**Manage TB**
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**Lecture – 32**
**Drugs for treating Tuberculosis and Principles of Chemotherapy**
**Session 02**

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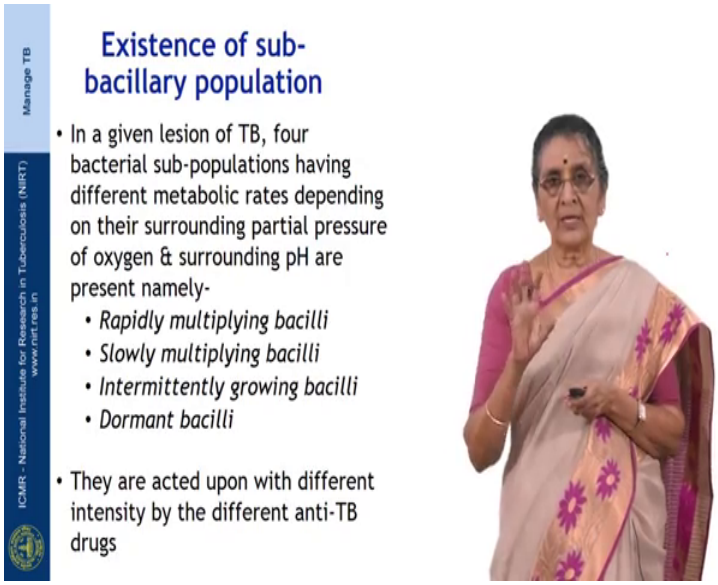


Now, we will come to the bacillary population; this is a very important slide I need your attention. In a given lesion of tuberculosis we have bacteria please told you it will be in millions, but when you look at their metabolic activity and metabolic rates that bacteria are not similar some are rapidly multiplying, some multiply very slowly, some intermittently in spurts they multiply and some remain dormant.

So, we have four different groups of bacilli and we need drugs that should act upon all these 4 groups of bacilli. So, once again this is a necessity for us to use multi drugs in the treatment of tuberculosis; where different drugs act upon different bacteria.

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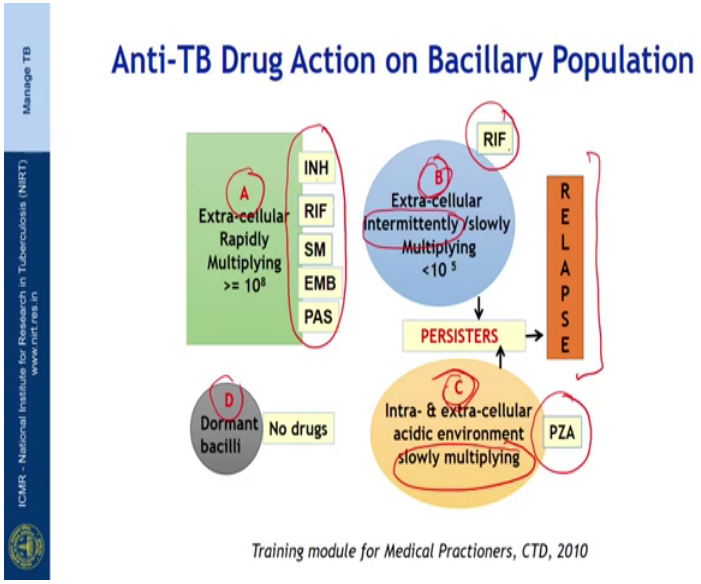


Now, this is a very interesting slide as I told you earlier you have four different types of bacteria ok; one is rapidly multiplying extracellular. Now, almost all the drugs INH rifampicin, streptomycin, ethambutol act upon this population of bacteria so you achieve a rapid kill then you use all the 4 drugs.

But when it comes to slowly multiplying bacteria group B and group C; group B is a bacteria characterized by slowly multiplying and also they multiply intermittently in spurts. So, the only drug that acts upon this group is rifampicin to take the third group once again slowly multiplying bacteria this these are found in acid environment the only drug that can act upon this group is pyrazinamide.

Yet another group is dormant bacilli as of now we have no clue about which drugs act upon this; usually they remain dormant for 20 to 30 years and they may come with relapses after 30 40 years. Now, let us go back to A B and C. When you use a regimen containing INH rifampcin, rifampcin and pyrazinamide they attack all the 3 groups of organisms and you achieve a rapid bacterial kill.

Now, what happens in well when you, but this B and C they may remain for some time and they are known as persisters and you need drugs for longer duration in order to reduce relapses. So, a regimen should achieve a rapid kill by using these drugs regimen should also use these two drugs to remove the persisters and to reduce relapses. So, in

order to achieve cure in order to reduce relapses you need to cover you need to include all these 3 groups of drugs.

