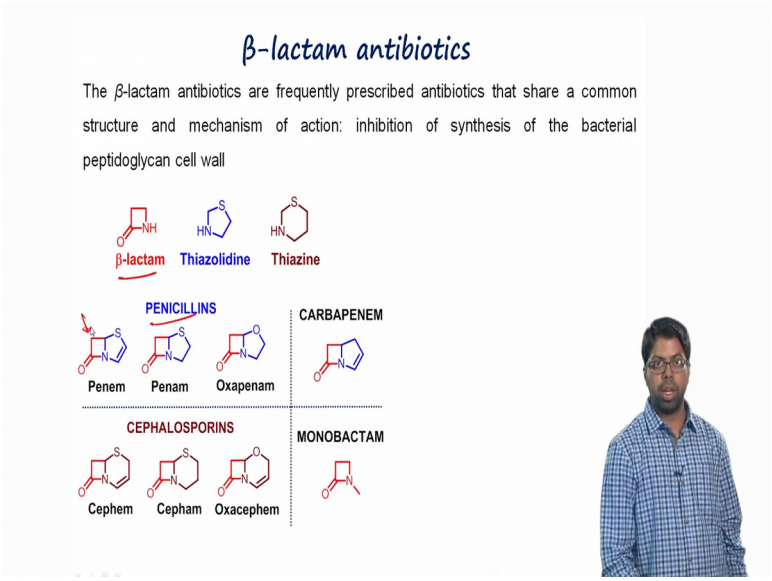

Let us look what these beta-lactam antibiotics are. So, these are one of the most commonly prescribed cell wall biosynthetic inhibitors, which have a common structure as well as the mechanism of action. That is there going to inhibit the peptidoglycan bio synthesis. So, here is the structure of beta-lactam Ring which is a highly strained 4 member ring, which consists of a cycling amide. Now, these beta-lactams can be classified into 4 different groups of antibiotics like penicillins, cephalosporins, carbapenum and monobactam, based on the variation on their core ring structure.

For example, in case of penicillin, they have a 4 member beta-lactam Ring, which is used to 5 members sulphur containing di hydrothisol ring and they are called penam. And if the 4 member beta-lactam ring is fused to 5 member saturated system, then they are called a spin. Remember in both the cases, the heteroatom present here is sulphur. Instead of sulphur, if it is oxigen, then it is called as oxapenam. Likewise instead of any heteroatom, if the carbon is present, then they are called as carbapenum.

In case of cephalosporin, the 4 member beta-lactam ring is fused to 6 members sulphur containing 2, 3 die hydro thiazine, then they are called as Cepham and if it is fuse to six-member sulphur containing thiazine ring, they are called Cepham. Again, in both the cases, the sulphur is the heteroatom present in this class of antibiotics. If it is oxigen instead of sulphur, then they are called as oxa Cepham. There is another unique class of beta-lactam antibiotics which have only monocyclic ring and did not used to any other thing and they are called as monobactam.

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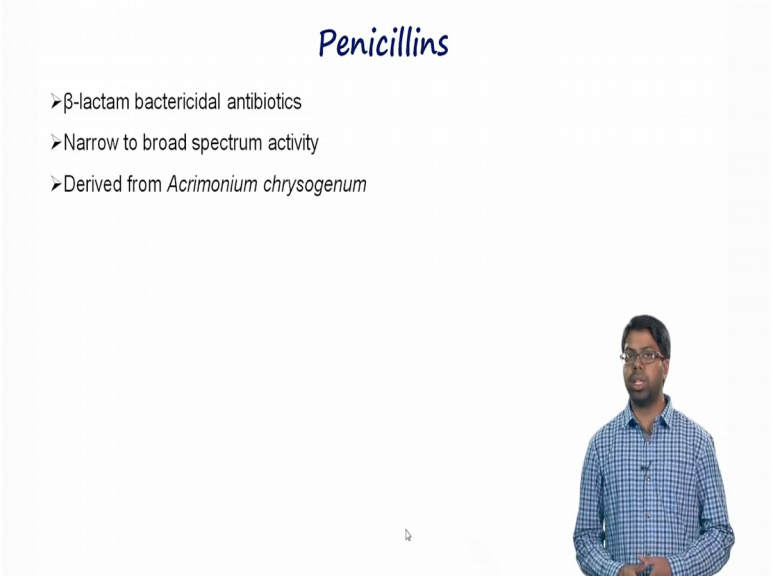

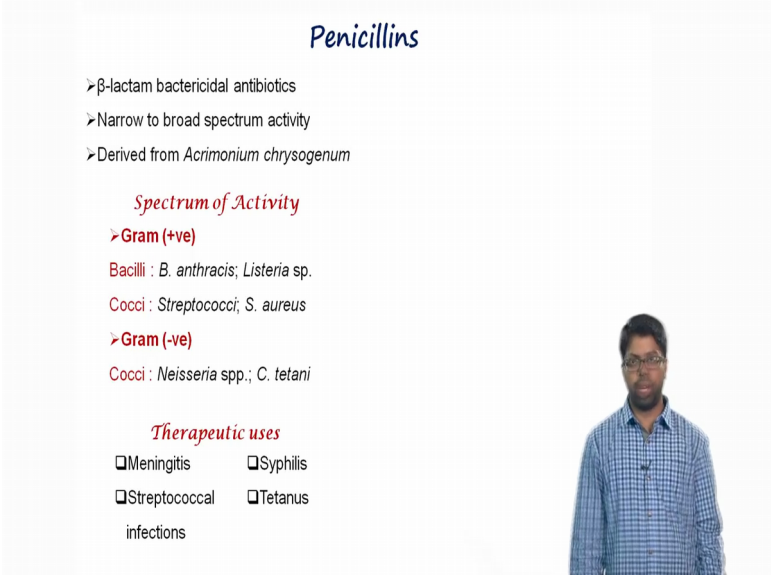

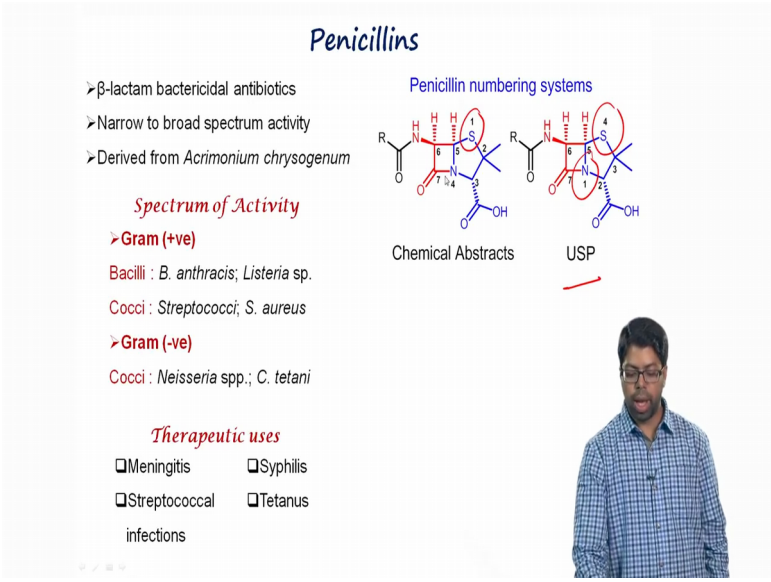

So this lecture will focus on detailed study of each of these class of beta-lactam antibiotics and now let us start with penicillin. So, these penicillins are again beta-lactam antibiotics and they exhibit spectrum of activity from narrow spectrum to broad spectrum. They are bactericidal antibiotics because directly kill the bacteria by inhibiting the peptidoglycan biosynthesis. It is derived from a fungus or less acrimonium chrysogenum. And these penicillins are used for a variety of infections, such as meningitis, which is associated with the inflammation of meningis, that covers your brain and spinal cord.

Likewise penicillins are also useful in streptococcal and Staphylococcus infections. Penicillins are also effective against sexually transported is this called as said syphilis, it is also effective against the bacterium callers Clostridium tetani, which is responsible for its assured callers Tetanus, which is associated with severe muscle spasms. This is the basic

course structure of penicillin analogues, there are 2 numbering systems for penicillins. According to USP, the nitrogen is numbered as position 1 and sulphur as position number 4. But according to chemical abstract system, sulphur is numbered as 1 and nitrogen is 4.

