**Manage TB**
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**Lecture - 48**
**Management of Adverse effects to anti-TB Drugs**
**Session 02**

So, welcome back. We have already discussed about the various side effects of anti-TB drugs, and now I welcome you to discuss about the management of the adverse effects of the anti-TB drugs. So, how do we manage the adverse effects anti-TB drugs?

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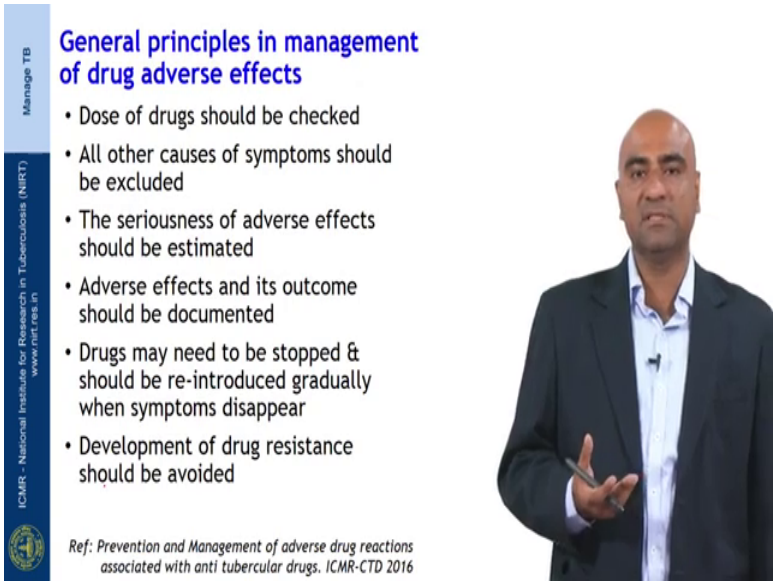


So, let us see what are the general principles in the management of adverse effects of anti-TB drugs.

First you should check the dose of the medicine. See many times the patients weight may be only around 40 or 30 and he may be receiving pyrazinamide of 1500 milligram. So, it is very very imperative that the dose of these medicine should be checked and we should see that it is appropriate to the patient's body weight. Then other causes of the symptoms should be excluded. For example, a patient having a sneezes it may be due to a sinus tuberculosis it may not necessarily be due to tuberculosis it may be not necessarily be

due to the side effect of the drugs. So, you should always exclude what are the causes for a patient having symptoms.

Similarly, for hepatitis, hepatitis it can be due to inner viral hepatitis or it can be due to other drugs other than the TB medicines which the patient is taking. So, all these things should be considered while managing adverse drug effect of tuberculosis. And the seriousness of the adverse effect should be estimated. For example, many patients can have a minor side effects like nausea or vomiting. So, it is not something for which it regimen needs to be changed you have to counsel the patients properly, you have to give a proper diet advice and if you had antacids or medicines for the gastritis this problem can be managed.

Similarly, skin rashes it can be managed with minimum antistaminics also. There are very few side effects which are really warranting a change in regimens like thrombocytopenia, and renal failure with rifampicin, if this is documented and if you are sure that it is due to these drugs then we can consider a change of regimen.

The adverse effects and its outcome should be documented. So, we have this treatment card which we will be showing later in that we should always document what are the adverse effects to which drug it is caused and how we manage this should be recorded. And sometimes you may have to stop the drugs, and we can introduce the drugs in a gradual manner this usually we do it in cases of hepatitis. So, when a patient has a hepatitis after starting ATT or if the patient is having a skin reaction then we can introduce the drugs in a gradual manner. We can find out which is the offending agent and try to eliminate the offending agent and continue with the other drugs.

The basic principle is that we should avoid the development of drug resistance. See we should have regimens in which there should be at least 4 or 5 drugs which are effective so that drug resistant tuberculosis does not develop in the first place, as you all know prevention is always better than cure.