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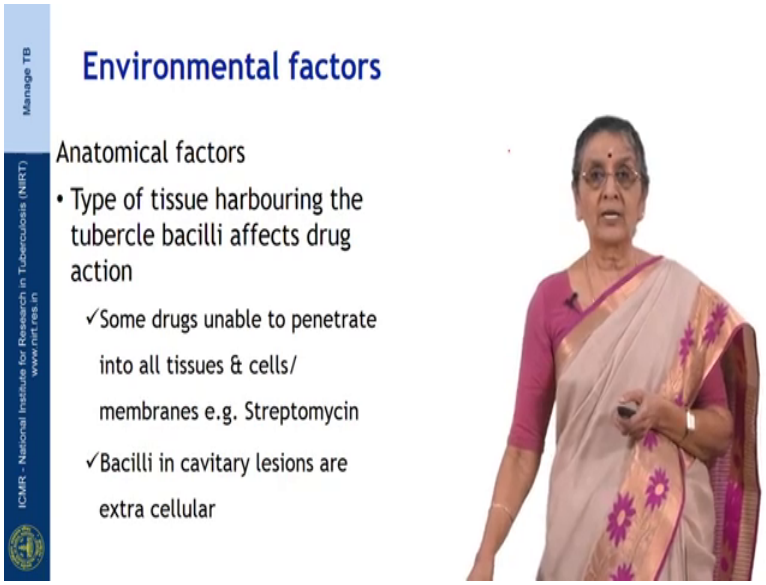


Coming to the environmental factors; some drugs are unable to penetrate into all tissues, membranes some are not able to penetrate brain barrier so you have to choose drugs accordingly.

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Coming to the pharmacological basis of treatment as we have already discussed earlier; it is important to achieve peak serum levels of all drugs simultaneously, so that maximum

bactericidal effect is obtained while treating the patient. This is achieved by administrating all the drugs in the same time; do not split INH into morning 100 milligram, afternoon 100 and evening 100; please give INH as a 300 milligram single dose along with the other drugs.

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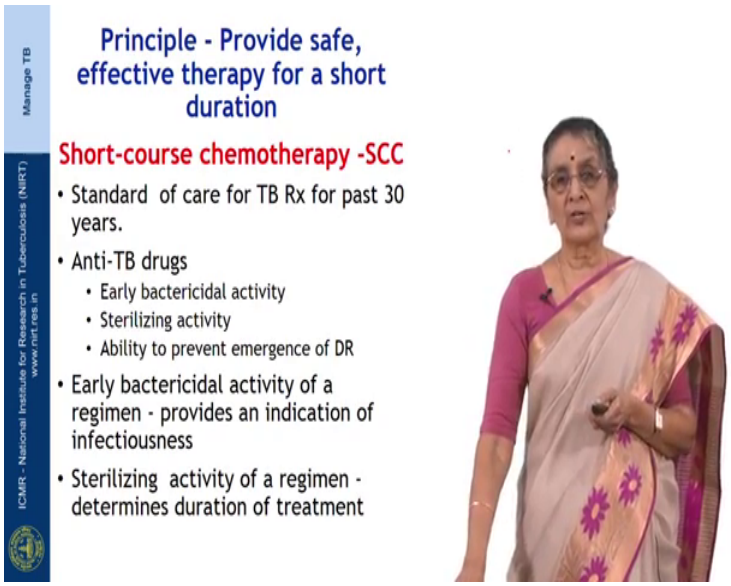


Now, so let us look into the short course chemotherapy like what based on what we discussed so far. We use rifampcin, INH, ethambutol, pyrazinamide for shortcut chemotherapy regimens and that has become the standard of care for TB treatment the last 30 years.

Now, these group of drugs exhibit three important activities; one early bactericidal, two sterilizing activity and three ability to prevent emergence of drug resistance; now early bactericidal activity of a regimen provides early kill and patient becomes non infectious and smear and culture become negative in more than 90 percent within 2 months.

So, each regimen should have drugs that has got bactericidal activity. Sterilizing activity of a regimen determines the total duration of treatment.

