AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB PATIENTS UNDER PMDT FOR SIX TO NINE MONTHS PERIOD IN TIRUNELVELI MEDICAL COLLEGE HOSPITAL

DR-TB UNIT

A STUDY OF 51 CASES

Dissertation submitted in partial fulfilment of the

Requirement for the award of the Degree of

M.D. DEGREE – BRANCH XVII

(TUBERCULOSIS AND RESPIRATORY MEDICINE)

DEPARTMENT OF CHEST MEDICINE

APRIL 2016

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY,
CHENNAI,
TAMIL NADU

DEAN CERTIFICATE

This is to certify that the dissertation entitled "**AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB PATIENTS UNDER PMDT FOR SIX TO NINE MONTHS PERIOD IN TIRUNELVELI MEDICAL COLLEGE HOSPITAL DR-TB UNIT "** submitted by **Dr.N.JAYAKUMAR** , in partial fulfillment for the award of the degree of Doctor of Medicine in TUBERCULOSIS AND RESPIRATORY MEDICINE by the Tamilnadu Dr.M.G.R. Medical University, Chennai , this is a bonafide original research work done by him in the department of **TUBERCULOSIS AND RESPIRATORY MEDICINE**, Tirunelveli Medical College, under the guidance and supervision of **Prof.Dr.K.KRISHNAMOORTHY,M.D.,** during the academic year 2013-2016.

DATE:
PLACE: Tirunelveli

DR.SITHY ATHIYA MUNAVARA M.D.,
DEAN,
TIRUNELVELI MEDICAL COLLEGE
TIRUNELVELI-11

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB PATIENTS UNDER PMDT FOR SIX TO NINE MONTHS PERIOD IN TIRUNELVELI MEDICAL COLLEGE HOSPITAL DR-TB UNIT**" submitted by **Dr.N.JAYAKUMAR**, in partial fulfillment for the award of the degree of Doctor of Medicine in TUBERCULOSIS AND RESPIRATORY MEDICINE for the april 2016 examination by the Tamilnadu Dr.M.G.R. Medical University,Chennai , this is a bonafide original research work done by him in the department of TUBERCULOSIS AND RESPIRATORY MEDICINE , Tirunelveli Medical College, under my guidance and supervision.

DATE:
PLACE: Tirunelveli

Prof. Dr.K.KRISHNAMOORTHY, M.D.
DEPARTMENT OF CHEST MEDICINE,
TIRUNELVELI MEDICAL COLLEGE,
TIRUNELVELI.

CERTIFICATE BY THE CO – GUIDE

This is to certify that the dissertation entitled **"AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB PATIENTS UNDER PMDT FOR SIX TO NINE MONTHS PERIOD IN TIRUNELVELI MEDICAL COLLEGE HOSPITAL DR-TB UNIT"** submitted by **Dr.N.JAYAKUMAR,** in partial fulfillment for the award of the degree of Doctor of Medicine in TUBERCULOSIS AND RESPIRATORY MEDICINE for the april 2016 examination by the Tamilnadu Dr.M.G.R. Medical University,Chennai , this is a bonafide original research work done by him in the department of TUBERCULOSIS AND RESPIRATORY MEDICINE, Tirunelveli Medical College, under my guidance and supervision.

DATE:
PLACE: Tirunelveli

DR.E.MATHAN., M.D.,
ASSISTANT PROFESSOR,
DEPARTMENT OF CHEST MEDICINE,
TIRUNELVELI MEDICAL COLLEGE,
TIRUNELVELI-11.

DECLARATION BY THE CANDIDATE

Registration number: 75616

I, **DR. N.JAYAKUMAR**, declare that the dissertation has entitled **"AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB PATIENTS UNDER PMDT FOR SIX TO NINE MONTHS PERIOD IN TIRUNELVELI, MEDICAL COLLEGE HOSPITAL DR-TB UNIT"** has been prepared by me. This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. Degree, Branch XVII (TUBERCULOSIS AND RESPIRATORY MEDICINE) degree examination to be held in April 2016.

DATE:
PLACE: Tirunelveli

DR.N. JAYAKUMAR,
Postgraduate,
DEPARTMENT OF CHEST MEDICINE,
TIRUNELVELI MEDICAL COLLEGE,
TIRUNELVELI-11.

ACKNOWLEDGEMENT

I am extremely thankful to **DR.SITHY ATHIYA MUNAVARA M.D.**, Dean, Tirunelveli Medical College, for his permission to carry out this study.

I am immensely grateful to **Prof.Dr.K.KRISHNAMOORTHY M.D.,** Professor and Head of the Department, Department of CHEST MEDICINE, for his concern and support in conducting the study.

I am very grateful to **Prof. Dr.G.SANGAMITHRA., M.D, Associate Professor Kanyakumari Medical College, Kanyakumari for** their constant motivation and valuable suggestions.

I am greatly indebted to my co-guide **Dr.O.M.RAHMAN SHAHUL HAMEED., DTCD., & Dr.P. SENTHIL ARASU., DTCD.,** for his inspiration, guidance, and comments on all stages of this study.

I am very grateful to Professor. DR. SURESH KUMAR., H.O.D., DEPARMENT OF ENT., DR. V.RAMASUBRAMANIAN., H.O.D., DEPARTMENT OF NEPHROLOGY., for their constant guidance.

I am thankful to **Dr. C. BASKAR.,** DR-TB M.O., and Dr. **T.NATARAJAN**., T.B.CELL M.O., for their guidance and help.

I am thankful to Mrs. Sundari., H.V., & Mrs. P.Kannammal., Sa/DEO for their immense help for finishing my dissertation.

I am thankful to Dr. RAVANAN., audiologist. Mr.N.vijayakumar for their immense help for finishing my dissertation.

I am thankful to all my colleagues for the help rendered in carrying out this dissertation.

I thank all the patients for willingly submitting themselves for this study.

I whole heartedly thank my partner Dr. SANGEETHA.D.O., & and my kutties J.Mithra & J. Kavin Karthik who should by me all the time.

ABBREVATIONS:

RNTCP – Revised National Control Programme

DR TB – Drug Resistant Tuberculosis

MDR TB – Multi Drug Resistant Tuberculosis

XDR TB – Extensively Drug Resistant Tuberculosis

AFB – Acid Fast Bacilli

STR – Standardised Treatment Regimen

DOT – Directly Observed Therapy

LPA –Line Probe Assay

CBNAAT – Cartridge Based Nucleic Acid Amplification Test

DST – Drug Susceptibility Test

SNHL – Sensori Neural Hearing Loss

DTO – Dirstrict Tuberculosis Officer

PTA – Pure Tone Audiometry

OAE – Oto acoustic Emission

ABER – Auditory Brain Stem Evoked Rasponce

Km – Kanamycin

HIV – Human Immunodficiency Virus

DM – Diabetes Mellitus

.