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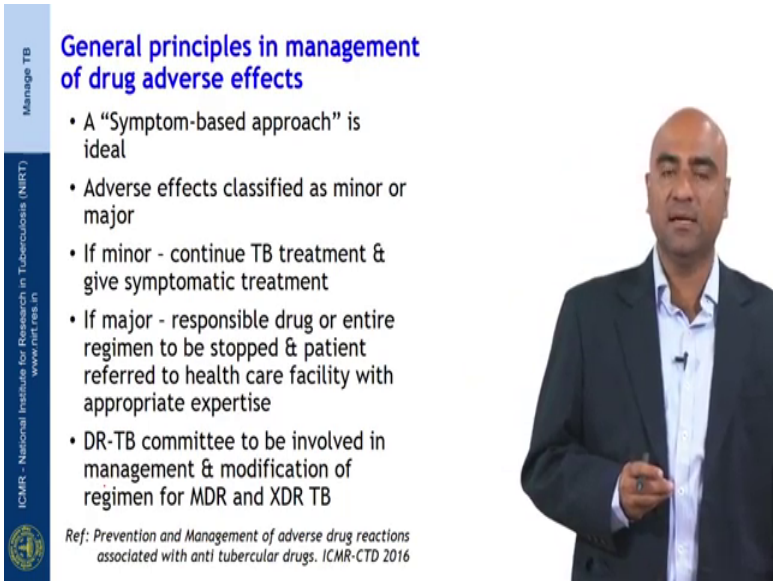


Continuing the general principles we should always have a symptom based approach. For example, you identify what is the symptom and you try to properly counsel or adjust the dose or give some added supportive care for the patient and have a symptom based approach to the drug adverse reaction.

So, you should classify the adverse reaction as minor or major and if it is minor you can continue the TB treatment and give symptomatic treatment. Like itching for itching you can just give antistaminics and you can continue with the treatment. If it is major if they like it is a way like we have a Stevens Johnson syndrome or we have a drug induced hepatitis, then you find out which is the responsible drug and either that drug or the entire regimen may have to be stopped and you have to refer the patient to an appropriate specialist for management of the patient. And we have drug resistant TB committee in most of the institutions who are involved in the management and modification of regiments of MDR and XDR TB. So, they will always they are always there to guide you on how to go about with this with such patients.

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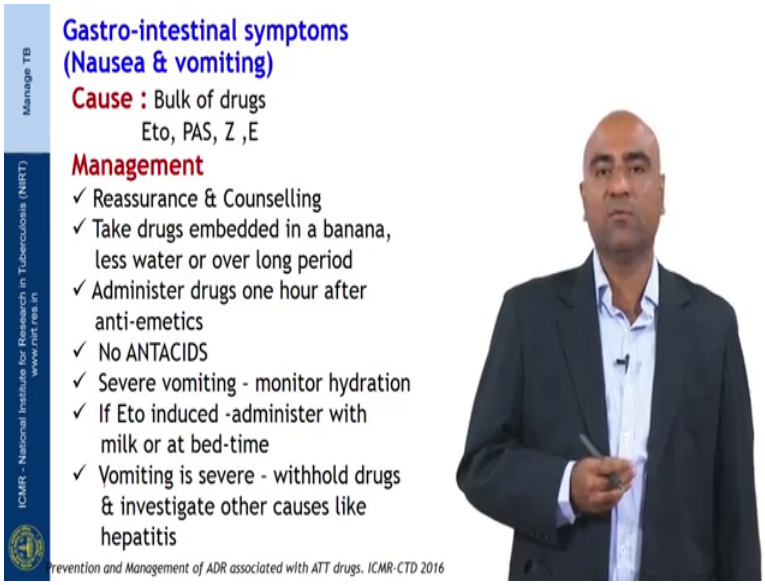


So, let us see each symptom and how to manage the symptoms. So, the common symptoms with anti tuberculosis drugs is, as we discussed time and again one third of the patients having ga symptoms like nausea and vomiting. So, it most of these drugs can cause ga symptoms and in second line the main in the drug resistance TB medicines the main drugs which are known to be associated with such symptoms are ethionamide, PAS, para aminosalicylic acid and ethambutol.

So, how do we manage this cases? Management mainly it involves reassurance and counselling and other options which we have are we can ask the patients to embed the tablet in banana or you can ask them to drink less water or take the medicines over a long period. So, see most of the patients whom we come across the main problem is they get frightened after seeing the size of the tablet us, most of the time in TB medicines are too big and when they see itself they start complaining to us that they are not able to swallow these medicines.

So, these are some options which you can give them and they can motivate them to continue with the treatment. And you can administer the drugs one hour after antiemetics. You can avoid antacids severe vomiting you should monitor the hydration of the patients and if it is ethionamide induce you can administer it with milk or at bedtime.

Vomiting is severe you should withhold a drugs and investigate other causes like hepatitis.

