Manage TB
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Lecture – 46
Treatment of Pediatric Tuberculosis-Session 01

Welcome to the session on Treatment of Pediatric TB. I am Dr. Varinder Singh from Lady Hardinge Medical College in Kalawati Saran Children Hospital, New Delhi and I will take you through with the philosophy of how we shall make a Chemotherapy of TB and how it is treated in children what are the salient differences.

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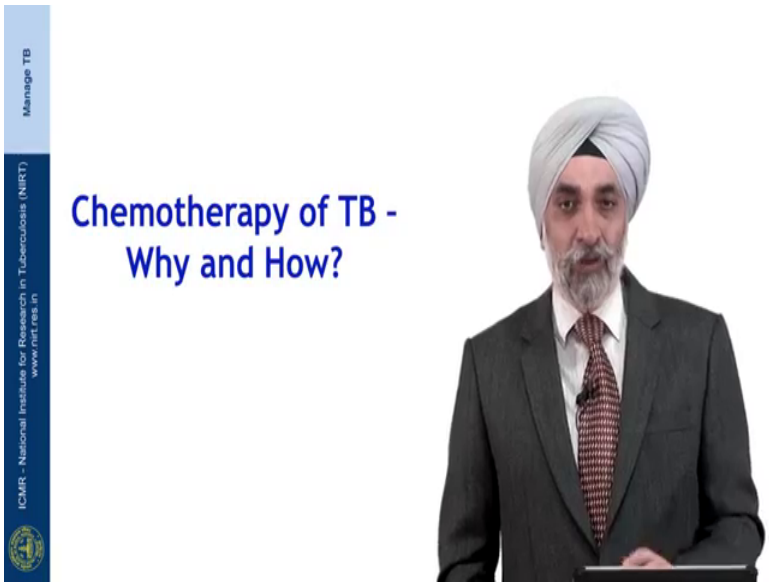

Quickly taking you through with why and how of chemotherapy of TB.

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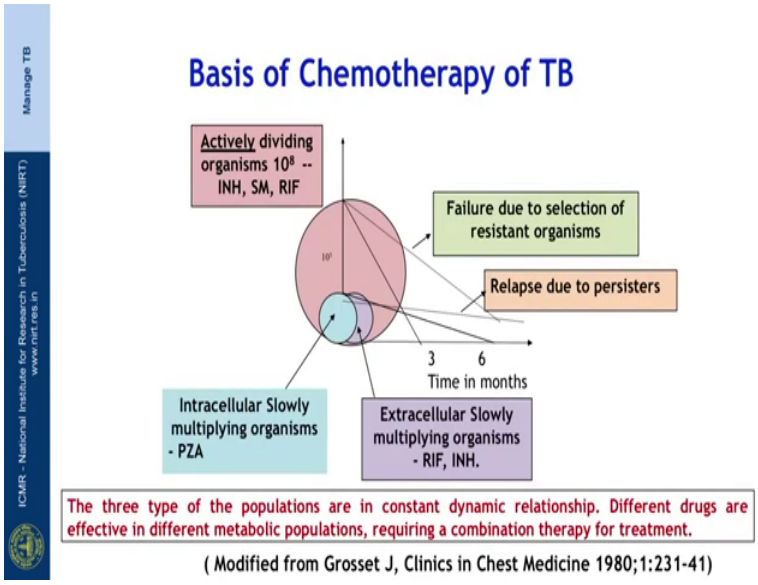

If it has been hypothesized that in a given case of tuberculosis there are three very important population or rapidly dividing or actively dividing group of organism, a intracellular slowly multiplying group of organism and an extracellular slowly multiplying persisting group of organism which just have spurt of growths in between. Why it is important to know?

Anti TB drugs act only when a bacteria is dividing. So, it is easier to kill maybe this larger population which is actively dividing and there the drugs which are most effective are Rifampicin INH and Streptomycin, INH being the most potent

If you look at rapidity of kill it is the rifampicin which kills faster when it comes to the intracellular slowly growing bacteria, this has an acidic pH where the drug which is most effective pyrazinamide. When it comes to the slowly persisting bacteria slowly dividing persisting bacteria, here it is the INH and rifampicin which are good.

What does it mean? Most of these rapidly dividing bacteria which are responsible for infectivity and the symptoms and the cachexia which the patient has can be brought down very quickly with the modern chemotherapy say in about 2 months time. While it is the slowly dividing persistent bacteria which take far longer because they are intermittently dividing and as I said they can be affected only when they are dividing and not otherwise.