INDEX

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 508/TB/2014/15

PROTOCOL TITLE: AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR MDR-TB PATIENT UNDER PMDT FOR SIX-NINE MONTHS.

NAME OF PRINCIPAL INVESTIGATOR: Dr. Jaya Kumar, MBBS., DCH.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MD Thoracic Medicine
DEPARTMENT & INSTITUTION: Department of Thoracic Medicine, Tirunelveli Medical College

Dear Dr. Dr. Jaya Kumar, *The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 14.05.14.*

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

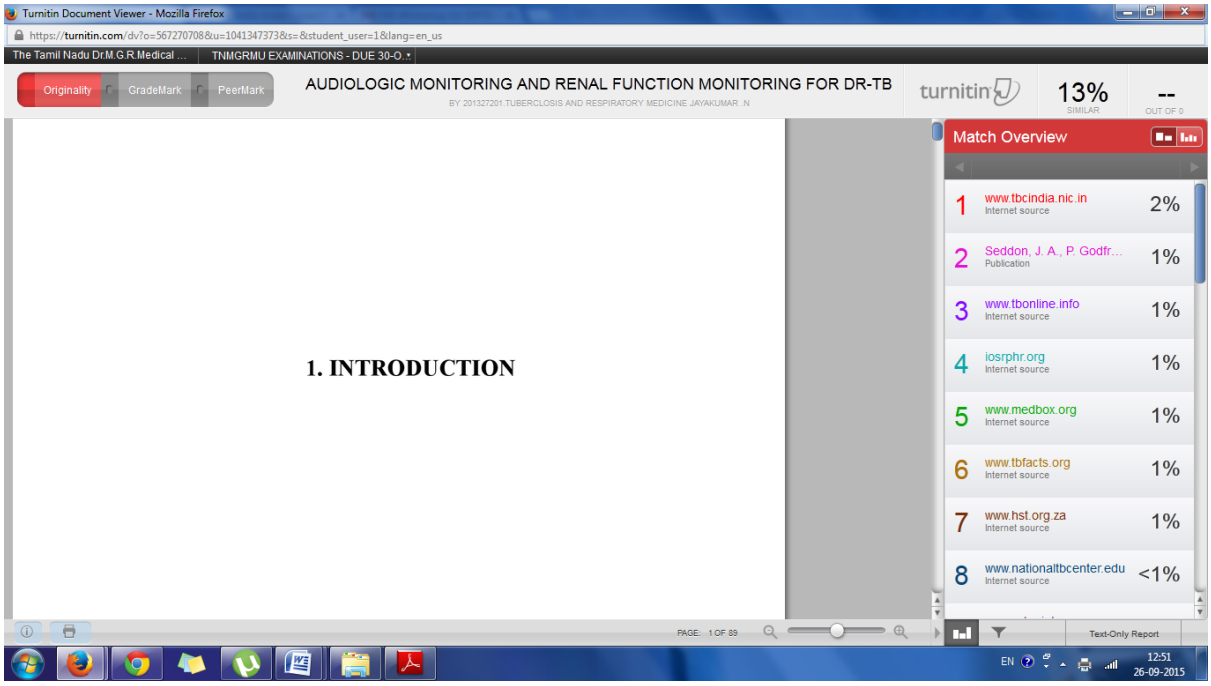
THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India


Turnitin Document Viewer - Mozilla Firefox
https://turnitin.com/dv?o=567270708&u=1041347373&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
TNMGRMU EXAMINATIONS - DUE 30-O...
Originality
GradeMark
PeerMark
AUDIOLOGIC MONITORING AND RENAL FUNCTION MONITORING FOR DR-TB
BY 201327201.TUBERCLOSIS AND RESPIRATORY MEDICINE JAYAKUMAR .N
turnitin
13%
SIMILAR
--
OUT OF 0
1. INTRODUCTION
Match Overview
1 www.tbcindia.nic.in Internet source 2%
2 Seddon, J. A., P. Godfr... Publication 1%
3 www.tbonline.info Internet source 1%
4 iosrphr.org Internet source 1%
5 www.medbox.org Internet source 1%
6 www.tbfacts.org Internet source 1%
7 www.hst.org.za Internet source 1%
8 www.nationaltbcenter.edu Internet source <1%
PAGE: 1 OF 89
Text-Only Report
EN
12:51
26-09-2015

ABSTRACT:

Aim :

Audiologic monitoring and renal function monitoring for Drug Resistant patients under programmatic management of drug resistant tuberculosis reatment for six to nine months period in Tirunelveli Medical College Hospital DR-TB UNIT, from January 2014 to December 2014.

MATERIALS AND METHODS;

Total of 152 newly diagnosed DR-TB patients those registered in DR-TB centre , Tirunelveli medical college hospital from January 2014 to December 2014 were screened.

INCLUSION CRITERIA

All newly diagnosed (n- 51) DR-TB patients with normal baseline audiometry and normal serum urea and creatinine levels were included in this study

RESULTS:

1. In this prospective observational study, during the intensive phase of CATEGORY IV regimen 43.3% patients developed statistically significant OTOTOXICITY , 2% patients developed NEPHROTOXICITY and 2% of patients

developed BOTH OTOTOXICITY AND NEPHROTOXICITY.

2. **OTOTOXICITY-** 63.63% patients developed bilateral hearing loss and 36.36% patients developed unilateral hearing loss. among the patients with ototoxicity 75% patients had mild hearing loss, and mostly during first three months period of the intensive phase.

3. In our study 64% patients with hearing loss are asymptomatic and 36% patients noticed symptoms associated with hearing loss

CONCLUSION:

In our study 64 % of asymptomatic hearing loss cases were picked up by using pure tone audiometry. Early detection of the hearing loss among these patients shall improve adherence to the treatment.

INTRODUCTION

Revised National Tuberculosis Control Programme (RNTCP) for tuberculosis treatment was started in India from the year 1997. PMDT services (Programmatic Management of Drug resistant Tuberculosis) in our country was started in the year 2000. PMDT covers all newly diagnosed Drug resistant tuberculosis which include programme based drug resistant tuberculosis diagnosis, and management. Newly diagnosed DR-TB patients are admitted in DR-TB units for initiation of CATEGORY IV regimen. DOTS PLUS (CATEGORY IV) regimen is given for a period of 24 months .