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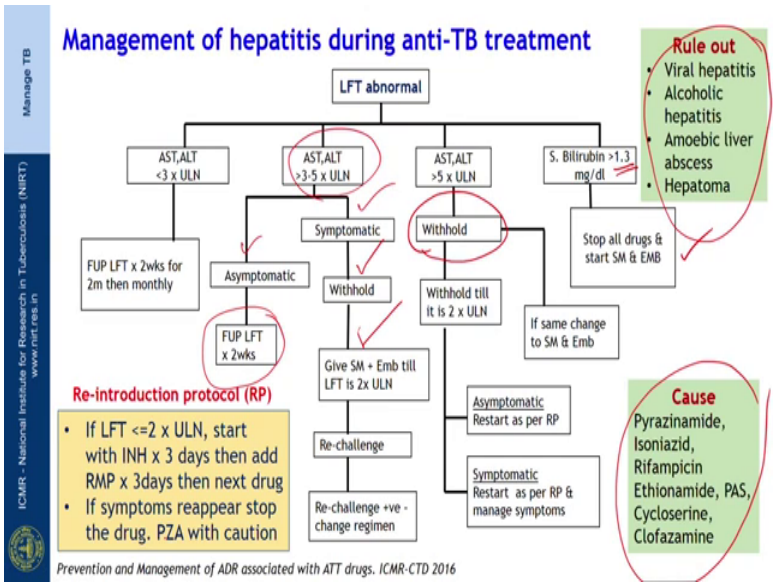


So, let us see how to manage a case of hepatitis during anti tuberculosis treatment statement. So, as we always discussed see many of the symptoms may not be due to the TB treatment and it can be due to many of the associated illnesses. For example, hepatitis it need not necessarily be due to anti tuberculosis treatment there are other factors which can cause hepatitis.

So, when a patient complains of vomiting the first thing which we should do is we should rule out other causes of hepatitis. Like you have viral hepatitis, this alcoholic hepatitis, amoebic liver abscess and hepatoma; so, investigation should be done for all these diseases and these diseases should be eliminated before labelling that the patients side effects are due tuberculosis treatment.

The common drugs which are usually associated with hepatitis during the treatment include pyrazinamide, isoniazed, rifampicin, ethionamide, para aminosalicylic acid, cycloserine and clofazamine. So, how do we manage when a patient is having an abnormality in a liver function test?

So, let us look at this flowchart. So, if the patients when the whenever a patient is complaining of vomiting or nausea or abdominal pain you get an LFT done and if the LFT if the liver enzymes are less than three times the upper limit of normal then you can just continue with the medicines, you can follow the liver function test and for 2 weeks for 2 months and then monthly. You can just what he needs is just reassurance and you can just continue with the regimen and you can just monitor the liver enzymes.

Suppose the liver enzymes are 3 to 5 times the upper limit of normal you have to see whether the patient is symptomatic or whether the patient is asymptomatic. So, if the patient is asymptomatic you can just follow him up you can just follow and get a repeat LFT done after 2 weeks. Whereas, if the patient is symptomatic with a liver enzymes elevation of 3 to 5 times the upper limit of normal then you definitely have to withhold the medicines and till his liver enzymes settle you can chose a non hepatotoxic regimen like streptomycin and ethambutol which is given till his liver function returns to twice the upper limit of normal. And once the LFT is back to normal then you can re challenge and again monitor the LFT. Suppose even after re challenge the patient purses and he still has the arranged LFT then you can consider a change in regimen.

Next is suppose the liver enzymes are more than 5 times the upper limit of normal then there is no question, but you have to withhold the regimen you withhold regimen and weight till the liver function returns to twice the upper limit of normal. And once it is less than twice the upper limit of normal if the patient is asymptomatic you can introduce you can reintroduce the drug and try to see whether is able to tolerate it at that point of time. And suppose the patient is still symptomatic then you have to restart as per the reintroduction protocol which we will discuss.

And other parameter which we have to see is the bilirubin. Suppose the bilirubin is more than 1.3 then you stop all the drugs and start a non hepatotoxic regimen like streptomycin and ethambutol. So, let us see the how to reintroduce ATT in such patients. So, if the liver function test is less than or twice the upper limit of normal then first drug which will give is INH, due we give INH for 3 days and then we add rifampicin for 3 days and then we had the other drugs one by one. So, while giving this drugs we have to monitor the LFT and look for whether the patient is having any symptoms. So, if the

same symptoms reappear then you stop the drugs and one drug which should always be reintroduce with caution is pyrazinamide.