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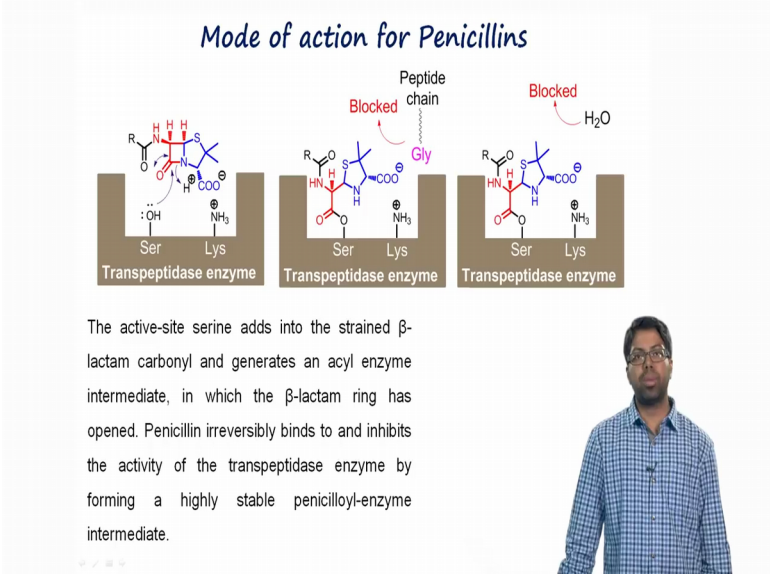

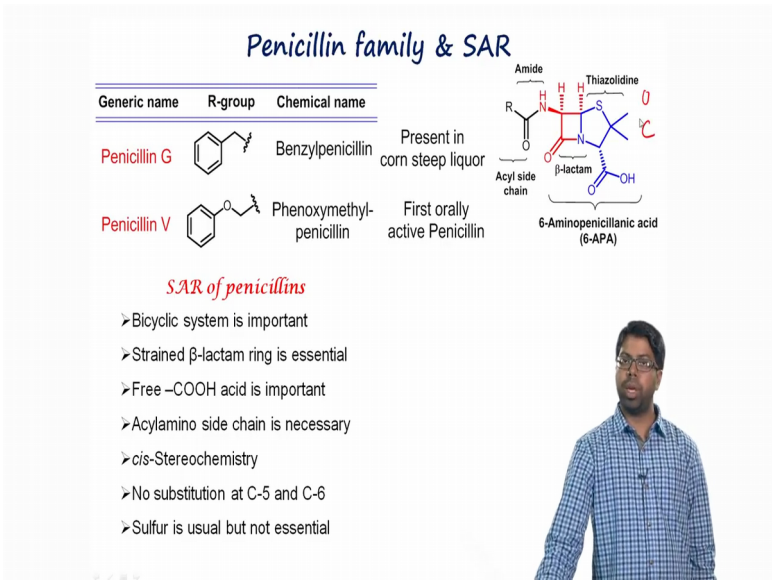

When it comes to mode of action, penicillins 1st come in contact with that trans peptidase enzyme, then due to the highly strained beta-lactam Ring, they are subjected to Newcastle lik attack by the serine residue of the trans peptidase enzyme. So, serine residue acts as the nucleophile, attacks on the carbonyl group of the beta-lactam ring and opens this beta-lactam ring. Which leads to the formation of acyl enzyme intermediate. Here the penicillins irreversibly bind to the enzyme and forms a highly stable penicilloyl-enzyme intermediate. And that is how it is going to inhibit the peptidoglycan biosynthesis.

So, here the penicillin has a beta-lactam Ring, that is fused to five-member sulphur containing ring called as thiozolidine. Without any acyl sidechain here, this is called as 6 amino penicillinic acid. No, this acyl sidechain weighs according to the components of the fermentation medium. The Corn sheep liquor was the 1st fermentation medium used for the biomass production of penicillin. It contains a component called as phenyl acetic acid and that is how you got penicillin G, which is also called as benzyl penicillin.

Another fermentation medium contains phenoxy acetic acid, that is how you got penicillin V, which is also called as phenoxy methyl penicillin. And this is the 1st orally active penicillin. Here are some of the characteristic structural features of the penicillin. The strained beta-lactam ring is essential, the carboxylic acid at the 2nd position is also essential. Usually this carboxylic acid is present if they are nice warm and that is the reason these penicillins are administered in the form of a sodium or potassium salt. The stereochemistry of this hydrogen is also essential, there is no substitution at 5th and 6th position.

Sulphur is usually necessary but not essential. You can substitute this sulphur by heteroatom such as oxygen and carbon. In only cases the penicillins will be as effective as the penicillin molecule. Bi cyclic system is essential because it provides strained to the beta-lactam ring. The greater the strain, the greater is the activity of the penicillin molecule. But here is the catch. The greater the steam, the greater is the instability of the molecule to several other factors, which we are going to discuss in detail in the next couple of minutes.

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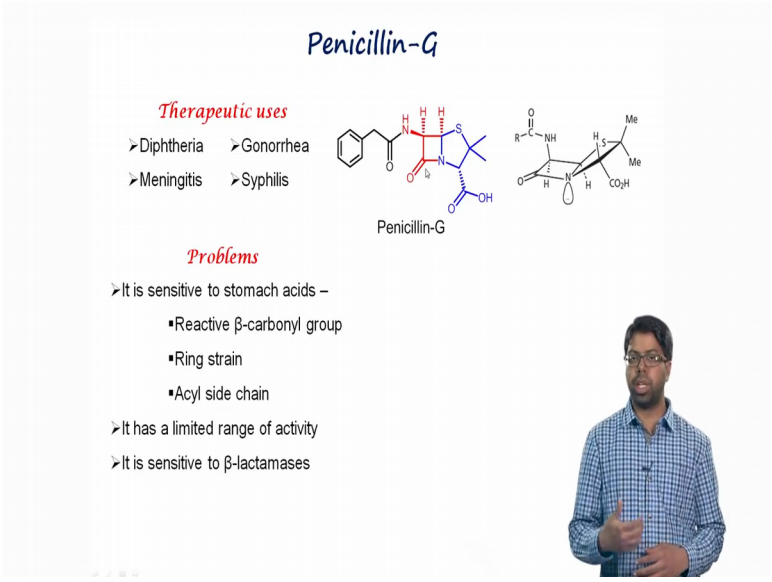

Penicillin G is one of the 1st naturally isolated penicillin analogue and this is the structure of penicillin G which is also called as benzoyl penicillin. And the structure is just like half open book. Penicillin G is used for variety of infections, such as Diphtheria, which is associated with severe nose and throat infections, it is also effective against sexually transmitted diseases such as gonorrhoea and syphilis. Penicillin G is also effective against meningitis, which is an infection caused by a bacterium called as miriria meningitis. However there are several drawbacks associated with this penicillin G.

The 1st major problem associate with this penicillin G is it cannot be taken by the oral route because it is highly susceptible to the assets that are present in the stomach, which will lead to opening of this beta-lactam ring and making this inactive. It is effective only against the gram positive organisms. So, therefore it has a narrow spectrum of activity. And there are many infections against which this penicillin G is completely ineffective. Especially those infections which are associated with bacteria that can produce an enzyme called as beta-lactamases.

So this beta lactamases opens the beta-lactam Ring of this penicillin G and making them an actor. Now, let us look how researchers like you and me came into picture with various strategies to tackle these problems and how these strategies lead to the development of new penicillin analogues with improved properties.

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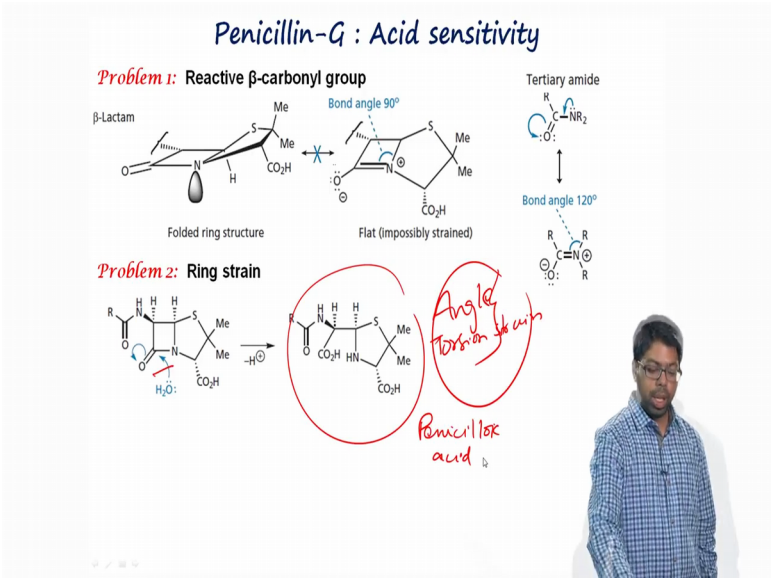