During intensive phase, injection Kanamycin, Levofloxacin, Ethionamide, Ethambutol, Cycloserine, Pyrazinamide is given for a period of six to nine months . In the continuation phase, Levofloxacin, Ethionamide, Ethambutol, Cycloserine is given for the next 18 months period. In the treatment of drug resistant tuberculosis , above mentioned second line drugs are associated with significant adverse effects which leads to permanent disability. Inj Kanamycin (15 -20 mg/kg) given as an Intramuscular injection daily for six days/week. Inj.kanamycin produces well documented ototoxicity and renal toxicity. Early detection of these adverse effects and their correction will improve the adherence to the treatment, and prevent permanent hearing loss.

Ototoxicity presents with hearing impairment or vestibular symptoms. Hearing dirsturbances in the form of hard of hearing, fullness in the ear and tinnitus. Hearing loss may be unilateral or bilateral.

Kanamycin induced ototoxicity initially involves higher frequencies then slowly progresses to lower frequencies, later it involves speech frequencies also. Vestibular symptoms like tinnitus, vertigo, giddiness, ataxia, nystagmus may be noticed by the patient taking inj .Kanamycin.

Kanamycin attains high concentration in the renal cortex, and its toxicity is directly related to the total amount of drug received by the patients. Aminoglycoside induced nephrotoxicity is reversible. Patients with renal failure leads to high blood plasma levels of kanamycin, excess drug is concentrated in labyrinthine fluid which directly destroys the hair cells in the cochlea.

In DR-TB patients periodic audiometry tests,monitoring of blood urea and serum creatinine levels is important to detect the adverse effects earlier and avoid the drug induced ototoxicity and nephrotoxicity.

2. MDR-TB / Category IV Regimen

Tuberculosis is one of the most common infectious diseases in the world responsible for more than nine million new cases, two million deaths per year [1]. India is the country with the highest burden of TB. World Health Organization statistics for 2013 gives an estimated new cases of 2.1 million cases of TB for India out of a global incidence of nine million new cases . The estimated TB prevalence in the year 2013 is 2.6 million . It is about 40 % of the Indian population is infected with TB bacilli , most of them have latent TB . In our country TB treatment after defaulters are high about (30%) , which leads to MDR – TB [2].

Giovanni Miglio ,TB expert says, "Resistance is man – made,caused by exposure to the wrong treatment , the wrong regimen , the wrong treatment duration" . A comprehensive approach to early detection , appropriate management and public health measures needs to be applied worldwide to cure TB patients and prevent further transmission of the disease to the community [3].

In the year 1998, CATEGORY IV regimen or DOTS PLUS regimen was included in the DOTS programme, in order to treat the patient and control the spread of DR TB bacilli transmission in the community. DR TB cases confirmed with laboratory investigation done in RNTCP accredited laboratory is accepted for initiating the CATEGORY IV regimen.

Definition for MDR-TB :

Tubercle bacilli that is resistant to at least the two most potent first line anti tuberculosis drug H (isoniazid) and R (rifampicin) .

Definition for XDR-TB :

Tubercle bacilli that is resistant to INH and Rifampicin and any one of the fluoroquinolones , and resistant to atleast one of the injectable second line drugs like capreomycin, kanamycin, and amikacin .

Primary MDR TB:

Presence of resistant strain of mycobacterium tuberculosis in a patient newly diagnosed with TB who has not been previously treated with TB drugs or treated with TB drugs for less than one month duration.

Acquired MDR-TB:

Presense of a resistant strain in a TB patient who has previously received at least one month of anti TB treatment.

Mono-resistance:

Tubercle bacilli that is resistant to one of the first line anti-TB drug in an RNTCP accredited laboratory.

Poly-resistance:

Tubercle bacilli that is resistant to more than one first line anti TB drugs, other than isoniazid and rifampicin

The prevalence of **drug resistant TB (DR-TB)** is very low in most parts of our country . Initial mono resistance to rifampicin is about 2 % of patients, initial mono resistance to H (isoniazid) is about 18% [4]. After the overall coverage of the CATEGORY IV regimen in entire country, outcome of DR –TB patients found to be improved in the form of high cure rate.

Incidence:

Globally Incidence of Drug resistance TB among the new cases is about 3.6%, and in previously treated cases about 15.3 % [5] . China and India carry about approximately 50% of the global burden [6] .

Drug resistance in India:

Incidence of the MDR -TB in new cases is about 2-3% and in retreatment cases about 12 to 17%. In India about 99,000 cases emerged in 2008. As per the Revised National Tuberculosis Control Programme (RNTCP) incidence of MDR -TB due to Treatment defaulters are higher in Uttar Pradesh[2] . India has second highest MDR-TB burden in the world after China . Estimated MDR-TB emerging annually are about 99,000 cases, out of which 73,000 (73.7%) cases are smear positive [7]. Incidence of the XDR TB cases among the re treatment cases is about 4%.

MDR-TB Suspects:

- New and previously treated patients with treatment failure in DOTS
- Previously treated patient who is sputum smear positive at the end of the fourth month of treatment or later.
- Contacts of MDR-TB found to be sputum smear positive for TB

Criteria used for MDR suspects :

Criteria A :

- All failure of new TB cases
- Previously treated Smear positive cases who remain positive for AFB at 4th month onwards**.**
- Contacts with known MDR-TB cases who become smear positive for AFB

Criteria B :

- In addition to criteria A ,
- All cases of smear positive previously treated cases
- Follow up smear positive for AFB among new or previously treated cases.

Criteria C :

- In addition to criteria B
- All smear negative , previously treated TB at diagnosis found to be smear positive during the follow up
- HIV positive individual co infected with TB at the time of diagnosis.

Definition for Confirmed MDR-TB case :

Suspected DR-TB patients who are sputum culture positive and culture report is mycobacterium tuberculosis is grown that are resistant to at least isoniazid and rifampicin (the culture and Drug Sensitivity Test from an RNTCP accredited laboratory). Patients with isolated resistance to rifampicin are also treated with CATEGORY IV regimen.

