Host-Pathogen Interaction (Immunology)
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Lecture - 76
Bacterial Infection – Anti-Tuberculosis Drugs

Hi. So in previous session we have discussed the Mycobacterium tuberculosis and we have studied how this Mycobacterium tuberculosis presence can be diagnosed by various tests and then we have also looked at the various spectrum, the spectrum of tuberculosis infected individuals. Now I am going to tell one good news about the tuberculosis that in terms of drugs, so we have a very efficient anti-tuberculosis drug.

But there is a problem with this drug which I will tell that the problem is not with the drug, this problem is associated with human ~~behaviour~~behavior. And due to that by and large this tuberculosis is a big problem in the society.

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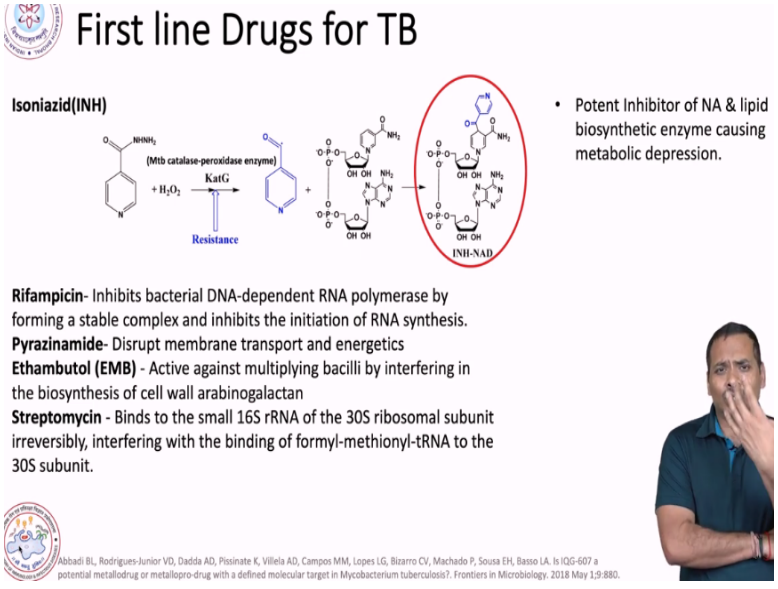

So in this session, I will talk about the anti-tuberculosis drugs and there are several drugs which we call it as first line of drugs against the tuberculosis and believe me this drugs are very efficient and very good. They can clear the Mycobacterium tuberculosis up to, not up to fully 100 percent if the individual will take this drug for whatever the course the doctor prescribed. Generally, it takes a 3 to 6 months, one has to take this drug, but here there is a problem.

The problem is that due to this long treatment individual's stop taking drug because these drugs are so efficient, very good in all kinds of clearance of this Mycobacterium tuberculosis and it also quickly relieves the symptom. And due to this human ~~behaviour~~behavior, this individual stop taking or ignoring the drug and then that problem arises and the problem is development of drug-resistant Mycobacterium tuberculosis.

So let us first look at what is the first line of drug and how it works. I will tell some mode of action for a few of these drugs. The first and foremost important drug is INH. This INH is a drug which is basically very efficient and this is basically inhibitor of this Mycobacterium catalase-peroxidase enzyme and if you look at this drug structure then you will or if you remember the structure of some vitamin, there is a vitamin known as pyridoxal phosphate.

So this drug is similar to the pyridoxal phosphate which is a vitamin and when the individual starts taking this drug, then the individual also suffers from deficiency of that vitamin. This drug basically target the Mycobacterium tuberculosis catalase-peroxidase enzyme and since this drug is close to the pyridoxal phosphate so individual need to take the this vitamin in order to because this is a competitive inhibitor if you see carefully.

Another drug is rifampicin. It basically inhibits the bacterial DNA-dependent RNA polymerase by forming stable complex and inhibits the initiation of RNA synthesis. This is also very efficient drug. Another is pyrazinamide, this basically disrupt the membrane transport and energetics. Another is ethambutol, this is active against multiplying Mycobacterium tuberculosis bacilli by interfering in the biosynthesis of cell wall arabinogalactan.

Another drug is streptomycin and this basically binds to the small 16S ribosomal RNA. If you remember the bacteria has a 17S ribosome and this 17S ribosome is again there will be 50S and 30S and there in 30S there will be a 16S RNA, so basically this molecule interacts with that. This binds to the small 16S ribosomal RNA of 30S ribosomal subunit irreversibly and interfering the binding of formyl-methionyl-t RNA to the 30S subunit.

Basically, this inhibits the protein synthesis processes in the Mycobacterium tuberculosis. So, all these drugs are highly efficient with very less side effect. One of the side effects I have

explained you there will be a deficiency of vitamin once the individual start taking the INH but that can be very easily managed, one can give this multivitamin or that pyridoxal phosphate, generally individual receives the multivitamin tablets.