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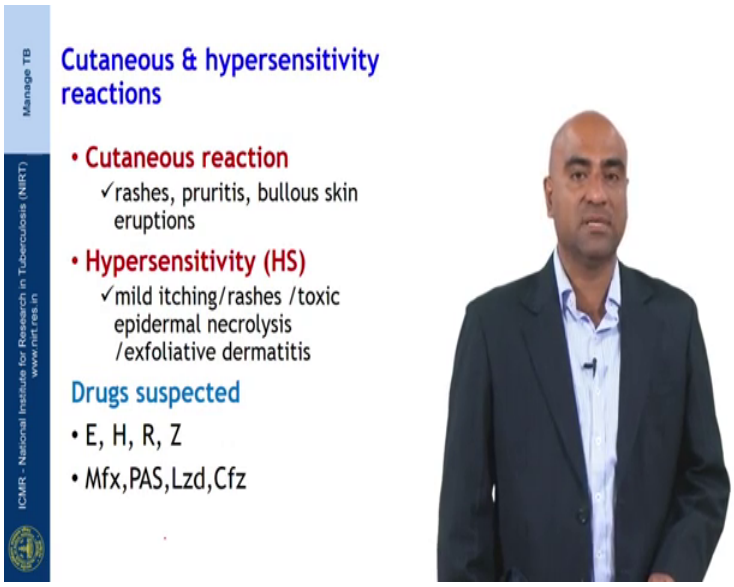


So, let us see the cutaneous and hypersensitivity reactions. Cutaneous reactions, the common cutaneous reactions which we encounter are rashes, pruritis and rarely bullous skin reactions, and hypersensitivity reactions like minor itching, rashes, toxic epidermal necrolysis and exfoliative dermatitis. This is how you classify the skin manifestations of skin manifestations adverse effects of tuberculosis regiments.

So, the drugs which we which are usually associated with cutaneous and hypersensitivity reactions are ethambutol, pyrazinamide, rifampicin and INH and other in the second line they which can be associated with cutaneous manifestations include moxifloxacin, para aminosalicylic acid, linezolid and clofazamine.

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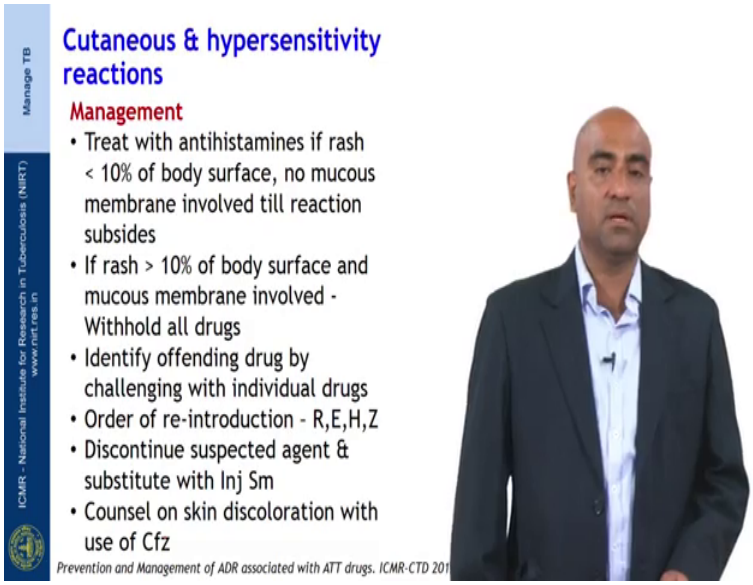


So, how do we manage these cutaneous and hypersensitivity reactions? So, if the reactions are minor you treat with antihistaminics, that is if the skin rash is less than 10 percentage of the body surface and there is no mucosal involvement then you can just manage with antihistaminics. Whereas, if the rash is more than 10 percentage of the body surface and the mucosal membranes are involved then you should withhold all the drugs. And then what you do is you challenge the patient, you identify what is the offending drug and you have to challenge with individual drugs, one by one you have to give the drugs.

The order of reintroduction of these drugs will be first you give rifampicin, see if the patient develops any side effects, then you give ethambutol, then you add INH and lastly you add pyrazinamide. So, in this order the drugs have to be reintroduce. And if the patient is developing skin rashes to any of these drugs then you discontinue the suspected agent and you substitute with injection streptomycin. Skin discolouration is usually very very commonly noted with the use of clofazamine.