Methods For Drug Susceptibility Testing (DST) :

Presently following three technologies are available for the diagnosis of MDR TB

1. Solid egg – based (Lowenstein- Jensen media)
2. Liquid culture (MGIT)
3. Rapid molecular assay such as line probe assay (LPA), cartridge based nucleic acid amplification test (CBNAAT)

   TIME REQUIRED FOR DST RESULTS :

Solid LJ media – 84 days

Liquid culture (MGIT) – 42 days

LPA – around 72 days

CBNAAT – results available in 2 hours .

Pre treatment evaluation:

Drugs used in CATEGORY IV REGIMEN among MDR-TB patients are known to produce many adverse reactions, and early identification and correct management of these adverse reaction will improve the adherence of the treatment, so at the time of initiation CATEGORY IV REGIMEN following assessment is recommended;

1.Complete clinical history

2. Weight measurement

3. Height measurement

4. CBC-complete haemogram and serum eletrolytes

5. Diabetes Mellitus screening FBS/PPBS

6. LFT-liver function test

7. Serum creatinine and blood urea to assess the current renal function

8. Thyroid function test T3/T4/TSH

9. Routine complete Urine Analysis

10. Pregnancy test (for Child bearing age group females)

11.Contact screening

12.Home visit /family planning counselling

Pre treatment evaluation will help to identify the high risk groups like diabetes, renal disorders, these baseline investigations are helpful in further follow up visits .

Routine Clinical monitoring

All DR-TB patients are initially examined by medical officer in the respective DTO for clinical examination, and every month during the intensive period, and once in three months period during the continuation phase till the end of treatment. During the follow up medical officer evaluate the patients for clinical improvement and possible drug adverse effects. Patient may be admitted in the DR-TB ward during the treatment period if they develops any adverse drug reaction. Chest X ray to be done routinely at the initiation of the treatment and completion of the intensive phase, end of the continuation phase treatment. Blood urea and serum creatinine level measurment to be done every month during intensive phase period, thereafter every three months period till end of the treatment.

2.A CATEGORY IV or DOTS PLUS REGIMEN :

CATEGORY IV REGIMEN:

RNTCP is using a Standardised Treatment Regimen (STR) for the treatment of MDR-TB cases and rifampicin mono resistance patients are also included in treatment of CATEGORT IV regimen . During Intensive phase (6-9 months period) of the Category IV regimen six drugs are used - Inj. Kanamycin,Ofloxacin (Levofloxacin), Ethionamide, Pyrazinamide, Ethambutol and Cycloserine . In the continuation phase four drugs are used, namely Ofloxacin (Levofloxacin), Ethionamide, Ethambutol and Cycloserine for next eighteen months period. P - aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any other above mentioned drugs are contraindicated .

Drug Administration ;

All drugs are to be given in a single daily dosage under supervision by a DOT provider. These drugs to be given to the patients under direct observation for six days of the week. On the 7th day (Sunday) the oral drugs will be administered unsupervised, whereas injection kanamycin will be omitted. During the treatment if any intolerance occurs to the drugs, Ethionamide , Cycloserine and PAS may be divided into two dosages and the morning dose is administered under supervision [8]. The evening dose will be self-administered. Pyridoxine is given routinely for all patients treated with CATEGORY IV regimen .

Dosage and weights band recommendations :

NO	DRUG	16-25 Kg	25-45 Kg	>45 Kg
1	Kanamycin	500mg	500mg	750mg
2	Ofloxacin (levofloxacin)	400mg (200mg)	600mg (500mg)	800mg (750mg)
3	Ethionamide	375mg	500mg	750mg
4	Ethambutol	400mg	800mg	1000mg
5	Pyrizanamide	500mg	1250mg	1500mg
6	Cycloserine	250mg	500mg	750mg
7	PAS	5gm	10gm	12gm
8	Pyridoxine	50mg	100mg	100mg

Monitoring of Adverse Reactions

Close monitoring for the patients receiving the CATEGORY IV regimen is a very important step, so early detection and proper treatment

of adverse effects caused by the above mentioned drugs is essential for good compliance of the patients and prevent the permanent hearing loss.

Common adverse reactions :

1.Inj- Kanamycin

- Hearing impairment
- Renal failure
- Vertigo
- Electrolyte disturbances

2 Quinolones - Llevofloxacin/ Ofloxacin

- Nausea , vomiting, epigastric pain
- Convulsions
- Phototoxicity / photosensitivity
- Tendinopathy / tendinitis
- Renal Insufficiency
- Skin Rash
- Cardiac Arrythmias
- Joint Pain and joint swelling

3 Ethambutol

- defective vision , colour blindness

4 Pyrazinamide

- Joint pain
- Increased uric acid level, hepatic injury
- Itching

5 . Ethionamide

- Epigastric pain, loss of appetite , nausea, altered taste sensation, vomiting, salivation,
- Psychiatric : hallucination rarely depression
- Injury to liver and altered thyroid function noted on long term use.

6.PAS

- Severe gastriris
- Persistent Nausea and vomiting
- Liver damage
- Hypokalemia
- Thyroid dysfunction
- hyper sensitivity
- skin rash

7. **cycloserine** [9]

- sleep disturbances, convulsion, altered behaviour
- suicidal tendency,
- depression

2.B.KANAMYCIN – DRUG PROFILE

KANAMYCIN

Kanamycin is isolated from streptomyces kanamyceticus (1957), it was the second systemically used aminoglycosidal antibiotic developed after streptomycin. Kanamycin produces ototoxicity and nepdrotoxicity , more cochlear toxicity than vestibular toxicity.

Mechanism of action:

Kanamycin is a bactericidal antibiotic. It exhibit the cidal action in two steps

a) transport of the aminoglycoside into the bacterial cell wall and cytoplasmic membrane

b) inhibits the protein synthesis by binding the 50 S ribosomal unit

T ½ : 2 to 4 hours [10]

Cidal action of aminoglycoside is concentration dependent i.e. rate of bacterial killing is directly proportional to peak antibiotic concentration. Because of this post antibiotic effect, despite of short t ½ once daily dosage of injection kanamycin is more effective when compare to divided doses.

Dose :

Adults- 15 to 20 mg /kg daily, maximum of 1000 mg

Adult with creatinine clearance < 30 ml/min – 12 to 15 mg /kg two to three times in a week

Safe in patients with hepatic disorder

Contraindication :

Pregnancy ,

myasthenia gravis

severe renal failure

hearing impairment

KANAMYCIN – SIDE EFFECTS :

1. **Ototoxicity:**

Aminoglycoside induced ototoxicity is dose and duration dependent manner, vestibular apparatus or cochlea or both can be affected by kanamycin. The drug is concentrated in the labyrinthine fluid and slowly removed from the fluid when plasma concentration falls.