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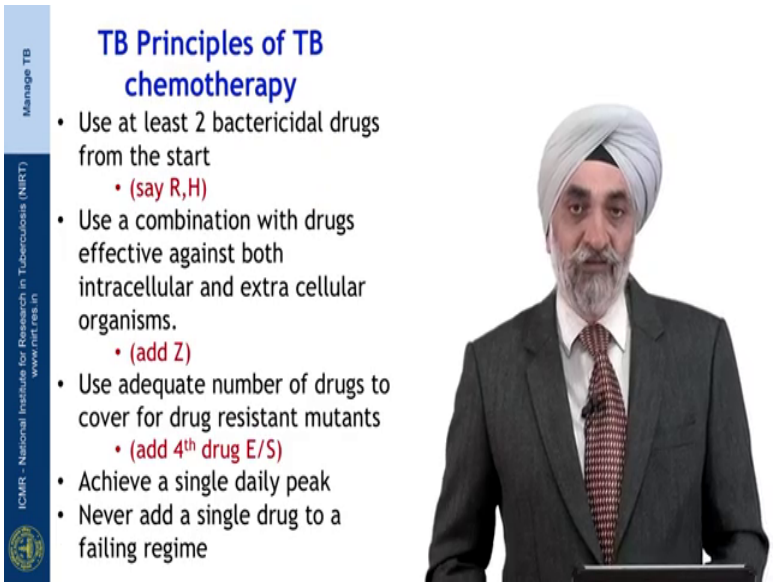

So, there is a constant dynamic relationship between these population and this understanding of bacterial population tells us that you need a combination chemotherapy you cannot work without that. So, you to begin with need at least two bactericidal drugs which are say rifampicin and INH because they work across all the 3 milieu less effective in intracellular.

But if you need something to work on intracellular bacteria also which will give a faster sterility then you add pyrazinamide to it which brings two things to us; one it will drink bring down the infectivity fast, two continuing this pyrazinamide longer than the intensive phase perhaps would not be useful because there not many intracellular actively deep multiplying, but bacteria after 2 months in most situations in a sensitive case.

You also want to prevent the emergence of resistance to these three drugs. So, in case you have increased level of background resistance to any of these drugs like in our country we have 2 INH, you may like to add a fourth drug to prevent emergence of resistance to these first line drugs which are using. So, that is the basis of using 4 drugs chem combination chemotherapy in children; you need HNR to rapidly which are two important bactericidal drugs to rapidly kill.

You add pyrazinamide for intracellular organisms; since there is a background resistance to INH and you want to prevent emergence of resistance to other drugs which you have

used you add ethambutol or streptomycin, ethambutol takes an edge over streptomycin because it can be given orally and not need needed to be given injective.

What is also important is the bacteria divides about in about 17 to 20 hours that is the dividing time for a micro bacterium tuberculosis. So, you and as I said it is killed only when it is dividing. So, you need a single daily peak, therefore, there is no benefit of dividing the anti my micro bacterial drugs or ATT into several different you know more than 1 dose a day.

Equally important is that if you have a failing regime you never add a single drug because you would then have some metabolic population which would not be receptive to this drug and you may have amplification of resistance in that situation.

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When we say intensive phase, it aims at rapid kill killing of the bacilli it is a to create a state of non-infectiousness say within 2 weeks that would be the ideal. What we commonly get is a quick relief of symptoms and what you get a smear negative where it can be seen in about 2 months time.

This would lead to prevention of development of drug resistance to because the large mass of actively dividing bacteria is affected and it goes down. What is equally important is these drugs are effective when taken and that is where it is not just the combination therapy which is important, it is equally important to make sure that patient

has been adhering to his therapy which can be facilitated by a direct observation and the role of DOT comes there.

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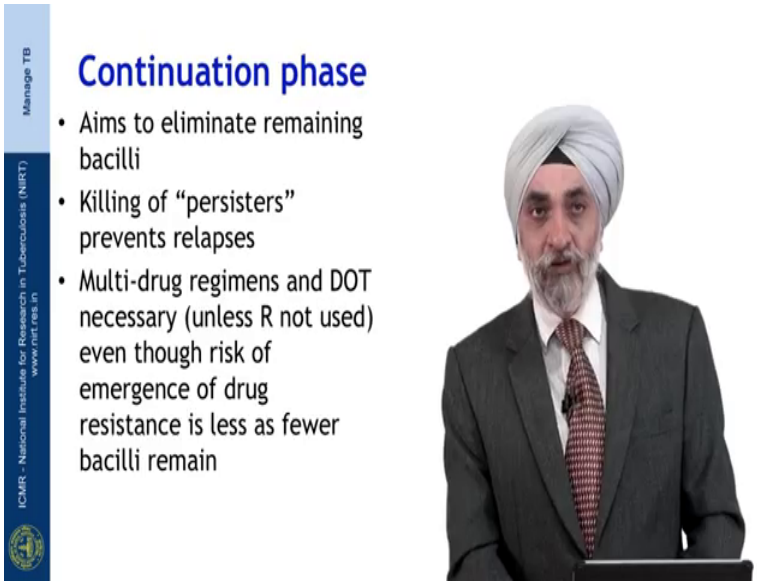