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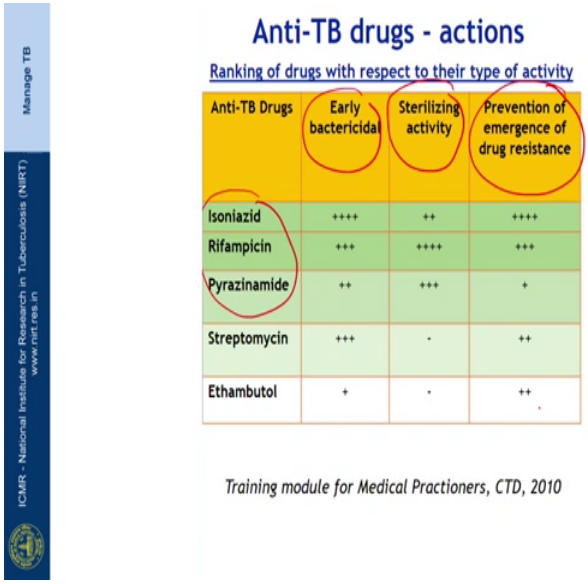


This slide tells you the different types of activity; early bactericidal, cell activity, sterilizing activity and prevention of emergence of drug resistance. An ideal drug should have all the three activities; look at isoniazid acid, look at rifampicin and pyrazinamide these 3 drugs have all the three activities in various proportions and when we use these three drugs in a regimen we achieve both early bactericidal activity and sterilizing activity.

The certain extent streptomycin is useful in early bactericidal activity so it is given for 15 days or 1 month in the beginning of the treatment and ethambutol helps in reducing the emergence of drug resistance.

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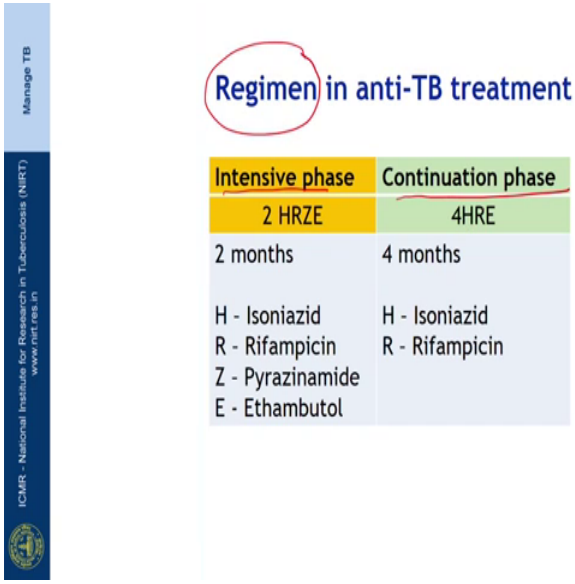


So, based on all these activities we design treatment regimens. What is a regimen? A Regimen is a group of drugs; given in a particular combination, in the particular dosage, in a particular for a particular duration. So, each regimen will have two phases namely intensive phase and continuation phase.

Intensive phase will have 4 drugs namely INH, rifampcin, ethambutol, pyrazinamide for 2 months and continuation phase will be for 4 months including H, INH, rifampcin and ethambutol.

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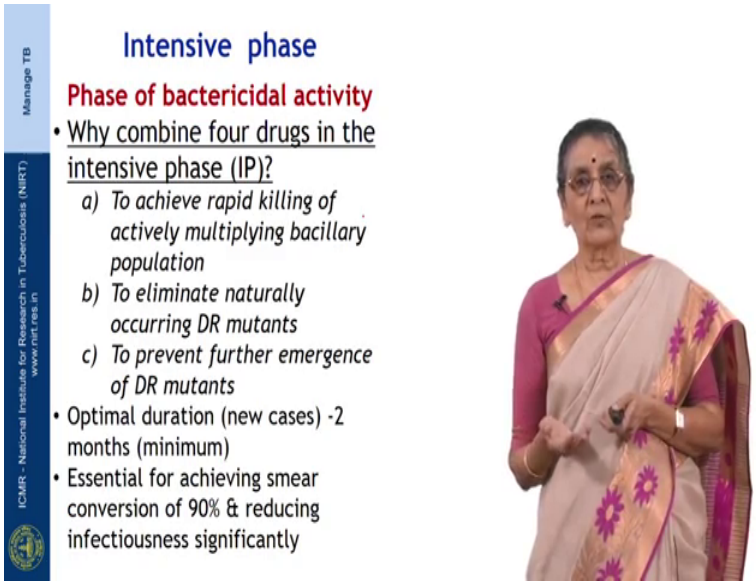

Why should we have intensive phase? Now, this clearly tells you why we should combine 4 drugs in the intensive phase of treatment; intensive phase is to achieve rapid kill of multiplying, rapidly multiplying bacillary population, metabolically active rapidly multiplying bacteria which from the majority of the population are killed by kill in this phase.