Hair cells present in the inner ear undergo concentration dependent destructive changes, initially it affects outer hair cell, later it affects inner hair cell, so kanamycin induced ototoxicity initially involves higher frequencies, then lower and speech frequencies [11].

Cochlear damage:

Aminogycoside induced damage first involves the base of cochlea and spreads to the apex of cochlea, so kanamycin induced hearing loss is progressive in nature. Free radicals produced by Kanamycin in the labyrinthine fluid , damages hair cells in the cochlea, once sensory hair cells are damaged due to any insult no regeneration of hair cells occur, hence kanamycin induced ototoxicity is permanent .

Initial ototoxicity is asymptomatic, may be detected by audiometry, then tinnitus appears one week later, at that time hearing loss developed to the particular frequencies persists life long.

Vestibular damage :

Acute phase - Headache is the first most commonly observed symptom then develops nausea, vomiting, nystagmus, ataxia

Chronic phase - it starts six to ten weeks after starting the aminoglycosides. It affects the balance mechanism and in this stage patient will have difficulty in walking. If the drug has been stopped in the acute stage patient may not enter into the chronic stage .

2) NEPHROTOXICITY:

Kanamycin induced renal toxicity is reversible, these drugs are highly concentrated in the renal cotex, toxicity is directly related to the dose of the drug patient received.

Elderly patients and diabetics are more prone to develop nephrotoxicity. In renal failure patients, high blood levels of kanamycin will produce ototoxicity.

3. Neuromuscular dysfunction

4. Electrolyte imbalance

5. Injection of kanamycin gives local side effects like pain, swelling , abscess

.

2.C.ADVERSE DRUG REACTION AND MANAGEMENT IN MDR-TB PATIENTS

MDR TB AND RENAL TOXICITY:

Prior to initiating CATEGORY IV regimen , renal function is to be evaluated in all patients. If the patients noticed symptoms or signs of renal insufficiency like reduced urine output (oliguria) ,absence of urine output (anuria), facial puffiness , pedal edema , all the drugs should be withheld, nephrologist opinion should be obtained [12]. Re-introduction of drugs will be decided by the DOTS-Plus site committee , along with frequent monitoring of renal function test . Common offending drug in MDR-TB patients on CATEGORY IV regimen is an aminoglycoside.

Renal function monitoring to be done every month for the first six months period of the CATEGORY 4 regimen and then every three months till the end of treatment . In asymptomatic patients renal toxicity may be picked up by these routine follow-up renal function test.

Renal insufficiency may be due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease . Great care should be taken in the administration of second-line anti TB drugs in patients with renal impairment [13]. Dose reduction is required for second line drugs such as ethambutol, quinolones, cycloserine and PAS in case of mild to moderate renal insuffciency . In case of severe renal failure most of the drugs in CAT IV regimen needs dose adjustments according to the

creatinine clearance. Potent non nephrotoxic drug may be substituted in case of severe renal failure

Management of nephrotoxicity :

Offending drugs; Streptomycin / Kanamycin / Amikacin / cycloserine

1. Stop the suspected drug in the regimen.

2. Alter the suspected drug dose 3 times per week and monitor creatinine clearance.

3. Adjust dose of all the drugs according to creatinine clearance.

4. Consider use of capreomycin if patient was on aminoglycoside.

Recommended Dose and Interval adjustment in renal disorder:

Dose adjustment and interval adjustment of kanamycin is needed in patients with renal insufficiency according to glomerular filtration rate – ml/mt.

- Less than 10 – 3mg/kg/48hrs
- 10 to 50 – 4 to 7.5 mg/kg/24 hrs
- More than 50 -7.5 to 15 mg/kg/24 hrs

DR-TB may also be associated with other serious disorders, such as HIV infection, alcoholism, renal failure, diabetes mellitus, cancers and drug abuse. The signs and symptoms of these conditions and their complications can easily obscure those of DR-TB and can also result in considerable delays in diagnosis or in misdiagnosis, especially in patients with HIV infection [14].

MDR-TB and Ototoxicity

Defective hearing is mostly due to the aminoglycosides used in CATEGORY IV regimen which is dose dependent . Hence periodical monitoring of ototoxicity by using pure tone audiometry is recommended. If patient develops tinnitus,vertigo audiometry to be done during the first six to nine months in the intensive period . Patients with history of hearing impairment should be counselled for the high risk of developing ototoxicity and counselling with written consent should be obtained before these aminoglycosides are used.

Drugs may causing Hearing loss in MDR/XDR Patients :

Km- Kanamycin

Am- Amikacin

Cm- Capreomycin

1. Conduct PTA and compare with baseline audiometry.

2. Consider reducing the drug administration to five times or even three times per week.

3. Reduce the dose of suspected drug if this will not compromise the regimen.

4. withheld the offending drug if this will not compromise the regimen.

If hearing loss is detected during the treatment, options available are to stop the drug, reduce the dose, increase the dose interval or retain current therapy and also suggest the alternative non ototoxic drugs.

Management of Adverse Drug Reactions

Importance to be given to treat the patients with CATEGORY IV regimen and also proper management of adverse reactions[12] . Drugs used in the CATEGORY IV regimen had more adverse drug reaction than drugs used in new and previously treated TB patients[13].

Early identification and correct treatment to be given if these Adverse drug reaction starts with pre-treatment evaluation

DIABETES:

Poor outcome of the MDR TB patients may be due to poor glycemic control and diabetes may augment these adverse drug reactions, long term uncontrolled diabetes itself may cause renal impairement , peripheral neuropathy and diabetic retinopathy

Oral hypoglycemic drugs can be safely given with second-line drugs, but ethionamide and prothionamide may affect the glucose metabolism this will reflect on management of diabetes .

MDR TB with Diabetes the following is recommended:

- Diabetes properly treated during the course of the CATEGORY IV regimen.
- **Patient education:** about the dietary management , walking, foot care, treatment compliance.

  Counselling for the symptoms of hyper and hypoglycaemia and how to manage them properly .
- **Glucose monitoring**

  1.) Aim for fasting capillary blood sugar level is about 80-120 mg/dl in morning, 100-140 mg/dl before bedtime. If patient experienced hypoglycaemia sugar values may be maintained in higher values.