In the continuation phase you your aim is to eliminate those remaining bacilli which are spurting in between, but persist in extracellular milieu. You want to kill these to decrease the per subsequent risk of relapse.

The multi drug regimen which are used in DOT the they will they are enough to deal with this situation and that is what is needed in the continuation phase; however, since the bacterial mass is less you do not need very many in drugs. So, pyrazinamide is not used in continuation phase in for these very reasons.

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When you go to the having understood the philosophy of chemotherapy, let me take you through with some standardized case definitions which are used by WHO or by revised national TB control program in our country. Those standardized case definitions are about new case and when we say new case it means the patient who has not taken treatment for more than 4 weeks or less than that has taken treatment for less than less than 4 weeks or never taken a treatment.

Some of these patient may have been who have taken treatment in the past are were lost to treatment and have come by or follow up case or a failure case who has failed on the initial regime or a relapse case. These are the patients were likely to have drug resistance bacilli and therefore, are treated differently. The other thing which determines the definition is by the site of TB whether it is pulmonary or extra pulmonary.

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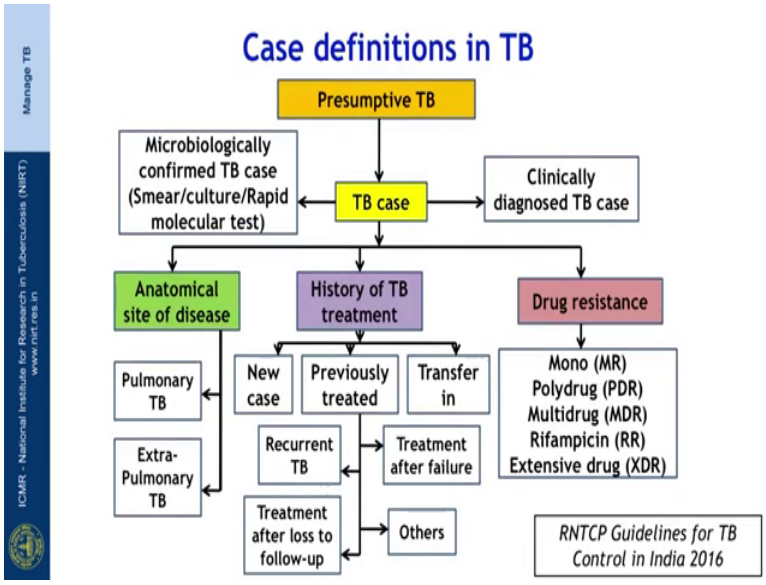

So, the case definitions in TB are first where what was erstwhile cause called as a TB suspect we use the terminology presumptive TB, someone who is likely to have TB. If it has confirmed microbiologically we call them as microbiologically confirmed TB case or it could be a clinically diagnosed TB case. Equally well depending on the anatomical anatomical site of the disease this child may have lung involvement where it is called pulmonary TB or may have other involvements of lymph node CNS or bone where or pleura where it is called extra pulmonary TB.

If this child has never taken treatment in the past it is called a new case, if this child has taken treatment in the past it is called previously treated case, where it could be either someone who was completely treated and it has come back then it is called recurrent TB or it could be after loss to follow up someone which was in the past call this defaulter or it could be someone who has failed on first line therapy.

Where drug resistance is known the sensitivity pattern is known this could be someone with the mono drug resistance or a poly drug resistance which is non RNH resistance to other drugs or it could be a rifampicin resistance or someone who could have XDR or extensive drug resistance which means you are resistant to rifampicin, INH, injectable and fluoroquinolone. These are the this is the way we define our TB cases. I am largely going to discuss with you today treatment of the drug sensitive variety of TB.