This phase also eliminates naturally occurring progressive mutants, this phase also helps to prevent further emergence of DR mutants and optimal duration will be for 2 months and usually we achieve a smear and culture conversion of 90 percent at the end of intensive phase.

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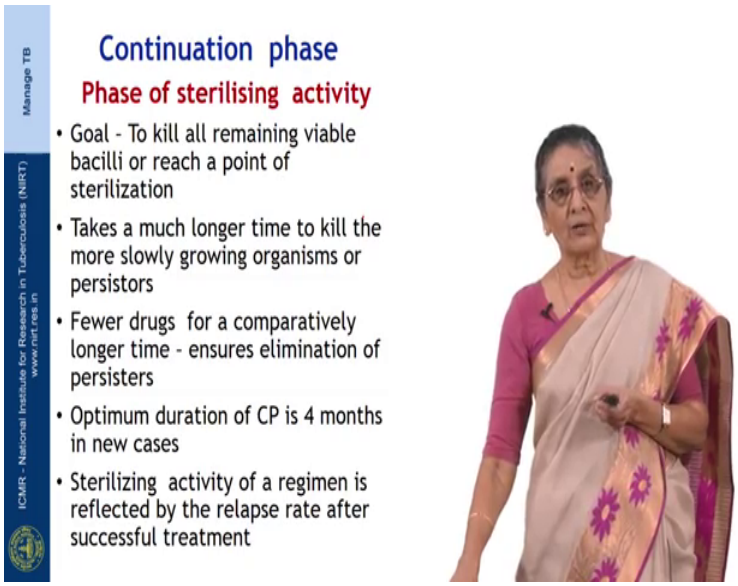


Now, this slide tells you about the continuation phase; this is the phase of sterilizing activity as I told you earlier at the end of 2 months we achieve culture negativity in 80 to 90 percent of the patients need to consolidate the culture conversion you treat them for 4 more months; so that they do not develop resistance or do not come back its smear possibility.

How the sterilizing activity is achieved? It is by giving drugs for 4 more months. Here you give fewer drugs, but for a longer duration optimum duration would be for 4 months that is totally in a regimen you will have intensive phase and continuation phase and total period of 2 plus 4, 6 months of treatment.

Now, sterilizing activity of a regimen is reflected by the relapse rates after you treat the patient after they are cured.

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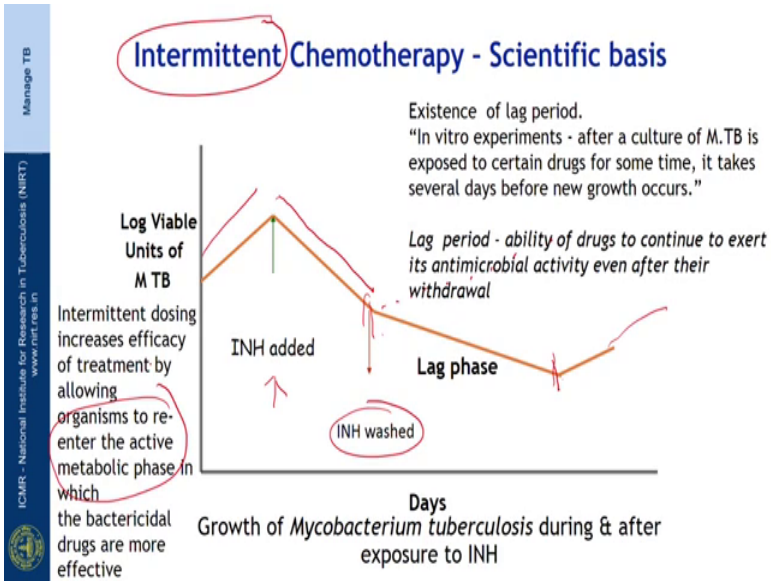


In the earlier years we used to give treatment intermittently that is thrice weekly or twice weekly. How is it possible to give 4 drugs thrice weekly, what is the scientific basis for this? If you look at this culture media, look at the log count; in the culture the bacterial count goes up.

Suppose this culture is exposed to INH and the culture media shows a drop in the bacterial count; even after removal of the drug say INH you expect after removal of the drug the culture media should show increase in the viable counts like this, but what you find is a continuation of the drop in the bacterial count and this is called lag phase. Even after removal of the drug the bacteria do not multiply, this may be for few hours or few days and after that the bacteria starts multiplying once again.

This principle of lag phase that is once the culture is exposed to your drug the bacterial count goes down even after removal of the drug the bacterial count continues to go down it takes some time for it to recover metabolically and to multiply; this principle is used in intermittent chemotherapy.