So this can be very easily managed and these drugs are so efficient that even if the individual is having a full-blown disease and if start the individual taking this drugs in a week or in a month's time the individual will feel very healthy, but here the story will not finish. So most of Mycobacterium tuberculosis will be eliminated first in this month or week's time right, but there are some mycobacteria which resides which needs to be cleared.

And for that clearance the individual has to take about 6 months or 3 months' drugs as per prescribed by the doctor. But the individual stops taking the drug and then there is a problem, then there is a development of drug-resistant Mycobacterium tuberculosis. Therefore, WHO made one treatment regime which we call it as DOT, direct observed therapy. So, what is this DOT? Basically, the doctor or the primary health care people they will give the calculated dose of the drug and they will monitor it.

Monitor the patient whether they are taking the drug or not. So this is one way by which the patient or the development of drug-resistant Mycobacterium tuberculosis can be avoided, but still there are some people who do not follow this DOT as well. They do not come to the primary health center after some time and then this problem arises.

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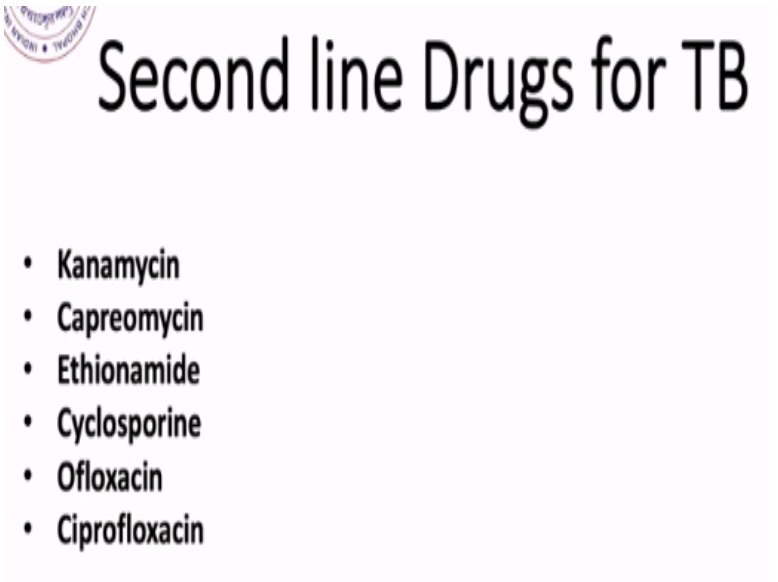

So in order to overcome there is second line of drugs, second line of anti-tuberculosis drugs which is having less potency but more toxicity and due to this, the second line of drugs are not so useful. It is less potent against Mycobacterium tuberculosis but it has more toxicity. So, these drugs are basically the antibiotics, probably you are aware of those drugs. These are kanamycin, capreomycin, ethionamide, cyclosporine, ofloxacin, ciprofloxacin like that. So these are the drugs which are used for drug-resistant tuberculosis.

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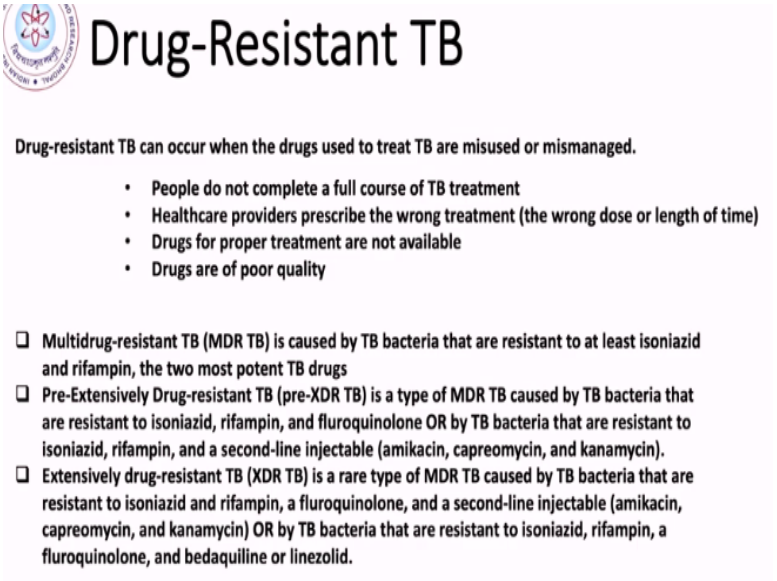

There is drug-resistant tuberculosis and this drug-resistant tuberculosis can occur when the drug used to treat the TB are misused or mismanaged. People do not complete the full course of TB treatment, healthcare provider prescribes the wrong treatment, there is a possibility also the wrong doses or length of time. Drugs for proper treatment is not available, drugs are of poor quality. So these are some of the reasons.