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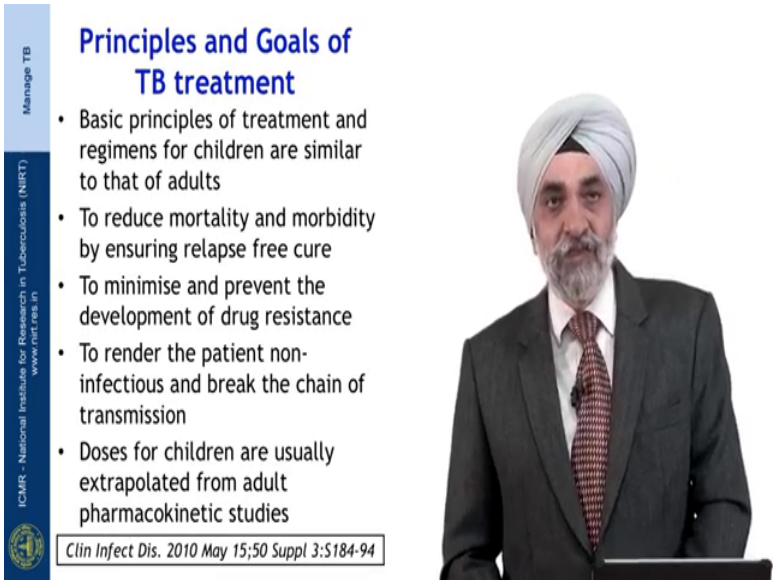

The principles and goals of TB treatment are very similar in children as they are in adults. The idea is to reduce mortality and morbidity and to ensure a relapse free cure.

And at the same time you want to minimize or prevent the emergence of drug resistance and you want to make the render the patient non infectious while many pediatric cases because they have paucibacillary are non infectious tools to begin with, but some are not who have large cavitary pneumonias and you want to render them non fixtures to break the chain of transmission within the household and in the community and that is an important principle or goal of TB treatment.

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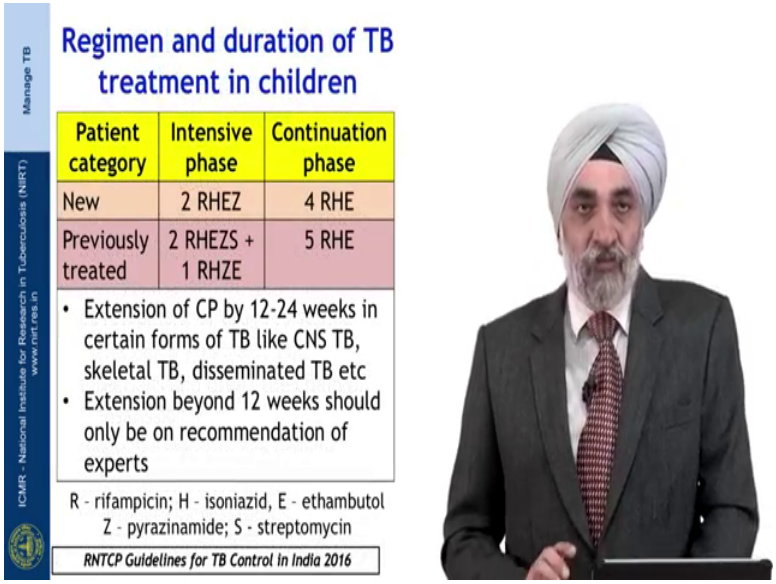

It is largely the doses for children are extrapolated from adult pharmacokinetic studies, but more recently we have pharmacokinetic studies available on children and which has also led us to understand that perhaps we need higher than commonly you currently used doses for most first line anti TB drug and I will discuss them later in the lecture.

What is the combination which is recommended if it is a new case which is either a case who has never been treated or treated for less than 4 weeks? We need 4 drugs in the intensive phase which is rifampicin, INH, ethambutol and pyrazinamide. You give this intensive phase for 2 months. The continuation phase has rifampicin, isoniazid ethambutol for 4 months in most situations. Except for some extra pulmonary forms like TBM, like osteoarticular TB where you would increase this to up to 12 months of therapy.

So, what is recommended is 6 months for most situations whether it is this parent pulmonary or extra pulmonary like skin or lymph node, but if it is extra pulmonary of CNS involvement or bone involvement then the recommendation is to use it for 24 months 24 for 12, 12 months.

The further extension of continuation phase is only recommended on an individual basis occasionally and not routinely. In a patient who has been treated in the past has been treated for more than 4 weeks either as a recurrent case or of someone who has come after interrupting treatment or someone who has failed on initial therapy then what is recommended is that they should be investigated for drug resistant TB and pending investigation for drug resistance they may be started on a retreatment regime which contains all the 5 first line drugs together.