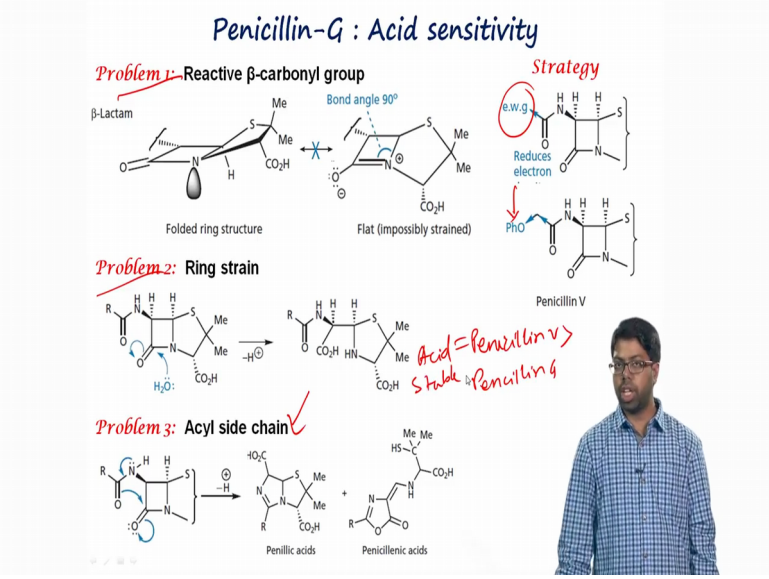

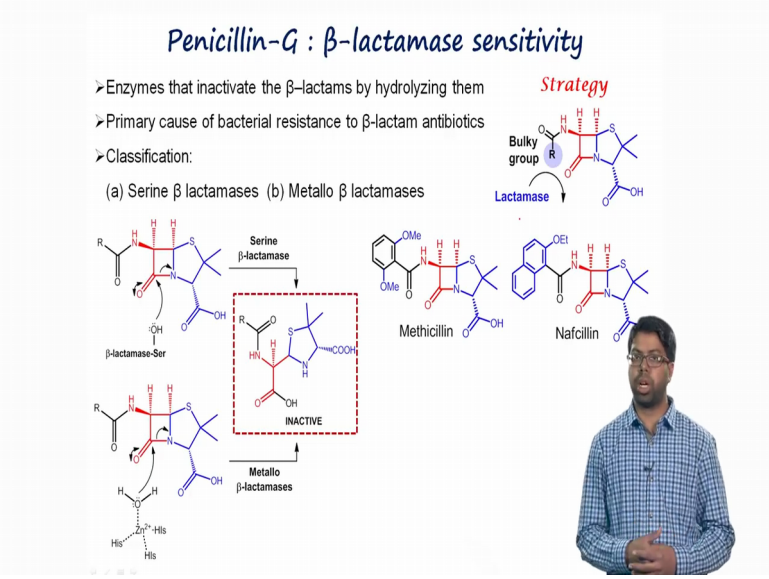

So, as I mentioned to you, one of the major problems associated with this penicillin G is acid sensitivity. Now, there are 3 major reasons behind this acid sensitivity. The 1st reason is the highly reactive beta carbonyl group. The carbonyl group of this penicillin G is highly reactive and it is very susceptible to nucleophilic attack. And does not behave like a normal tertiary amide. In case of normal tertiary amide, they are not electrophilic because here the carbonyl group is in Resonance with the neighbouring nitrogen.

So the nitrogen can donate its lone pair of electrons and thus forming this dipolar resonance structure with a bond angle of around 120 degree. This, this kind of resonance stabilisation is impossible in the beta-lactam ring due to increased angle strain, which would result in having a double bond in the 4 member beta-lactam ring. The preferred bond angle for double bond is 120 degree, which is constrained to 90 degree in case of penicillin G. That is the reason why

the loan pair of electrons is delocalised on the nitrogen atom only and the carbonyl group is more reactive than one would expect for a normal tertiary amide.

Another major reason behind the acid sensitivity of the penicillin G is its ring string. The beta-lactam Ring is fused to this five-member sulphur containing thiozolidine ring and because of this by cyclic system, it induces angle and torsional strain. Because of this reason when you take this penicillin G via oral route, it can be easily attacked by acid that is present in the stomach which can lead to opening of this beta-lactam ring. So, opening of the beta-lactam Ring can relieve these angles and torsional strains. So, therefore this is the more favoured pathway for the degradation of the penicillin G.

The degradation product that is obtained from this opening of the beta-lactam ring is called as the Penniciloic acid. Another major reason behind the acid sensitivity of the penicillin G is the participation of the neighbouring group. So, here is the acyl group actively participates in the opening of this beta-lactam ring, which leads to the formation of inactive intermediate, such as pennilic acid and penicillinic acid. Therefore penicillin G has a self destruct mechanism built in the structure.

It can be seen, countering this problem of acid sensitivity is a very difficult task. Nothing can be done for the 1st 2 problems because beta-lactam ring is essentially for this anti bacterial activity. You cannot do any further modifications in the beta-lactam ring. However, the 3rd problem can be tackled. This can be tackled by reducing this neighbouring group participation and how we can do that, by incorporating an electron withdrawing group. So, this electron withdrawing group will pull away the electrons from the carbonyl oxygen, reducing its tendency to act as a nucleophile. And that is how penicillin V was launched into the market.

In case of penicillin V, it has a electronic active oxygen atom attached on the side chain of the beta-lactam ring. And therefore it is more stable against acids when compared to penicillin G. Therefore penicillin V can be taken via oral route because it is not susceptible to degradation by Stomach acids. The another problem associated with this penicillin G is its sensitivity to the beta-lactamase enzyme. So, these are the enzymes which can open up the beta-lactam Ring of the penicillin G, making them inactive. And this is one of the major defensive mechanisms that the bacterium brings to avoid this beta-lactam antibiotics.

Again, this beta lactamase enzyme can be classified based on the active site residue, that is involved in the opening of this beta-lactam ring. Some contain serine residues at the active site, that opens this beta-lactam Ring. And in some cases, they have a Zinc metal which is involved in this opening of the beta-lactam ring. Whatever the type of beta-lactamase it is, ultimately it leads to opening of this beta-lactam ring and this is the product that is being formed and this is called as the Penniciloic acid.

However this is not a stable product, it can undergo further decomposition. For example, it can undergo decarboxylation and give an intermediate called as Penniloic acid. This intermediate can undergo further degradation to give you pennilo aldehyde and penicillin amine. The problem of this beta-lactamases became very critical in 1960s, due to the widespread use of this penicillin G that led to the increased rate of penicillin G resistant Staphylococcus aureus infections. However, the solution to this problem was just around the corner and that is how the design of beta-lactamase resistant penicillins came into picture.

Here the use of study shield to block the access of penicillins to beta-lactamase active site was a useful strategy and this was achieved by incorporating a bulkier group. Again, here is the problem. If the group is too bulky, it can also restrict the access of these penicillins to the trans peptidase enzyme, which is its target, right. So, therefore a great deal of work has to be done to identify an ideal shield which will allow the penicillin to access the trans peptidase enzyme, but block the access of penicillin to the beta-lactamase and drive.

Fortunately, we got an ideal shield and that is how methicillin came into the market. So, here methicillin has a methoxy group on the either side and that is how it is going to block the access to the beta-lactamase enzyme. However this is not an ideal drug because it does not have any electron withdrawing group here. And therefore you cannot take this drug why oral route because it would be easily broken down by the acids that is present in your stomach. So, this methicillin must be given via intravenous route of administration.

However, this is not a clinical drug because some of the bacteria have developed resistance against this methicillin and they are called as MRSA, which is abbreviated form of methicillin resistant Staphylococcus aureus. Therefore it led to the development of other beta-lactamases resistant penicillin, such as naphthalene. Again it has a naphthalene group here, this cannot be aggressive why oral route, it must be taken via parental route only. However these beta-lactamases resistance penicillins are kept as reserve groups and are introduced only into the fray when an infection develops resistance against many broad-spectrum penicillins.

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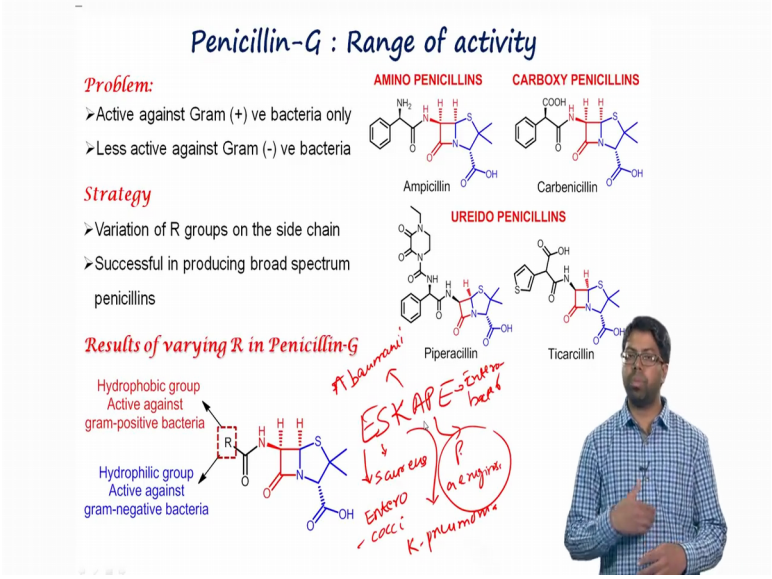

Another major problem associated with this penicillin G is its narrow spectrum of activity. That means, it is only effective against gram positive organisms, whereas against gram negative organisms it is completely ineffective. Now, the major reason for the spectrum of activity for any antibiotic, here for example in case of penicillin, it depends on many factors, such as it depends on the ability of the penicillin G to bind to the trans peptidase enzyme, how efficient this penicillin G is to get inside the gram negative bacteria.

Again the gram negative bacteria have different mechanisms, they have flush pumps which kicks out any antibiotic that gets inside the gram negative bacteria cells. And all these factors vary from bacteria to bacteria. Therefore there is no clear-cut tactic that can be used to increase this spectrum of activity of penicillin G. However, researchers found that the presence of hydrophobic group on the acyl sidechain allows these penicillins to be effective against gram positive organisms. So the thought, why do not we incorporates some hydrophilic functional groups like amino functional groups and carboxylic functional groups.

And they found that introduction of hydrophilic fossil groups on the Alpha position of the acyl sidechain allows these penicillin molecules to be effective against gram negative organisms also. And that is how broad-spectrum penicillins and extended spectrum penicillins came into the market. Here are the broad-spectrum penicillins like amino penicillins and carboxyl penicillins. In case of amino penicillins, you have an amino functional group on the Alpha position of the acyl sidechain. One such example is Ampicillin. Carbonicillin is an example of carboxy penicillin, where there is a carboxylic functional group on the Alpha position of the hydrophilic sidechain.