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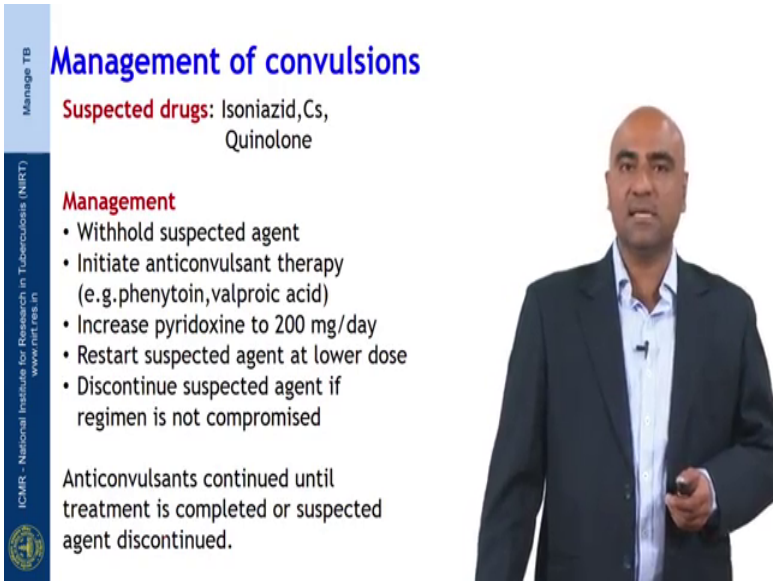


So, next let us see how to manage convulsions in patients who are on ATT. So, the suspected drugs in patients who develop convulsions are isoniazid, cycloserine and quinolone. So, these are the three drugs which generally can cause convulsions. But like we discussed earlier, so let us first rule out that this convulsions are not due to tuberculosis and then if we still suspect it is due to the drugs then we can make some changes in the protocol.

So, how do we manage suspected convulsions due to anti tuberculosis drugs? So, the first thing you do is you withhold the suspected agents and initiate anticonvulsant therapy like phenytoin or valproic acid in consultation with the consult specialist and you can increase the dose of pyridoxine to 200 milligrams per day. And you can resuspect the started suspected agent at a lower dose and if the regimen is not compromised then you can discontinue the suspected agent. That is if you have adequate number of drugs to treat the patient without using the suspected agent you can discontinue that and continue with the regimen. So, anticonvulsants should be continued until the treatment is completed or until you withdraw the suspecting agent.

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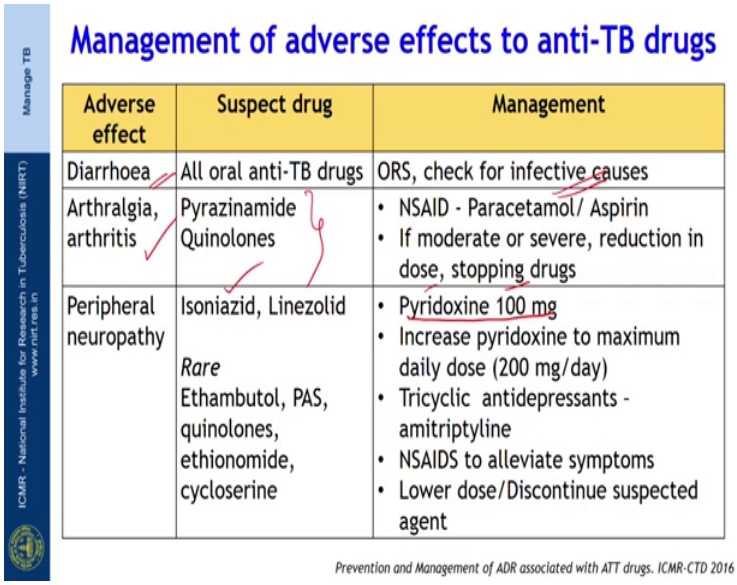


So, let us see the management of common adverse effects of anti-TB drugs. So, the one the first common adverse effect is diarrhoea. So, how do you manage diarrhoea? It can be due to any of the anti-TB drugs. So, generally first we should rule out infective causes for diarrhoea and once having ruled out the infective causes you can manage symptomatically with oral dehydration solution or just supportive care.

The other adverse effects which is commonly noted is arthritis and arthralgia. This is usually due to pyrazinamide and quinolones. So, these are the two drugs which are generally associated with arthritis and arthralgia. Most of the times this is self limiting and it disappears, but sometimes you may have to give minor NSAIDS like paracetamol, or aspirin, and if it is very severe then we have to consider change in the dose or stopping the drugs.

So, the other side effect is peripheral neuropathy. Peripheral neuropathy is usually associated with isoniazid and other drug which is associated with linezolid, rarely it can be due to ethambutol, PAS, quinolones, ethionamide and cycloserine. So, what we do for this?. We generally give pyridoxine 100 milligrams along with the ATT regimen, and sometimes you may have to increase the dose of pyridoxine to 200 milligrams per day. If it is still not manageable then we can consider adding tricyclic antidepressants like

amitriptyline and giving NSAIDS like a paracetamol or aspirin to alleviate the symptoms. And we can continue the, either we can continue the medicines at a lower dosage or if it is still not manageable we can discontinue the drug and plan for a switch off regimen.