So, rifampicin, INH, pyrazinamide, ethambutol and streptomycin are given together for 2 months. If you get a bacteriological diagnosis in this child and you know the sensitivity you fine tune the therapy thereafter based on sensitivity and the guidelines. In if that is not the case then we continue these for 2 months and after 2 months this intensive phase we reduce this streptomycin and we continue this intensive phase with 4 drugs for another month.

So, the intensive phase in retreatment is biphasic 2 months with 5 drugs, 1 month with 4 drugs, thereafter we give 5 months of 3 drugs continuation phase. This 3 drugs

continuation phase will also be expanded extended by 3 months in case of TBM and osteoarticular as we were doing for new cases.

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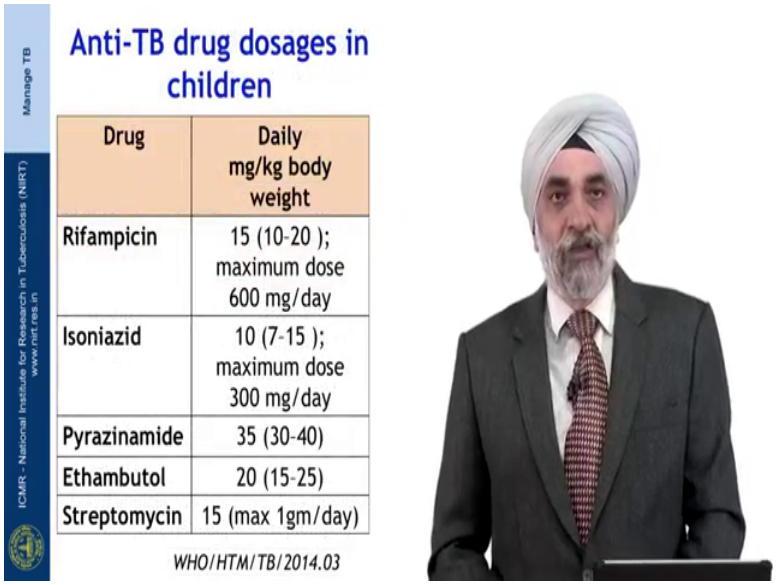

The drug doses in children are higher rifampicin by 15 milligram per kg say between 10 to 20, isoniazid by 10 milligram per kg, pyrazinamide by 35 milligram per kg body weight per day, ethambutol by 20 milligram per kg body weight per day and streptomycin by 15.

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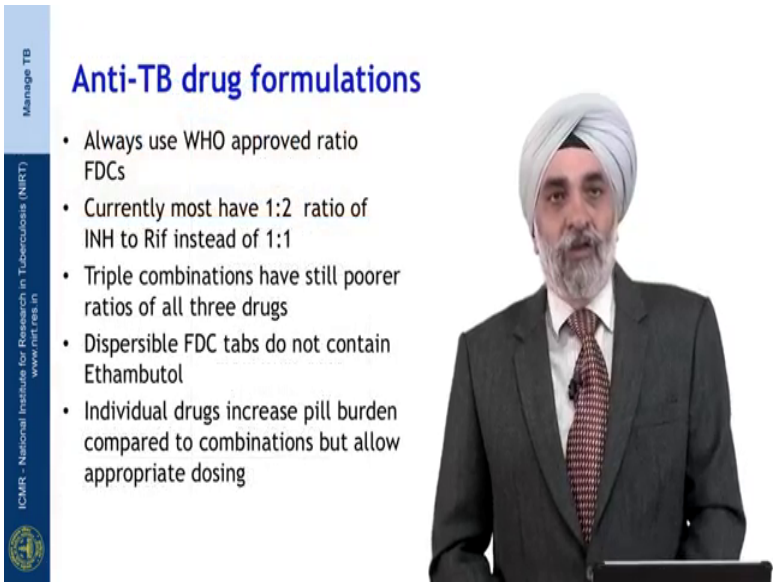

What is important to remember here is when we use these drugs individually it adds to the pill burden which sometimes can affect the adherence and therefore, often what we use is a fixed drug combination. When you use currently available fixed drug combination most of them do not have the right ratio.

So, what WHO has approved a right ratio is 1 is to 1 or 1 is to 1.5 of INH to R. What we use is 1 is to 1.5 50 milligram of INH with 75 milligram of rifampicin. But most of the available and well known formulations available in our country do not have this right combination. So, remember when you write any FDC that they are in right combination. It is particularly these ratios go much worse when you have triple drugs.