So they are broad-spectrum penicillins, that means they are effective against both, gram positive as well as gram negative organisms. Another class of penicillins are called as Ureido penicillins and they are extended spectrum penicillins. Here, in these cases they have a urea functional moiety that is present on the Alpha position of the acyl sidechain. They are effective against both gram positive as well as gram negative organisms but also effective against some of the bacteria strains of a panel of landscape pathogens.

Here, escape is the abbreviation of a panel of pathogens such as enetro coci, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, pseudomonas aeruginosa, bacto. Ureido penicillins are effective against pseudomonas aeruginosa which belongs to this panel of escape pathogens. So, these escape pathogens are highly resistant to majority of antibiotics. Therefore targeting these and escape pathogens will be very cool thing. So, that is what these Ureido penicillins do.

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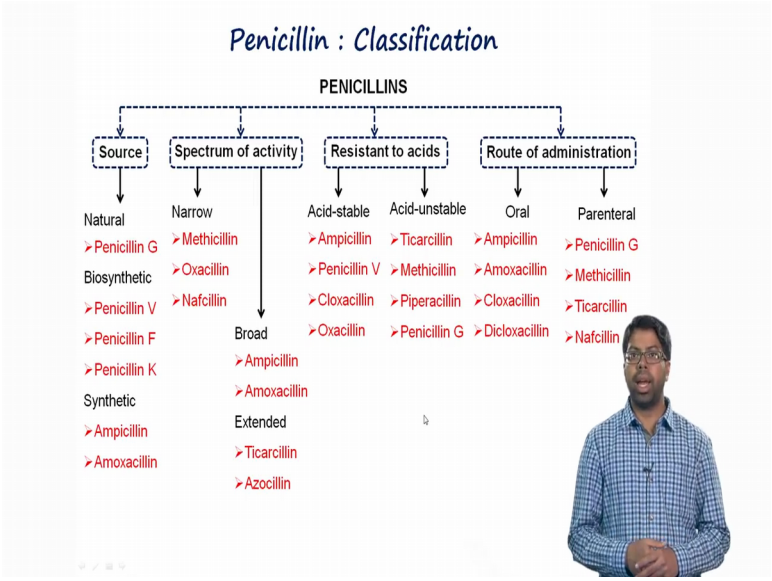

Now, as you are familiar with many penicillin analogues, let us have a quick look at the classification of the penicillins. They can be classified based on the source it is obtained from, for example penicillin G even naturally opted penicillin, whereas penicillin B is bio synthetically derived penicillin. There are some penicillin analogues such as ampicillin and amoxicillin are man-made. Similarly, penicillins can also be classified into narrow spectrum penicillins, broad-spectrum penicillin and extended spectrum penicillin. The examples are wave already seen previously, like diacelin and azocilin, these are extended spectrum penicillins which belong to the family of Ureido penicillins.

Whereas, amino penicillins and carboxy penicillins are broad-spectrum penicillins and methicillin, oxycilin, naphthalene, these are narrow spectrum penicillins, so that means they are highly effective only against the gram positive organisms. Again, the penicillins can be classified based on their acid susceptibility. For example, penicillin G cannot be taken why oral route because it is susceptible to stomach acids. So therefore it is acid unstable, whereas penicillin V, it is acid stable, it can be given why oral route of administration.

The same penicillin analogues can also be classified based on the route of administration. The penicillin analogues which can be given why oral route, they are acid stable. Whereas the penicillin analogues, which acid labile, they must be given via parental route. For example, penicillin G is given by a parental route of administration. And that is the same thing that occurs even with methicillin and ticarcilin, etc. Whereas ampicillin and amoxicillin, they are acid stable and they can be given in the form of a tablets or capsules via oral route of administration.

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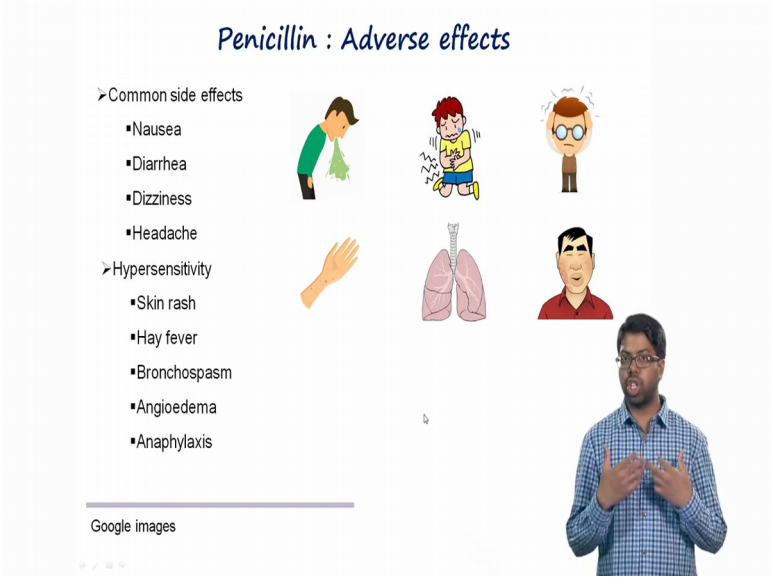

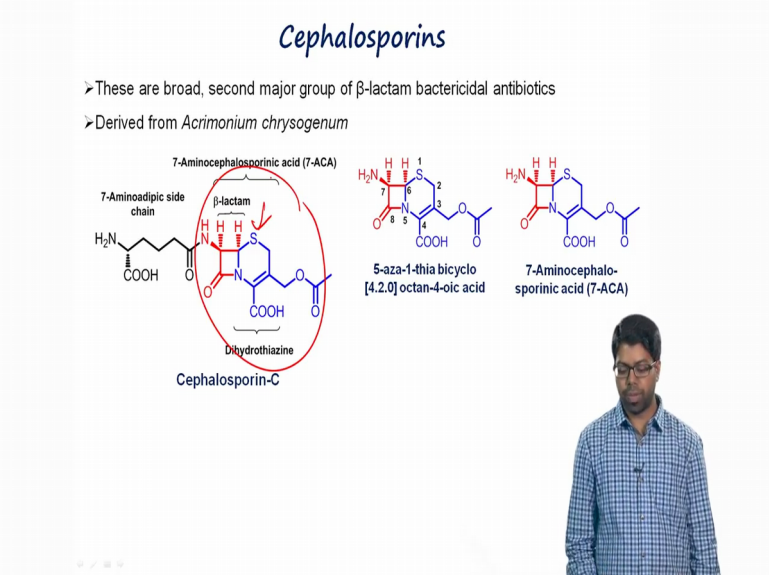

When it comes to side-effects, penicillins are associated with common side effects such as nausea, diarrhea, dizziness, headaches. But the most common side effect associated with this penicillin is allergy or hypersensitivity reactions. Which can range from immediate response, that can offer within minutes or hours to something that can happen days after taking the administration of penicillin. And these are called as delayed reactions and this include skin rash or hives or anaphylaxis or bronchospasm or angioedema .

So, bronchospasm is the process of construction of airwaves of the lungs, whereas angioedema is associated with the inflammation of face, mouth and lips. Anaphylaxis is a severe allergic reaction that can be fatal if not treated appropriately. Another major class of beta-lactam antibiotic is cephalosporins. Again these are not spectrum antibiotics and they are also bactericidal in nature. This cephalosporin C was the 1st cephalosporin that was isolated from acrimonium chrysogenum during the mid-1940s. In case of cephalosporins, they also have a beta-lactam ring, which is used to sulphur containing 6 member ring called as Di Hydro thiozine.

And this is the core structure of the cephalosporin C or the cephalosporin class of antibiotics, which is called as 7 amino cephalosporiniic acid. The sidechain present in the cephalosporin C is the 7 amino adipic acid. These cephalosporins are one of the most potent and Tibetan religions, they are well tolerated and their development was paralleled that of the penicillins. If you look at the numbering systems, according to chemical abstract system, sulphur is numbered as position 1 and nitrogen is numbered as position number 5.

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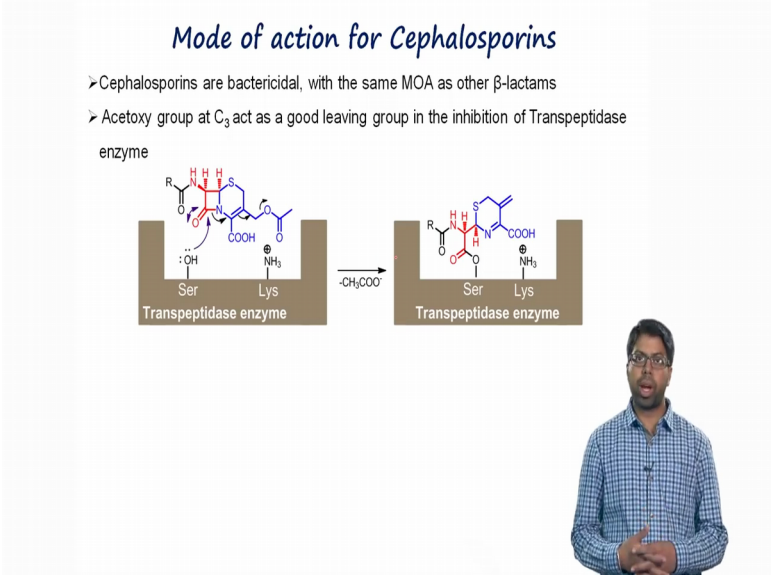