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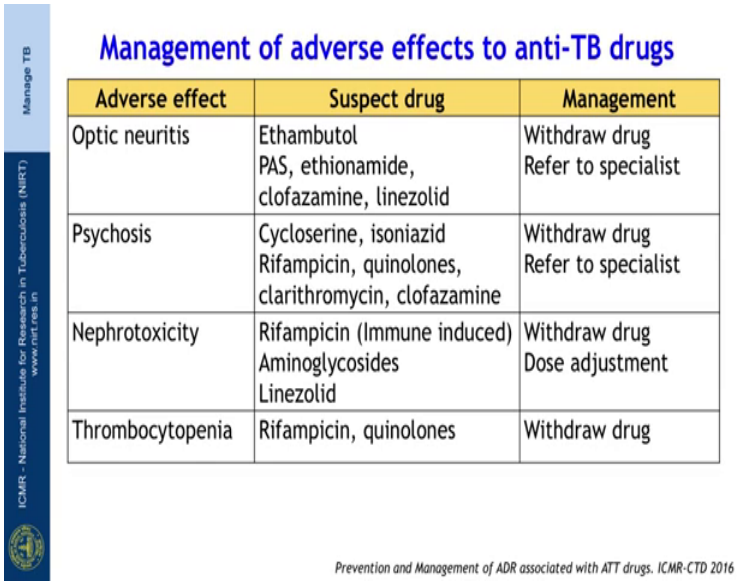


Let us see the other side effects of ATT optic neuritis. Optic neuritis is usually seen with ethambutol though it is a very very rare complication, and it can also be seen with the PAS, ethionamide, clofazamine and linezolid. So, if it is documented that it is due to the appending agent then we withdraw to agent and we refer to the specialist.

Psychosis can be due to cycloserine, isoniazid, rifampicin, quinolones, clarithromycin and clofazamine and again what we do we withdraw the drug and refer to the specialist. Nephrotoxicity it can be due to rifampicin. One traded complication of rifampicin is immune induced nephrotoxicity and other drugs which can cause nephrotoxicity are aminoglycosides and linezolid, in all these cases we withdraw the drug or we adjust the dose of the medicines.

Thrombocytopenia can be due to rifampicin and quinolones and we have to withdraw the drug. It is always prudent to involve the concerns specialist while these adverse effects

develop and you can discuss with them and manage this side effects.

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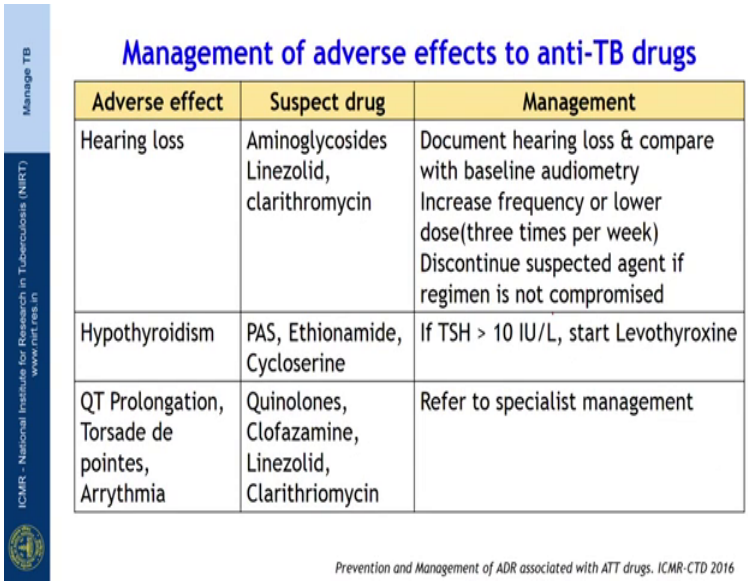


Hearing loss can be due to aminoglycosides, linezolid or clarithromycin. So, we have to document the hearing loss and compare with a baseline audiometry increase frequency or lower the dose of the medicines and discontinue the suspected agent if the regimen is not compromised.

Hyperthyroidism is associated with the para aminosalicylic acid, ethionamide and cycloserine. And if the TSH values are more than 10 international units per litre we can start the patient on replacement therapy with levothyroxine. QT prolongation and cardiac arrhythmias are noted with quinolones, clofazamine, linezolid and clarithromycin in such cases you have to refer to the concerned specialist for management.