A word here which is important to remember while 4 drug FDC's are available for adults they are not available for children because the ethambutol is a hygroscopic drug and in children most of the FDC's are dispersible tablets and you cannot add ethambutol to these dispersible tablets. So, children ethambutol needs to be given separately you would get a triple combination or 3 drug combination of R H N G for your as an FDC and remember to use them in the right ratio as I mentioned.

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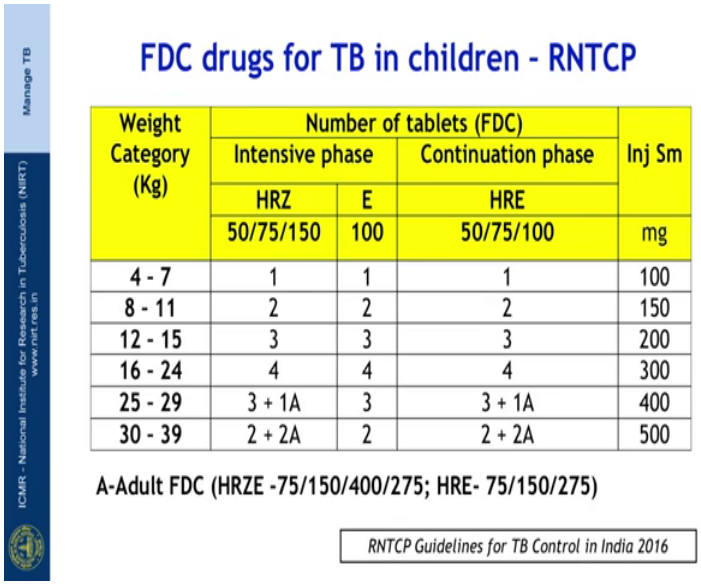

If you have the right ratio product of 50 of INH, 75 of rifampicin and 150 of pyrazinamide, then depending on the age band one would need 1 to 4 of these tablets which are actually not adding to pill burden because they can all be dissolved in 5 ml of water they are dispersible.

In an older child about 25 you can add a 4 drug adult FDC. This table describes and as you can appreciate this now breaks down into much bigger weight bands because it gives you bigger flexibility and therefore, one is able to ensure that children in all the weight bands with at the beginning or end are not under or overdose by any of these drugs.

So, this table comes handy, I would not repeat it you do not need to remember it, but you should keep it as a ready road source reference to you on your table if you are treating TB children.

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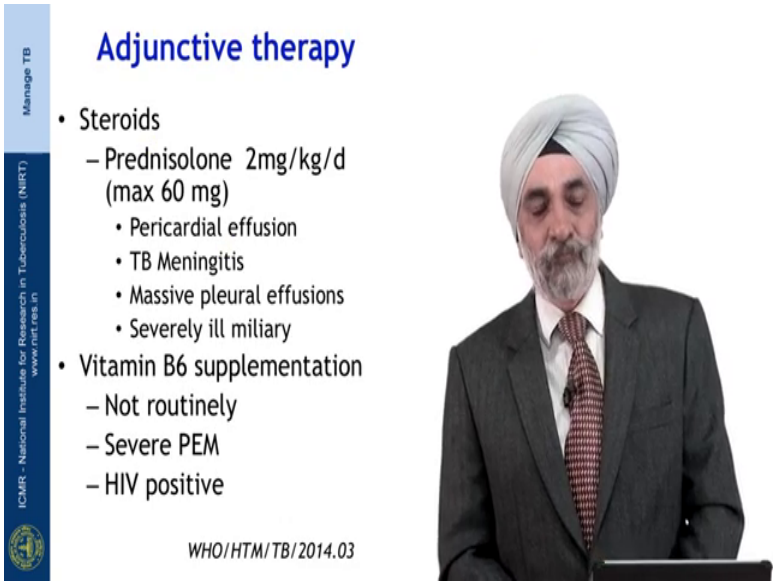

What does a adjunctive therapy one needs? There may be a need for additional steroids in some form of childhood TB. We use prednisolone 2 milligram per kg per days maximum 40 to 60, in our older child 60 otherwise 40 milligram per kg.

Pericardial effusion, TB meningitis, massive pleural effusions or severely ill hypoxic miliary children are the situations where you need steroids; particularly pericardial effusion and TB meningitis. You may need B6 supplementation, in children who has severe malnutrition or are HIV positive because they may have malabsorption.