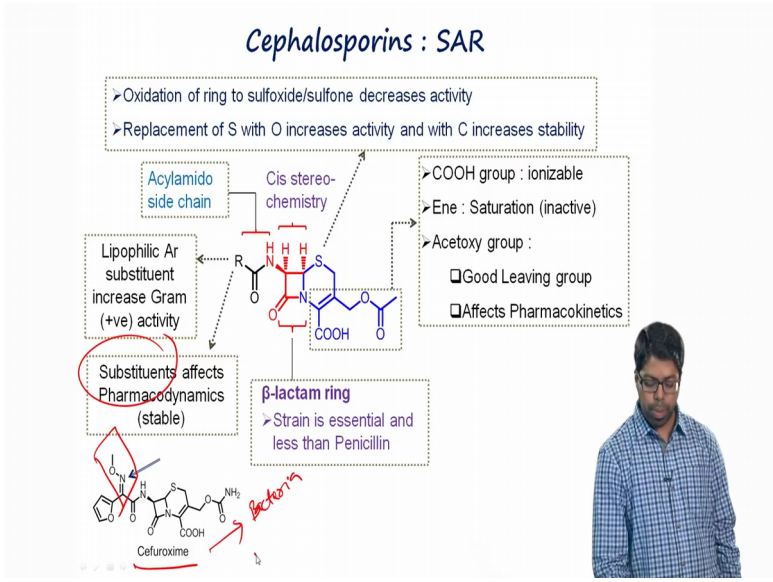

Now, like penicillins these cephalosporins are also bactericidal and their target is also the same, that is trans peptidase enzyme. So, here also cephalosporin comes in contact with the trans peptidase enzyme and because of the strain in this beta-lactam Ring, it is subjected to nucleophilic attack by the serine residue of this enzyme. So, here is the serine residue acts as a nucleophile, attacks the beta-lactam ring and opens it. But, here you have also acetoxy group that is present in the 3rd position of the cephalosporins family of antibiotics. And because of that it acts as a very good living groups.

And that is the reason it inhibits the trans peptidase enzyme irreversibly. And that is how these cephalosporins are going to inhibit the peptidoglycan biosynthesis. If you look at the structural activity relationship of cephalosporin, it has beta-lactam Ring, which refused to this

six-member sulphur containing by Hydro Thiozine ring. And now the strain present in this beta-lactam ring is less when compared to that of penicillin, but it is effective to inhibit the chance peptidase enzyme. Again, the 6th standard chemistry of Hydrogen is essential, the sulphur is important but it is not essentially.

For example, you can replace the sulphur by other hetero atoms such as oxygen and in that case they are called as oxa Cephams. They are also as effective as the cephalosporins. Similarly, the sulphur can also be replaced by carbon and in those cases, those analogues are also effective like parents cephalosporins. But if the sulphur is undergoing Oxidation to give sulphoxide or csulphone, the activity of these cephalosporins goes down. Similarly the carboxylic acid and the 2nd position's ascension and generally this carboxylic acid if we deionised farm and therefore these cephalosporins are also administered as sodium reputation salts.

The double bond here is essentially, if you remove the double bond, the cephalosporin loses the activity. Likewise, the estoxy group is very important in terms of activity. It access a very good living groups and therefore these cephalosporins are going to inhibit the last peptidase enzyme irreversibly. But again, the problem here is, it is an ester bond. And because of that, the enzymes are called as esterysis present in your body which can open up this bond and making this cephalosporin less active.

Therefore, this acetoxy group determiness the pharmacokinetic parameters of the cephalosporins, again the acyl amino sidechain is essential for the antibacterial activity of cephalosporins. Like penicillins if you can incorporate hydrophilic fossil groups or the acyl sidechain, the become more and more effective against gram negative organisms. And if there is a hydrophobic group, they will be effective against the gram positive organisms. But here, there is one additional thing, there is an influence of the substituent that is present of the acyl sidechain.

For example, amino methoxy group, which is a substituent present in cefuroxime, which is the second-generation cephalosporin. Due to the presence of this amino methoxy group at this acyl sidechain, this cefuroxime is effective against bacteria that can produce beta-lactamase. Because of this hysterically hindering substituent, it cannot be claimed by the beta-lactamase enzyme and therefore it is stable against many beta-lactamases. Now, these cephalosporins can also be classified into different generations like first-generation, 2nd, 3rd and 4th generation.

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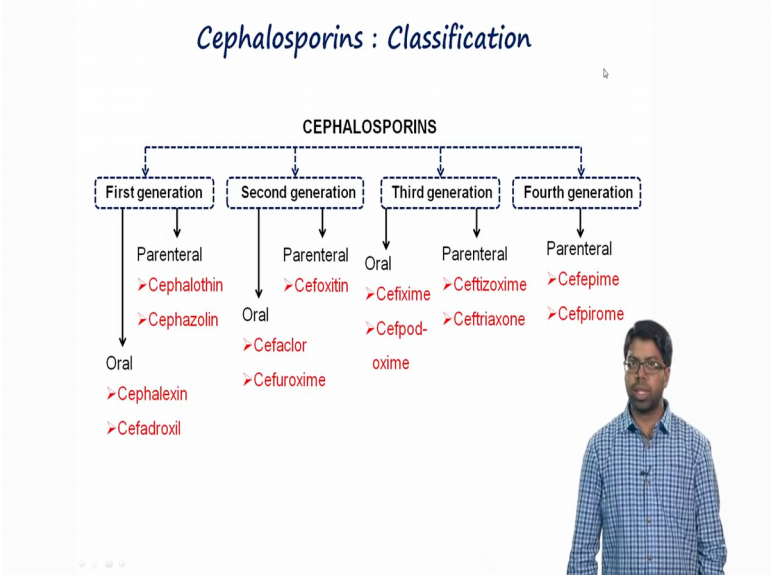

Now you may ask, is it relevant to know which cephalosporin belongs to which generation? In short, the answer is yes. Because each generation of cephalosporin tells you something about the spectrum of activity. I example, earlier generation cephalosporins, like first-generation, they were highly effective against gram positive bacteria. But they have diminished activity against gram negative organisms. But obviously they are broad-spectrum antibiotics and is there activity is less comparable to that of penicillin.

But the mid-generation cephalosporins like second-generation and third-generation, they are highly effective against both gram positive as well as gram negative organisms and therefore they are broad-spectrum cephalosporins. And the 4th generation is called as extended spectrum cephalosporins because they are effective against gram positive and gram negative organisms obviously, along with that it is also effective against some of the bacteria shapes included in the escape panel of pathogens, such as pseudomonas aeruginosa and Klebsiella pneumonia.

And therefore they are highly effective against many of the drug resistant bacteria. Now, again each generation of cephalosporins can be further classified based on their route of administration. First-generation cephalosporins like cephalothin and cephazoline, they have a basic structure like this. In case of first-generation cephalosporins, they have acetoxy group that is present at the 3rd position. Because of that, it is metabolically very labile and it can be easily broken down by stomach acids. Therefore, these 1st generation cephalosporins like cephalothin cannot be given via oral route, it must be administered via intravenous route of an restoration.

Now the scientists thought why do not we remove this acetoxy group. Instead of this acetoxy group, if we just keep methyl group here like this, the rate is metabolically stable and it turns out that it is well absorbed and therefore it can be given via oral route, such as cephaloxine and sulphadoxine. When we move from this first-generation to second-generation cephalosporins, they are highly effective against gram negative organisms and they are also effective against some of the bacteria that can produce beta-lactamases.

The 1st generation cephalosporins are effective against gram positive bacteria but less effective against gram negative bacteria. Whereas second-generation cephalosporins are highly effective against gram negative bacteria but they have diminished activity against gram positive organisms. But the good thing is they are also effective against bacteria that can produce beta-lactamase enzymes. And the same thing goes even with the 3rd generation cephalosporins.

They are also effective against gram negative bacteria but with the diminished effect on gram positive organisms, they are also effective against many of the bacteria that can produce beta-lactamases. And the additional advantage to this second-generation and third-generation cephalosporins are that they are highly hydrophobic. Because of this reason, they can easily cross a blood brain barrier and that is why they are used for meningococcal infections such as meningitis. In case of 4th generation cephalosporins, they are effective against both gram positive as well as gram negative organisms, along with that they are also effective against Klebsiella pneumonia and pseudomonas aeruginosa.