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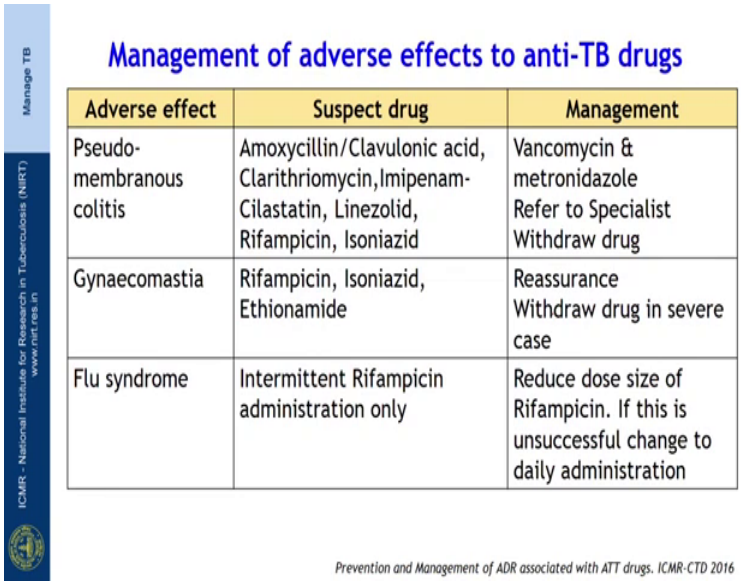


Pseudo membranous colitis is seen with amoxicillin, clavulonic acid, clarithromycin, imipenam, cilastatin, linezolid, rifampicin and isoniazed. The management is vancomycin and metronidazole and you have to refer to a specialist and consider withdrawing the offending agent.

Gynaecomastia can happen with the rifampicin INH and ethionamide. Most of the time it requires only reassurance, but if the manifestation is very severe then you can consider withdrawing of the drug.

Flu like syndrome is noted with intermittent rifampicin administration, but generally what we do is we reduce the dose of rifampicin and we can switch out to a daily regimen.

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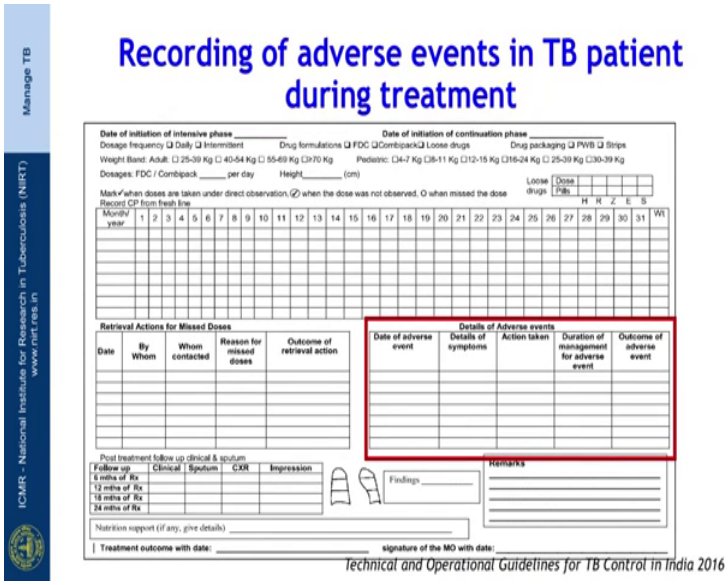


So, it is very important that we have to record the adverse effects of the drug. So, in the treatment card there is a column for noting the adverse effect you have to see which is the offending agent what are the reactions and how it has been managed, it has to be documented in the treatment register.

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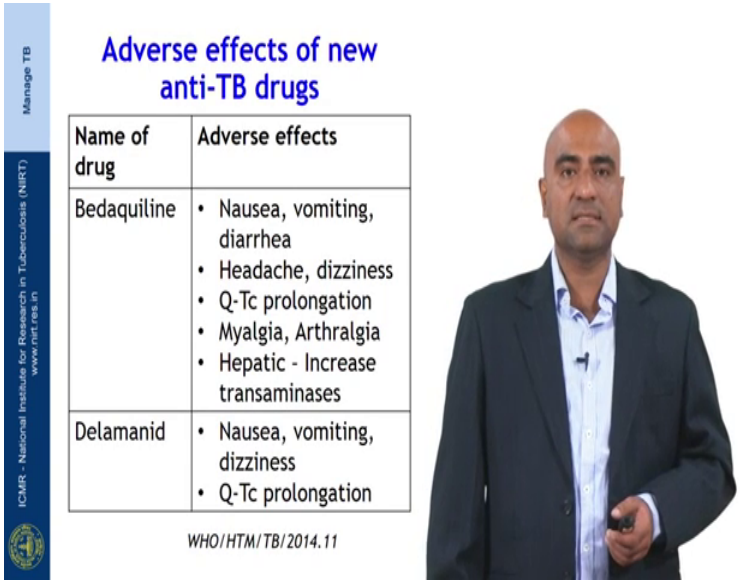

So, let us now see what are the adverse effects of the new anti-TB drugs. So, all of you are aware of bedaquiline which has been increased lately, and delamanid which we are going to introduce very shortly. And it is very important that we know what are the side effects of these drugs two.