Now, using this principle of lag phase intermittent doses they are given maybe thrice weekly or twice weekly; the main principle here is intermittent dosing increases the

efficacy of the treatment by allowing the organisms to re enter the active metabolic phase, in which the bactericidal drugs are more effective.

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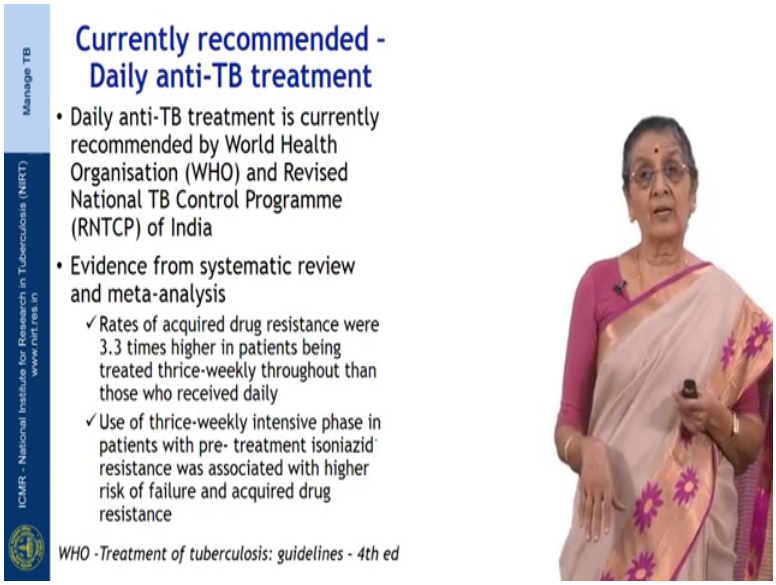


Currently WHO and national TB control program of India recommends daily anti TB treatment, this is based on the systematic review and meta analysis, but they have observed higher rates of resistance when intermittent regiments are used; also among patients harboring INH resistant organisms the rates of failure was more and also acquired resistance was more.

So, currently the national TB control program of India recommends daily anti TB treatment.

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It is not enough if we design a proper regimen and a proper dosage and start treatment; it is equally important that we ensure treatment adherence and see that the patient is treatment compliant and completes the envisaged chemotherapy.

And for this one of the methods used is directly observed treatment; where patient is helped either a community worker or a person from the from their own house to complete the treatment. Long term self administration of drugs is always problematic and patients may not complete treatment because they are symptomatically better you invariably after the intensive phase and they do not find the need to take treatment completely.

So, directly observed treatment helps to reduce loss to treatment from the program point of view and it may ensure adherence to prescribed chemotherapy.

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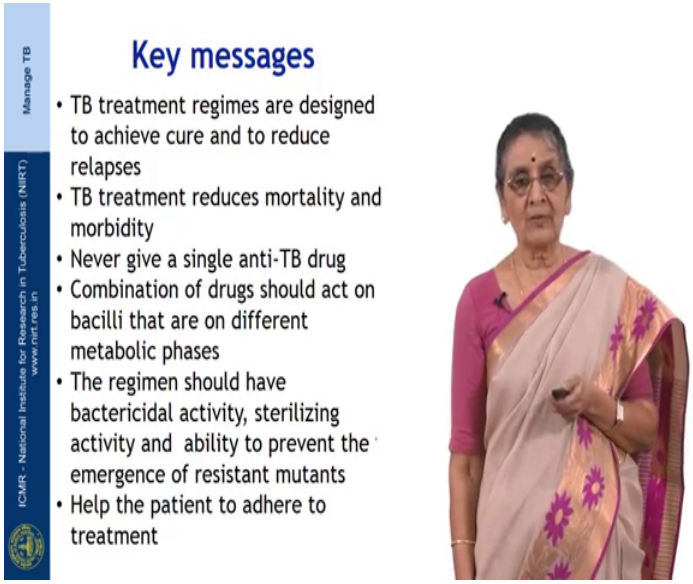


To conclude my talk I would like to tell these key messages. One TB treatment regimens are designed to achieve cure and to reduce relapses. TB treatment reduces mortality and morbidity the dictum is never ever give a single anti-TB drug or never had a single drug to failing regimen.

Always a combination of drugs should be given that act on different bacillary population that was described to you earlier. The regimen prescribed should have bacterial activity, sterilizing activity and ability to prevent emergence of resistant mutants. Apart from all this it is equally important to see that the patients complete their treatment, adhere to the treatment and do not stop treatment half way through.

This has to be done by someone in the family or from the community. Thank you for patient listening and I hope you have understood the principles of chemotherapy.

Thank you.