2.) Advice to do a periodic glucose monitoring until patient had a stable glycemic status. If patient achieved stable glucose level, glucose monitoring done at monthly interval.

- **Regular monitoring**

1.) serum electrolyte monitoring done for every month for the first six months in the intensive period and then every three monthly period till end of the treatment.

2.) If the serum creatinine level rises, creatinine clearance should be checked and the second-line anti-TB drugs should be adjusted accordingly. Once the dose is adjusted, the serum creatinine should be checked weekly until it has stabilised.

3.) HbA1C to be done for every three months period if patient had poor glycemic control . In patients with good glycemic control HbA1C to be done for every six months period. Target HbA1C <7.

4.) ophthalmological examination is to be done annually.

- **Screening and treatment for hypertension**

  1.) Measurement of blood pressure for every month as a routine measurement

  2.) Hypertensive patients with diabetes treated with ACE-inhibitor.

- **Prevention of diabetic nephropathy**

  1.) Dose adjustment to be done in the second line injectable anti TB drugs based on the creatinine clearance.

  2.) Consider using an ACE inhibitor in patients with 24 hours urine albumin level >300 mg.

2.D.The Physiology of Hearing and Balance

The Physiology of Hearing and Balance

Auditory sounds are conducted from pinna to tympanic membrane via external auditory canal, from here these vibrations transmitted to the middle ear by auditory ossicles (the malleus, incus and stapes) . Handle of the malleus is attached to the back of tympanic membrane. Foot plate of the stapes is attached to the oval window, and then vibration entering the cochlea reach the hair cells which is situated in the Organ of Corti. spiral ganglion located in the base of the hair cell.

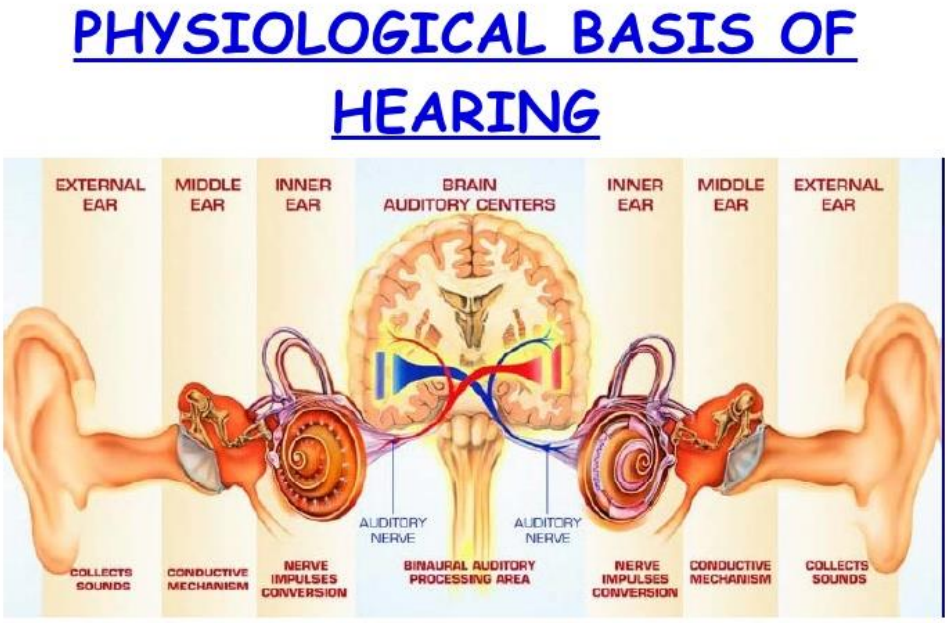


Fig.1:

Afferent signals from vestibulocochlear nerve ends in the dorsal and ventral cochlear nuclei, from here auditory impulse reaches inferior colliculi , then medial geniculate body which is situated in the thalamus ,then signals ends in the primary auditory cortex (Brodmann area 41).

In the auditory canal most commonly blocked by wax, discharge from the middle ear can interfere process of hearing . Perforations of the tympanic membrane , middle ear effusion, and ASOM, CSOM (Suppurative otitis media) leads to condutive type of hearing loss.

Acute and chronic supurative otitis media , multiple perforation in the tympanic membrane are more common in HIV-infected patients, so careful pre treatment auditory evalution is mandatory for HIV patients with DR-TB .

Physiological Mechanism of Balance :

Balance is a complex process involves rotational acceleration and linear acceleration, this process involves the scala vestibuli situated in the cochlea. Movement of labyrinthine fluid through the three semi-circular canals, and into the maculae, utricle and saccule , stimulates hair cells which in turn create signals in the vestibular nerve. This vestibular nerve runs along with the cochlear nerve it is called as the vestibulocochlear neave . Eighth cranial nerve nuclei is situated in the

brainstem (medulla) , from medulla afferent signal is transmitted to the auditory cortex .

Vestibular nuclei are primarily related to the position of the head , signals descend from these nuclei control head on neck and head on body movements, ascending signals from these nuclei concerned with extra ocular movements.

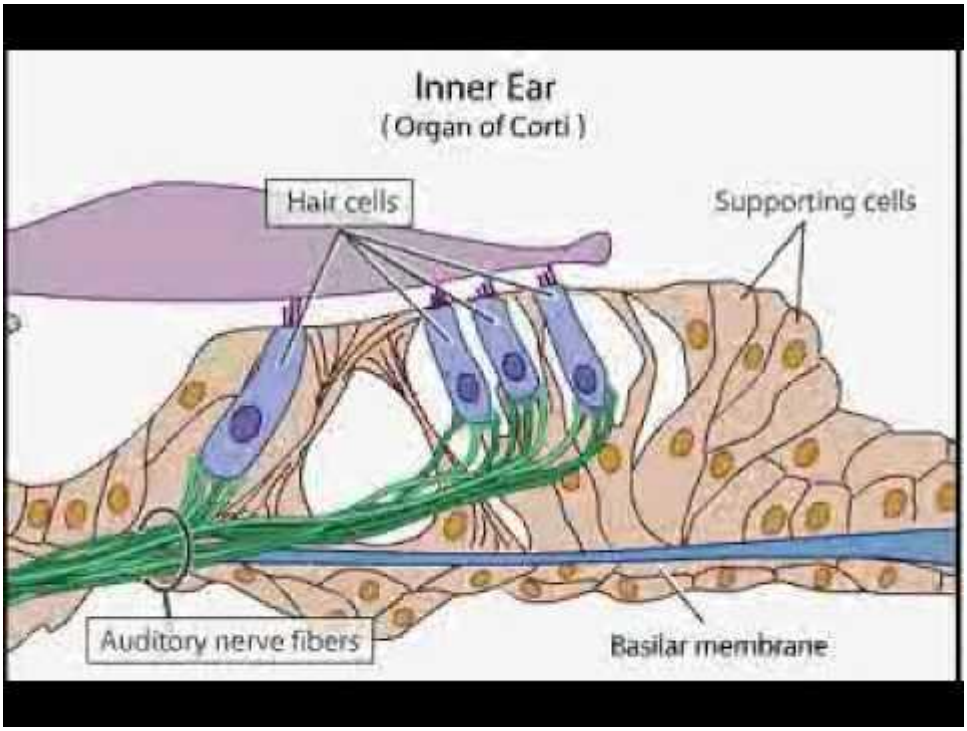


Fig.2:

The aminoglycoside drugs selectively destroy the hair cells which is present in the basilar membrane, these outer basal hair cell is important for high frequency hearing, inner hair cell responds for low frequency hearing [15]

Aminoglycoside induced hearing loss usually starts with high frequency loss , because these drugs are concentrated in the labyrinthine fluid which selectively destroys the outer hair cell. If aminoglycoside used for longer duration it also affects the lower frequency then lastly affects speech frequencies by destroying the inner hair cell. Destroyed hair cell does not have the capacity to regenerate[16]. These damage produced by aminoglycosides is usually irreversible. Aminoglycoside also affects the vestibular function leading to impaired balance mechanism.

Importance of The hearing test in MDR-TB patients :

In India audiological examination is usually done in patients with hearing problem. If hearing test is widely available , it may be done as a screening test for all MDR TB patients who are going to start CATEGORY IV regimen. PTA is available in tertiary care hospitals and usually done in patients who complaints of problems with communication,by that time hearing loss may involve speech frequencies which is usually irreversible.

If PTA is carried out in a regular interval in MDR –TB patient and high frequency sensory neural hearing loss is detected in earlier stage of the treatment course, it is possible to alter the drug regimen with non ototoxic drugs before hearing loss involves speech frequencies. It is also

useful to suggest the hearing aid for improve the hearing. Success of the treatment outcome in an MDR-TB patients also depends on management of this adverse drug reaction as mentioned earlier.

2.E.TESTS FOR HEARING

Test for hearing :

- **Clinical Examination**

  otoscopy - visual inspection of the external auditory canal and tympanic membrane by using an otoscope

  auditory canal- look for furunculosis , foreign body , wax or mass

  Otoscopic Examination of the tympanic membrane- look for any perforation , fluid collections and infections.

- **Tympanometry**

  Tympanometry is used to assess the middle ear function. Probe used for tympanometry is placed in the patients external ear canal and the movement and mobility of the tympanic membrane is assessed .

- **Audiometry**

  For adults and older children with normal mental status the current method for the test of hearing is pure tone audiometry. This test is done in a sound-proof room , headphones placed over the patient's ears. The patient is asked to raise a hand when they hear a sound.

Sound frequency tested for audiometry are in the range of 125Hz to 8,000Hz[17]. For both ears sound frequency was tested seperately by using masking method. Audiometry report was given in the prescribed format as given in figure 1.

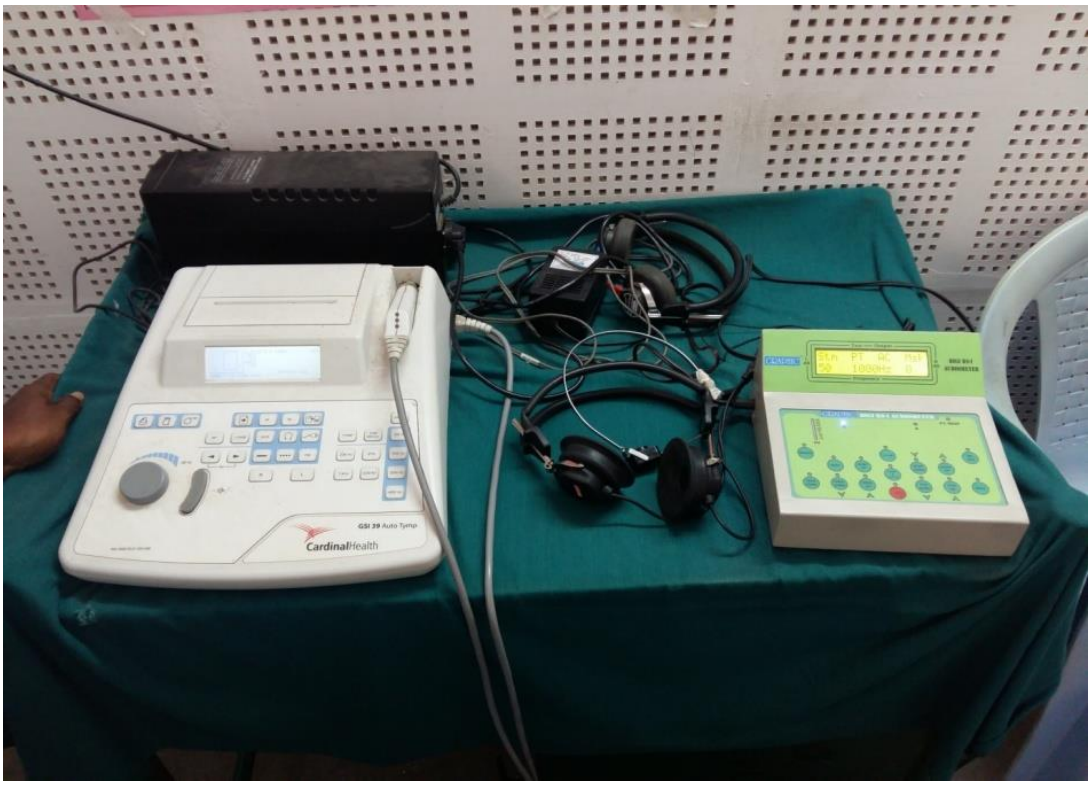


Fig 3. Pure Tone Adiometry

PTA should be done in co-operative patients with normal mental status. PTA can be done in normal children age above five years by using play techniques. In an expert hands children less than five year can be encouraged to participate and usually it is very difficult to get a cooperation for audiometry. In such cases oto acoustic emission test is useful.