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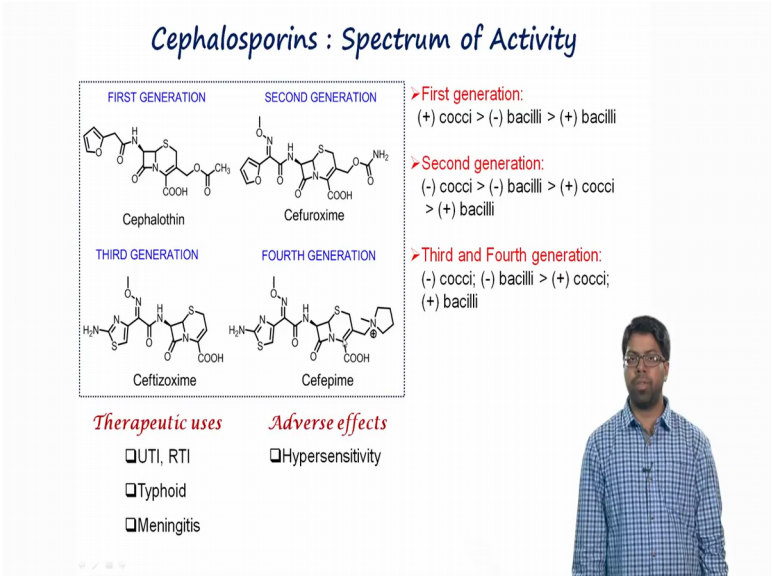

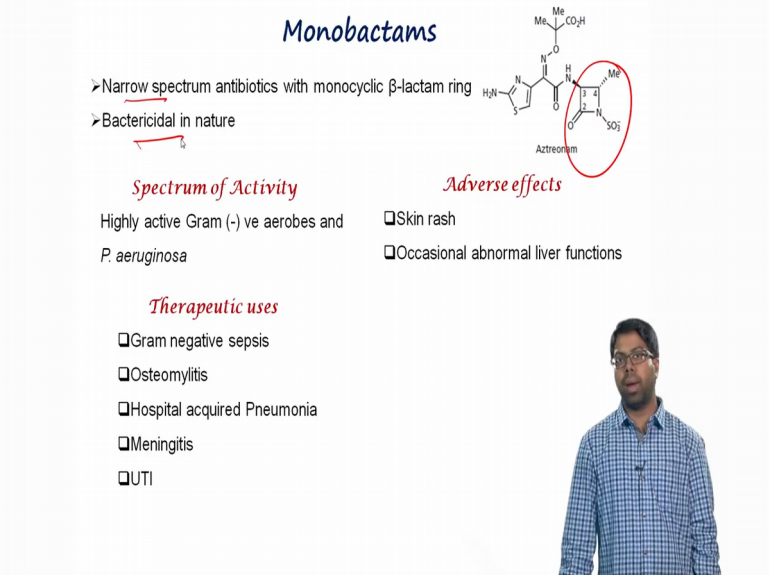

Because of that reason they are called as extended spectrum cephalosporins. For example cephipim and cephipyrom. So, in a nutshell, as the generation of cephalosporin progresses, they become more and more active against the gram negative organisms. Let us have a quick look at the structure of some of the generation of cephalosporins. For example, if this is cephalothin, which is a first-generation cephalosporin and you can see the reason acetoxy group present here, which is very metabolically labile, therefore it cannot be given via oral route.

But when you go from first-generation to second-generation, it has amino methoxy group, the effort is highly effective against gram negative organisms and some of the bacteria that are producing beta-lactamases, here it has urethane moiety, because of that it is metabolically stable. And the same thing goes even in case of third-generation cephalosporins. But in case of third-generation cephalosporins, the substituent present here is amino thiozole. Because of that it is highly effective against gram negative organisms as well as majority of the bacteria reducing beta-lactamase enzyme.

In case of 4th generation cephalosporins, there is a positively charged substituent present at the 3rd position and carboxylic acid at the 2nd position. Therefore they behave as cited ions at the physiological pH and they are effective against pseudomonas aeruginosa, Klebsiella pneumonia and many gram positive as well as gram negative organisms. And they are highly resistant to majority of the beta-lactamases. Like cephalosporins, there also used for over IT of infections such as urinary tract infections, respiratory tract infections, there also effective against typhoid and bacteria called as nusilia meningotitis, which is a positive agent for meningitis.

They have a common side effect, that is allergy or hypersensitivity reactions. Let us move to another class of beta-lactam antibiotics, which are monobactam. The name itself suggests these are unique beta-lactam rings, which are monocyclic and they are not used with any other ring. Again these are narrow spectrum antibiotics and they are bactericidal in nature. So, here the monobactams are highly effective against gram negative organisms as well as pseudomonas aeruginosa. They are preferred for infections such as hospital-acquired pneumonia, meningitis, urinary tract infections and osteomartus, which is associated with the inflammation of boards of arms and likes.

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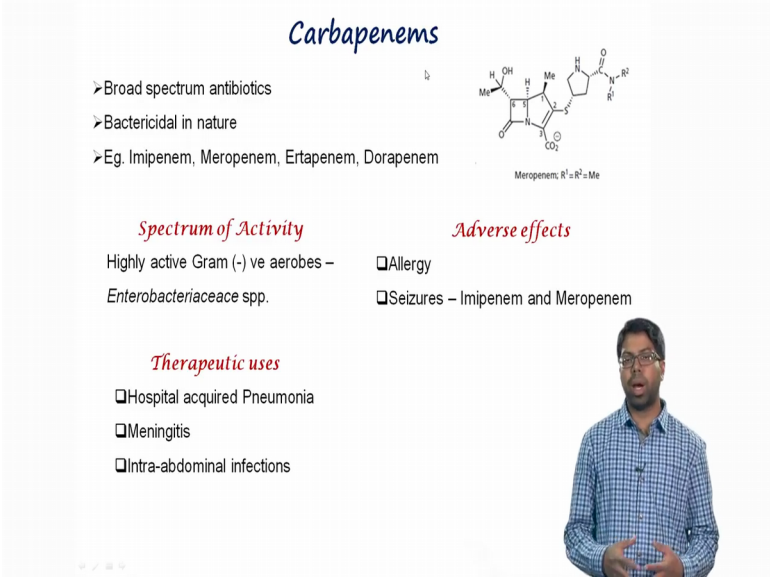

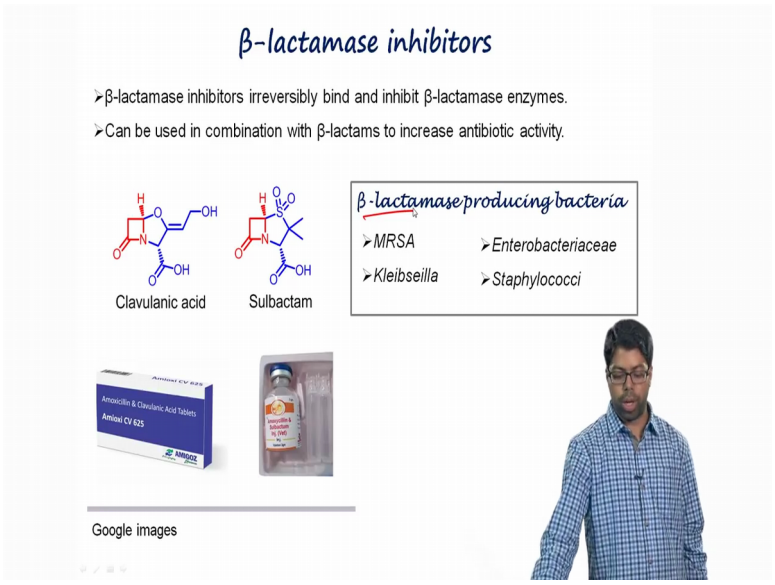

Like penicillins, they have a common side-effect of skin rash and abnormal liver function. Another class of these beta-lactam antibiotics are carbapenums, they are broad-spectrum

antibiotics and they have bactericidal nature. They have a 4 member beta-lactam ring which is fused with a five-member carbon containing ring and that is why they are called as carbapenum. So, some of the well prescribed carbapenums include imipenum, miropenum, Itapenum, Dorapenum, etc. Again, like monobactams, they are highly effective against gram negative organisms including intero bacterial.

They are preferred for infections such as hospital-acquired pneumonia, meningitis and intra-abdominal infections. The carbapenum's are associated again with the common side-effect of allergy but one of the another side-effect, that is observed with the use of imipenum and miropenum are seizures, which are also called as epilepsy, which is categorised by symptoms of abnormal muscle spasms, abnormal bladder and bowel movements, and blackouts, followed by a period of confusion when the patient can remember for a short period of time.

One of the major problems associated with many beta-lactam antibiotics is that they are highly susceptible to the enzyme called as beta-lactamases, which is produced by a bacteria in a defensive way to get rid of these beta-lactam antibiotics. So, now scientists thought why do not we make any bitters of these beta-lactamase enzyme itself. And that is how these beta-lactamase inhibitors such as clavulanic acid and sulbactam came in the market. So, here, these inhibitors irreversibly bind to the beta-lactamase enzyme and inhibit them. And therefore when these beta-lactamase inhibitors are given in combination with beta-lactam antibiotics such as penicillins or cephalosporins, they will show synergistic effects.

Here are such examples. Amoxicillin is always given in combination with a clavulanic acid which is a beta-lactamase inhibitor and the same thing goes along with sulbactam. For your information, these are some of the bacteria that can produce beta-lactamase and therefore these bacteria are very difficult to target by many beta-lactam antibiotics. Methicillin-resistant Staphylococcus aureus, Klebsiella pneumonia, enterobactericeae and staphylococci.