So, bedaquiline the common side effects which we encounter are mainly gi which is very minor like nausea or vomiting and diarrhoea, sometimes it can cause headache dizziness. And one concern is Q-Tc prolongation especially when it is used in combination with other drugs other side effects are myalgia, arthralgia and hepatic increase in transaminases. Delamanid is associated with nausea, vomiting, dizziness and Q-Tc prolongation.

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So, what is pharmacovigilence? Pharmacovigilence is defined as the science and activities relating to the detection, the assessment, the understanding and the prevention of adverse effects of any other or any other drug related problem. So, the program of pharmacovigilence has been setup by the ministry of health and family welfare from July 2010 and it is very very mandatory that we all report and monitor what are the side effects which we encounter with anti tuberculosis treatment.

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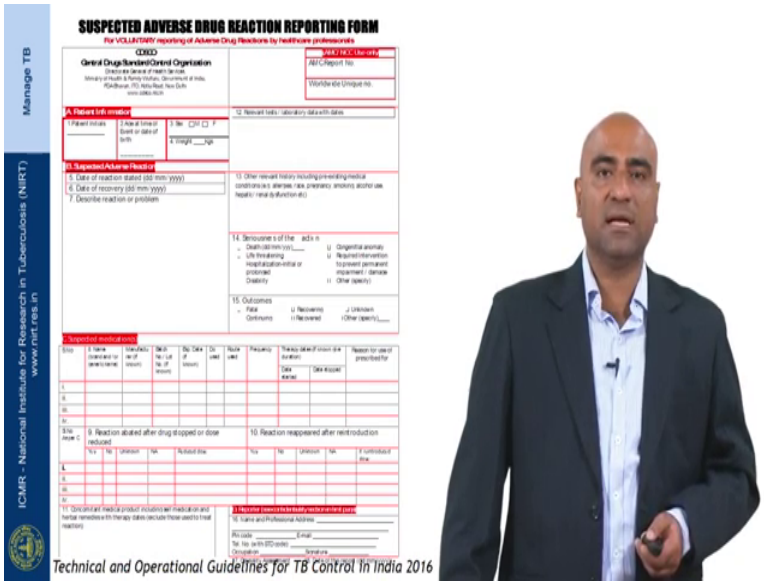


So, this is the form for reporting the suspected adverse reactions to for pharmacovigilence purposes.

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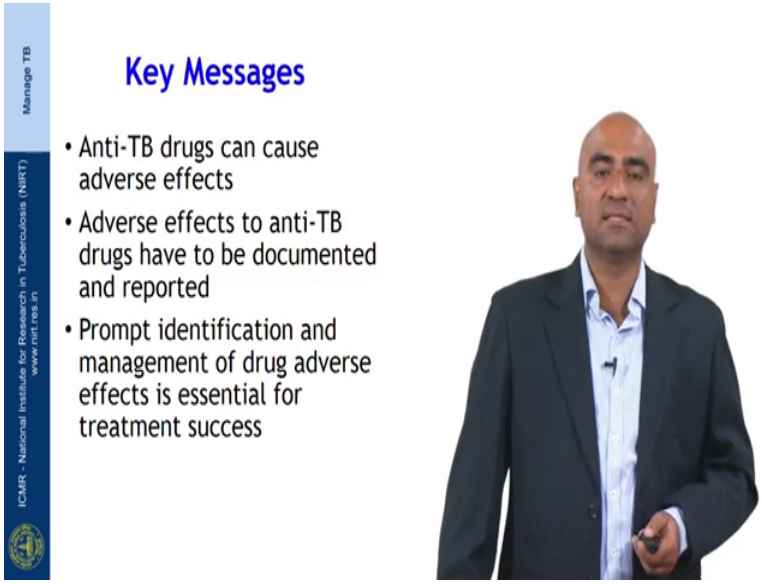


To summarize anti tuberculosis drugs can cause adverse effects. Adverse effects to anti-TB drugs have to be documented and reported from identification, and management of

drug adverse reactions is essential for the success of the treatment.

Thank you.