Then that result to the development of multidrug resistant-~~resistant~~ tuberculosis which we call it as a MDR TB is caused by TB bacteria and that are resistant to at least isoniacinamide, rifampicin and the two most important potent drugs which are first line of drug. The pre-extensively drug-resistant tuberculosis or pre-XDR so that result to the development of extremely drug-resistant tuberculosis.

It is a type of MDR which is multiple drug resistant by TB bacteria that are resistant to isoniacinamide, rifampicin or rifampin, fluoroquinolone or TB bacteria that are resistant to the isoniacinamide, rifampin and second line of injectable drugs. So when there will be a

drug-resistant Mycobacterium tuberculosis then the patient need to receive those less potent drug as an injection in order to eliminate those things.

There is extensively drug-resistant or extremely drug-resistant Mycobacterium tuberculosis which is a point of concern for India mainly because in India there are lots of tuberculosis cases or several part of Asia and in the world. So if there will be extremely drug-resistant Mycobacterium tuberculosis then it is difficult to manage. It is a rare type of multiple drug-resistant tuberculosis caused by TB bacteria.

That are resistant to the INH isoniacinamide, rifampicin, fluoroquinolone and the second line of injectable, these are the drug or the TB that are resistant to these drugs. So sometime back or still it is used there is one drug known as bedaquinine or quiline and this drug is basically a drug which is used against this multiple drug-resistant Mycobacterium tuberculosis. And this drug basically target the ATP synthase, their efficiency is less.

Again its efficiency is less and it is associated with array of side effects and this drug should not be used, there is some very clear information about this drug this drug should not be used for latent tuberculosis or drug sensitive tuberculosis individual is thinking that this is a XDR and but it is not XDR so it should not be treated by this drug. And this is associated with lots of side effects like nausea, arthralgia, you know the joint pain.

There will be headache, there will be a blood in the sputum after taking this drug, there will be chest pain, there will be anorexia. And this will also increase the transaminase in the blood, you probably remember or you may aware that there are two very key enzymes which we call it as a SGOT and SGPT which is used to understand the function of liver, SGOT and SGPT. So these enzymes will increase which demonstrate that it is kind of a hepatotoxic also.

There will be rashes and there will be enhanced blood amylase. So these are the side effects of this drug known as bedaquiline, although it is used in multiple drug-resistant tuberculosis, this in recent past it was started using in clinic.

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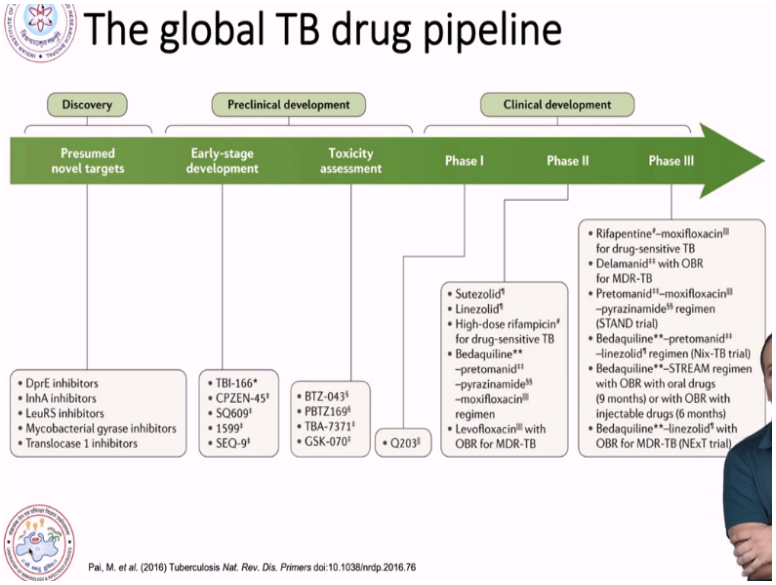

So globally there is a lot of effort going on in order to eliminate the Mycobacterium tuberculosis. So here you can see that there is a presumed novel target, basically this is the inhibitor of several enzymes. There is an early stage development. There is toxicity assessment and some molecules are in phase 1 trial, some are in phase 2 trial and some are in phase 3 trials. So, this is just an overview of a global effort against the tuberculosis.

The people are still working in order to eliminate the Mycobacterium tuberculosis. So, with this I am finishing the bacterial infection and the tuberculosis and I am also finishing the week 11 and next week I will discuss about the fungal and parasite infection and with that I will finish the whole syllabus. Thank you.