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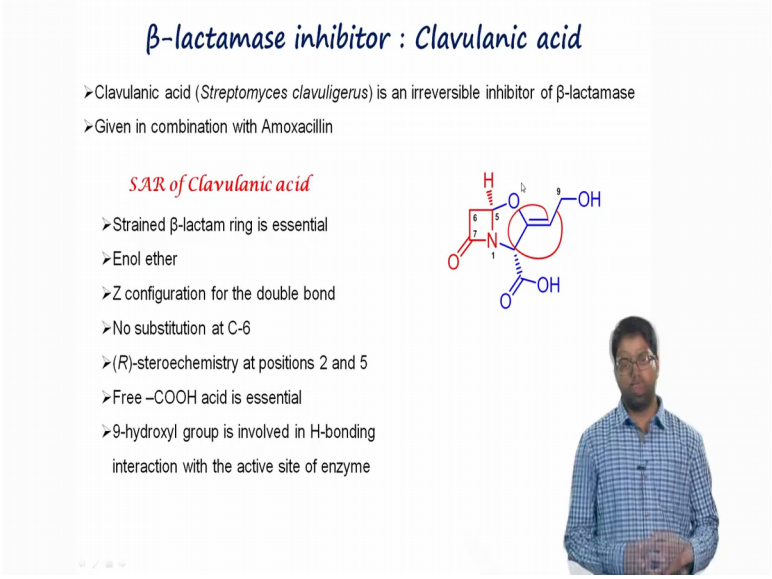

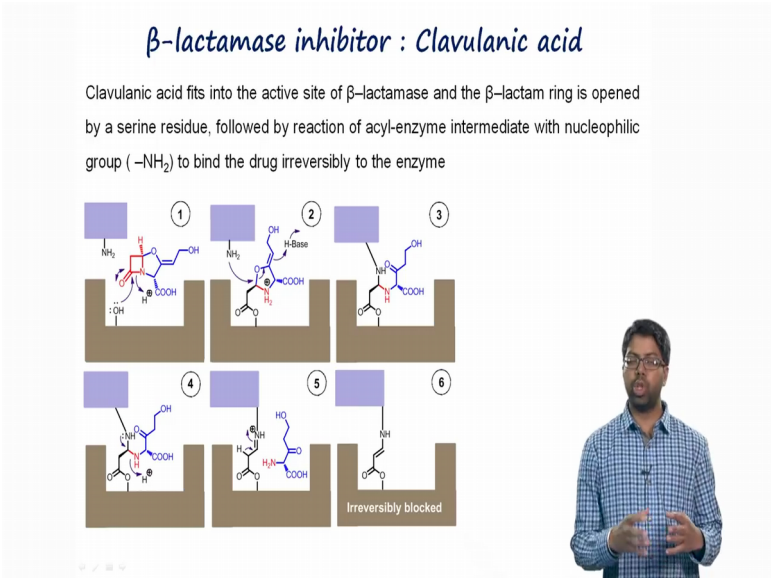

Let us take an example of beta-lactamase inhibitor, clavulanic acid. This was 1st isolated from streptomyces clavuligerus and it is an irreversible inhibitor of beta-lactamase. Clavulanate acid is given in combination with amoxicillin. This is the structure of clavulanic acid, where the 4 member beta-lactam ring is fused to oxygen containing 5 member saturated system. The strained beta-lactam ring is essential, the carboxylic acid at the 2nd position is also essential because again this is present in the ionised form and clavulanic acid is also given in the form of potassium salt.

If you notice, here there is no substitution at the 6th position. The stereochemistry of the hydrogen and carboxylic acid must be in R configuration, so there is a Enol ether present at the 3rd position, the configuration is Z for a double bond and the hydroxyl group present at

the 9th position is involved in the hydrogen bonding interaction with the residues of the beta-lactamase enzyme. 1st, the clavulanic acid comes in contact with the beta-lactamase enzyme, due to the strained beta-lactam ring, it is subjected to do nucleophilic attack by the nucleophile of this beta-lactamase enzyme which leads to opening of the beta-lactam ring.

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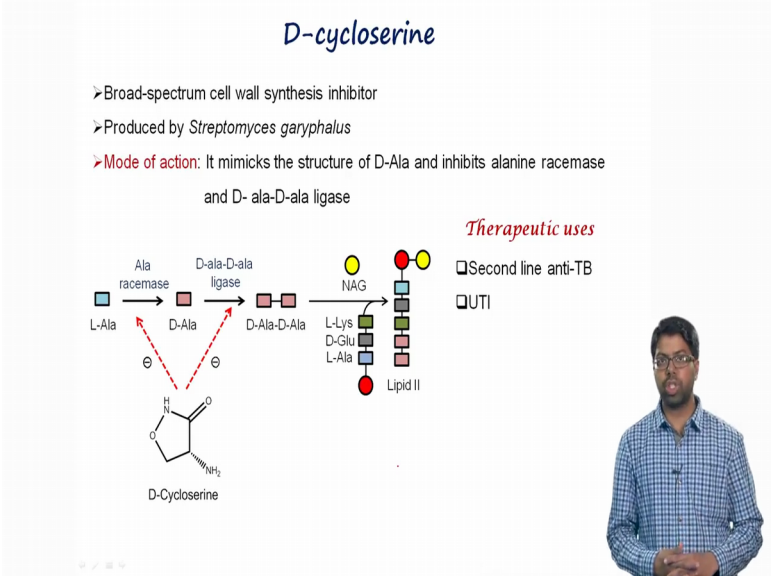

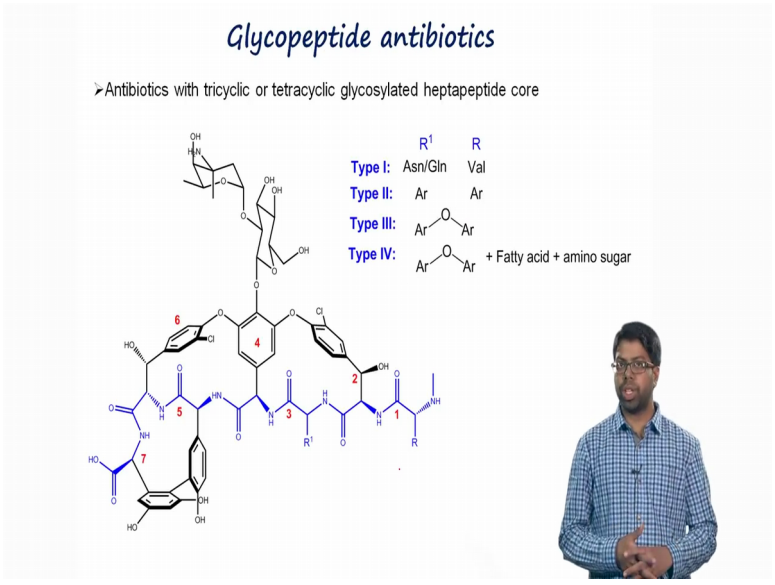

This is further followed by the attack of nucleophile of the enzyme and thus it binds the drug irreversibly. And this is how clavulanic acid irreversibly inhibits the beta-lactamase enzyme. Let us move to another class of antibiotic which inhibits the cell wall biosynthesis but by a different mode of action, for example, Cyclo serine. Cyclo serine is a broad-spectrum antibiotic and it was 1st produced by a fungus called as Streptomyces garyphalus. It has a

unique mode of action, if you remember, told you the peptidoglycan biosynthesis is mediated in 3 phases and these initial phase is called the cytoplasmic phase.

Where the D alanine unit is being formed, this is formed from an enzyme, called as Alanine rest remains which converts the alanine . Further this D alanine units are ligated in the presence of D alanine-D alanine legates. Once this D alanine-D alanine units is being formed, it is then added to the peptidoglycan component and that is how the peptidoglycan is being synthesised. Cyclo serine targets this alanine resimase and D alanine D alanine ligates and this is how it is going to inhibit the cytoplasmic phase of the peptidoglycan biosynthesis.

The D Cyclo serine is prescribed for urine and tract infections and it is a 2nd line agent in the treatment of tuberculosis. Obviously it is given in combination with other anti-TB agents to target the Mycobacterium tuberculosis. Another class of cell wall biosynthetic inhibitor includes glycopeptide antibiotics. As the name itself suggests, they contain try cyclic or tetracycline glycocylated hepta peptide course. This is the macromolecular structure and again they can be classified based on the R and R1 subsequent. Type I glycopeptide antibiotics have asparagine or glutamine at R1 and valid at the R position.

Type II antibiotics have aromatic residues on the R delta prime but they are not connected with each other. But in case of type III glycopeptide antibiotics, the 2 aromatic residues are connected via ether bridge. In case of type for glycopeptide antibiotics, they have 2 aromatic residues attached with the ether Bridge, along with that they also contain fatty acids as well as amino sugar. One such example of glycopeptide antibiotic is the vancomycin.

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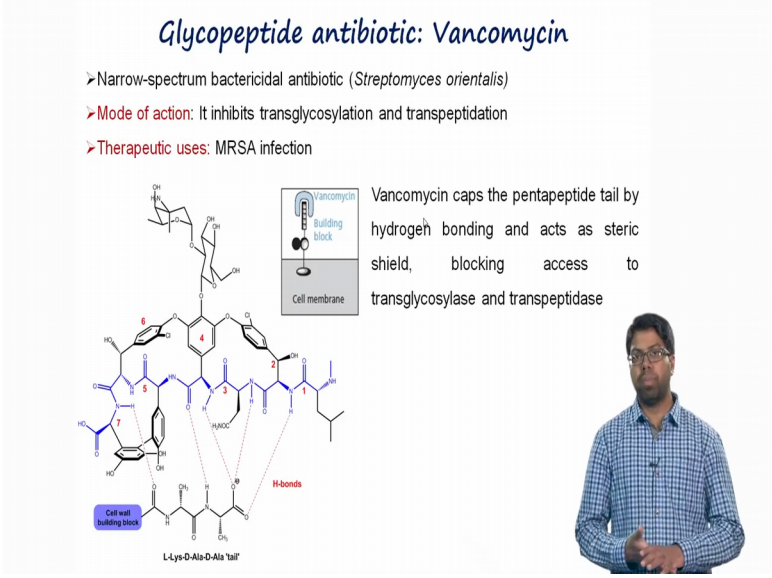

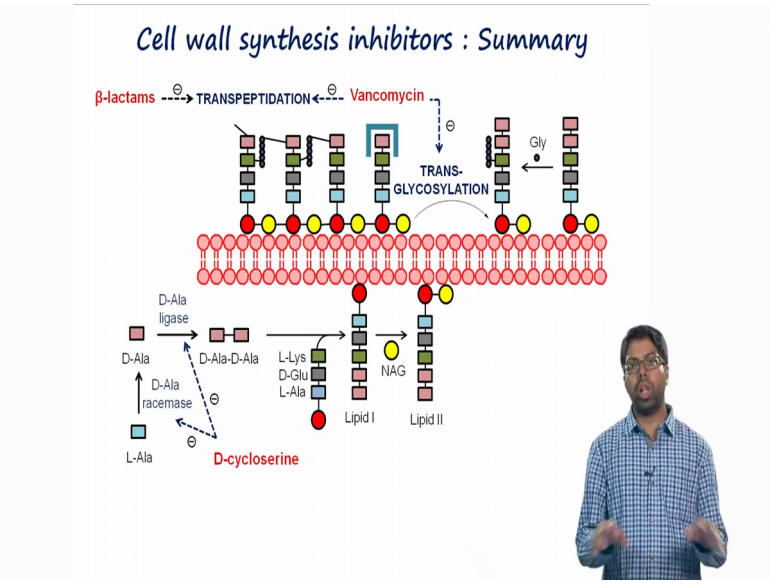

This is a narrow spectrum antibiotic but it has a bactericidal effect, that means it is going to kill the bacterium. So it has a unique mode of action, like penicillins, vancomycin is also inhibit the trans peptidase enzyme, but along with that it also inhibits the trans glycosylase enzyme. Because of this macromolecular structure, vancomycin caps the Penta peptide daily by hydrogen bonding and thus it acts as a steric shield, blocking the access of this Penta peptide to membrane-bound enzyme such as trans glycosylase and trans peptidase.

That is how it is going to inhibit the peptidoglycan biosynthesis in the extra cytoplasmic phase. Vancomycin is mostly prescribed to treat methicillin-resistant Staphylococcus aureus infection. Unfortunately few of the bacteria strains also have developed resistance against vancomycin and they are called as VRSA, vancomycin resistance Staphylococcus aureus. To summarise, we have talked about various antibiotics that inhibit the cell wall biosynthesis. So, either they are going to inhibit the cytoplasmic phase or they are going to inhibit the external cytoplasmic phase of the peptidoglycan biosynthesis.

For example, D Cyclo serine is going to inhibit the alanine resimases and D alanine ligates, that is how it inhibits the cytoplasmic phase out of peptidoglycan biosynthesis. But once the peptidoglycan components are biosynthesis, they are translocated to the extra cytoplasmic phase, where they are assembled in the presence of trans glycosylase and trans peptidase enzyme. Trans glycosylase enzyme is a target for vancomycin and trans peptidase enzyme is a target for both, beta-lactam antibiotics as well as vancomycin.

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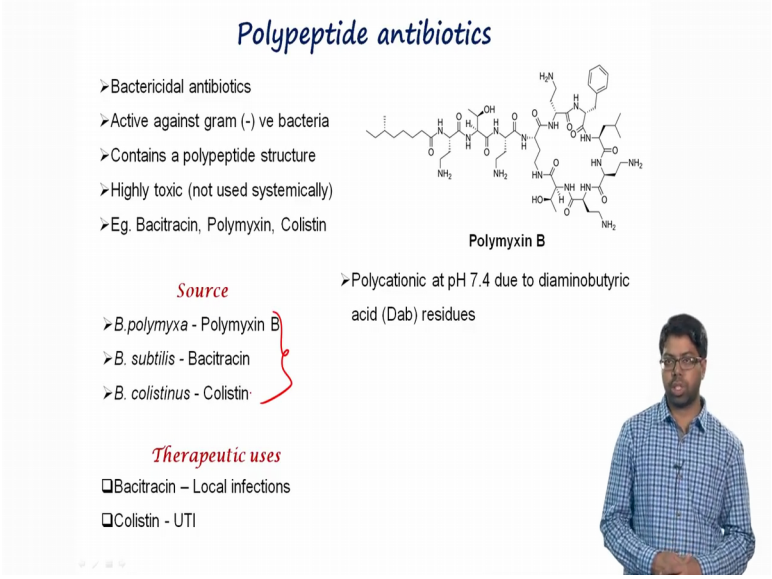

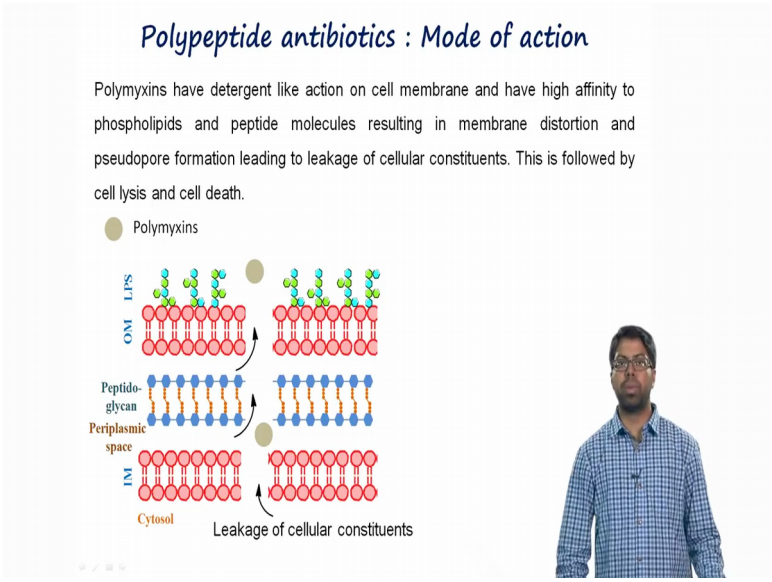

That is how all these antibiotics inhibit the cell wall biosynthesis. Let us move onto another class of antibiotics that target the cell membrane and these are called as polypeptide antibiotics. As the name itself suggests, they have a polypeptide structures, these are bactericidal in nature. They are highly effective against gram negative organisms. Some of the commonly prescribed polypeptide antibiotics include agents such as basicrasin, polymixin and colistin. Here are the sources of various polypeptide antibiotics.

Bacillus polymix is a source for polymixin B, Bacillus is obtained from Bacillus subtilis and colistin is often from Bacillus colistinus. Generally these polypeptide antibiotics are given in the form of topical agents because they cause systemic toxic. For example basicrasin is given for local infection in the form of topical agent and colistin is used for urinary tract infection.

This is a structure of polymixin B and if you see, it has a 2, 4 dime no butyric acid residues. Because of which it exists as a poly cation at a physiological pH. Polypeptide antibiotics have a unique mode of action.

They have detergent like action or decyl membrane and they have high affinity to the phospholipids and peptide molecules, which results in the membrane distortion and pseudo-pore formation. This leads to the leakage of cellular consequence, followed by cell lysis and death of the bacteria. So, therefore these polypeptide antibiotics are bactericidal because they are directly killing the bacteria by disrupting the cytoplasmic membrane.

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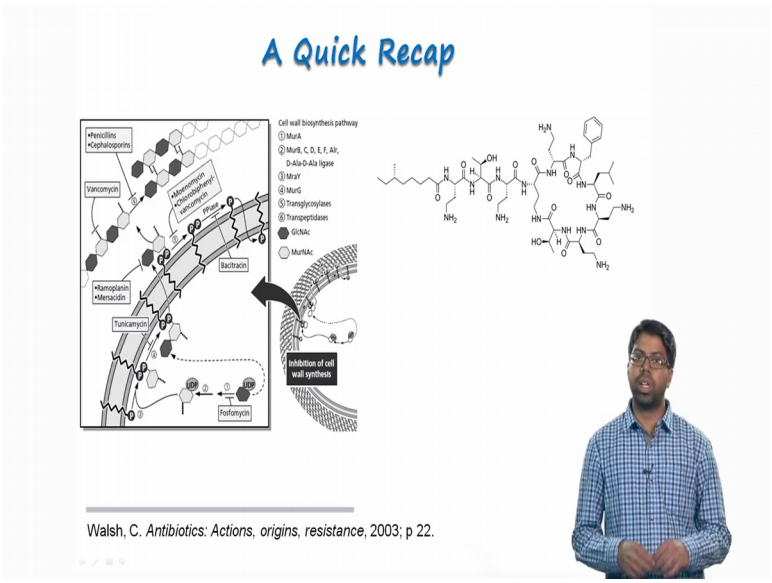

So, in a nutshell, in this lecture we have talked about the antibiotics, the target, the cell wall biosynthesis, which includes beta-lactam antibiotics such as penicillin, cephalosporins, Cyclo serine and glycopeptide antibiotics such as vancomycin. We also talked about another class of antibiotics that disrupt this cell membrane and kills the bacteria and those are called as polypeptide antibiotics. So, in the next upcoming lecture, we will talk about another class of antibiotics which either inhibit the nucleic acid biosynthesis or protein biosynthesis or metabolic pathways. Thank you.