OAE - Oto Acoustic Emissions:

OAE is a spontaneous sound produced by a normally functioning cochlea, these sounds produced by a motion of the cochlear sensory hair cell, which is measurable with sensitive microprobes in the external auditory canal. It is a simple , non invasive test used in new born babies, younger children and

patients not able to co-operate for audiomerty. These sounds are produced spontaneously but can also be stimulated (figure2).

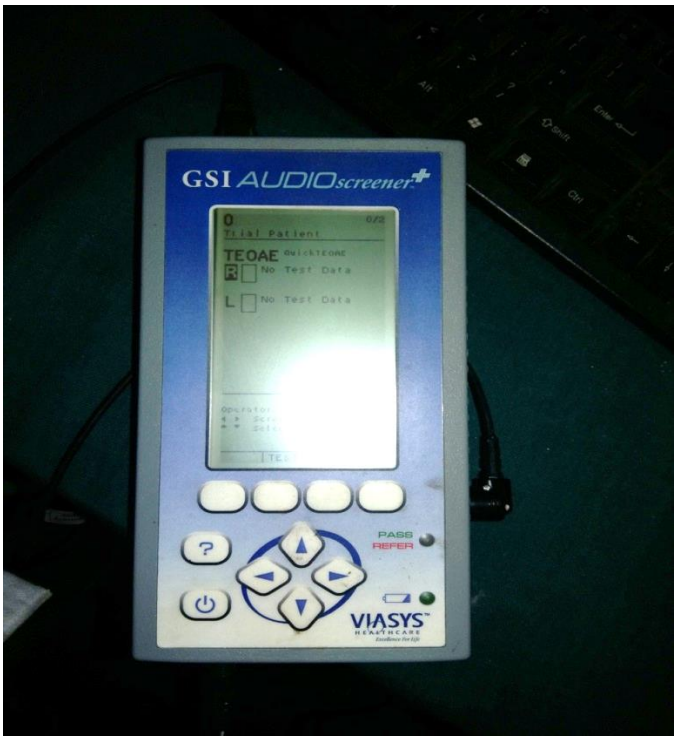


Fig 4. Oto Acoustic Emissions

These tests can determine the patency of the auditory circuit within the cochlea but do not establish if the patient can actually hear or not. Functions of the outer and inner hair cells is assessed by using the OAE.

Injection kanamycin induced ototoxicity is due to damage occurring in the hair cells,so detection of hearing loss by using oto acoustic emissions is likely to be satisfactory.

Advantages for this procedure

- Results will be available immediately
- OAE can be done in chronically ill / bed ridden patients
- Patient concentration not required

ABER- Auditory Brainstem Evoked Response :

It is an objective way of demonstrating the brain stem potential in response to audiological click sound, Used to measures the entire sensorineural pathway of hearing, these waves are recorded by electrodes placed over the scalp. Multiple electrodes are placed in the scalp at various points, BERA probe is placed in the auditory canal. Click sound is given to the Auditory canal and the signal in waveform is received from the scalp electrodes.These waveforms are analysed by an audiologist.

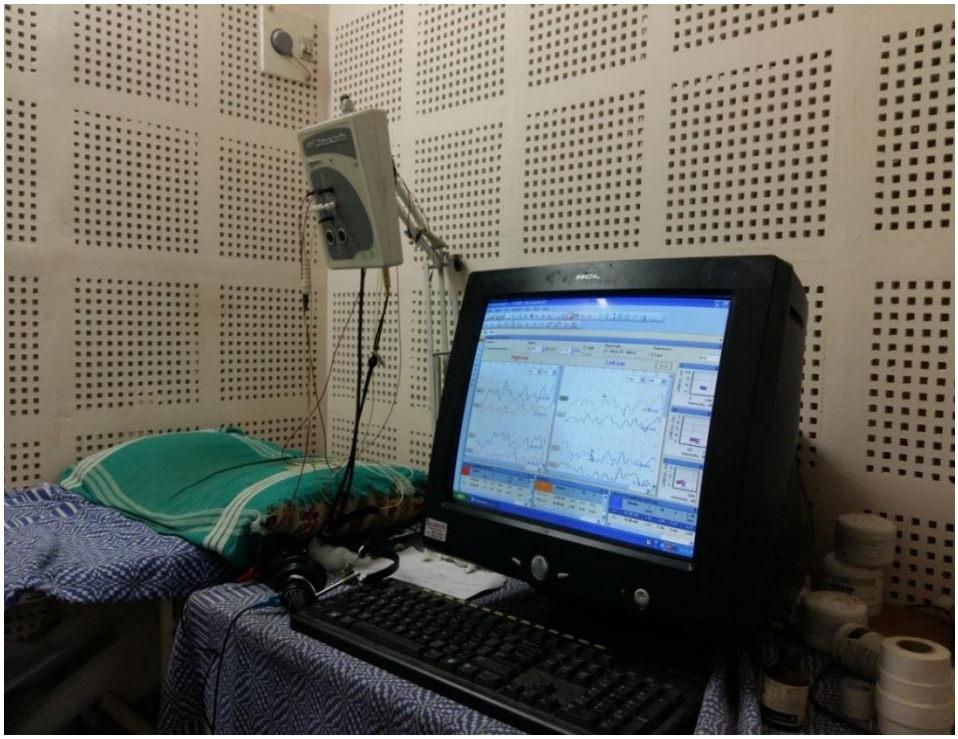


Fig 5. Auditory Brainstem Evoked Response

ABER can be done in newborn period, intensive care unit patients, patient with demyelinating disorder.

Disadvantages:

For this procedure younger children needs sedation.

ABER is available in limited centre

Categorising hearing loss

1) Hearing loss may be conductive or sensorineural or both
2) Unilateral or bilateral
3) Mild , moderate , severe, profound

WHO CLASSIFICATION OF HEARING LOSS [18] :

Classification	Decibels (dB)
Normal	< 25
Mild	26 to 40
Moderate	41 to 55
Moderately severe	56 to 70
Severe	71 o 90
Profound	>90

Definition for ototoxicity (American Speech and Hearing Association) is any of:

a.) 20dB decrease at any one frequency,

b.) 10dB decrease at any two adjacent frequencies or

c.) loss of response at three consecutive test frequencies where responses were previously obtained.

How to read Audiometry reports ?

In the Audiogram graph, frequency (Hz) is measured in the horizontal axis from low (125Hz) to high(8000Hz) range. Intensity of the sound is measured in decibels, range between -10 dB to 120 dB (soft to loud) in the vertical axis.

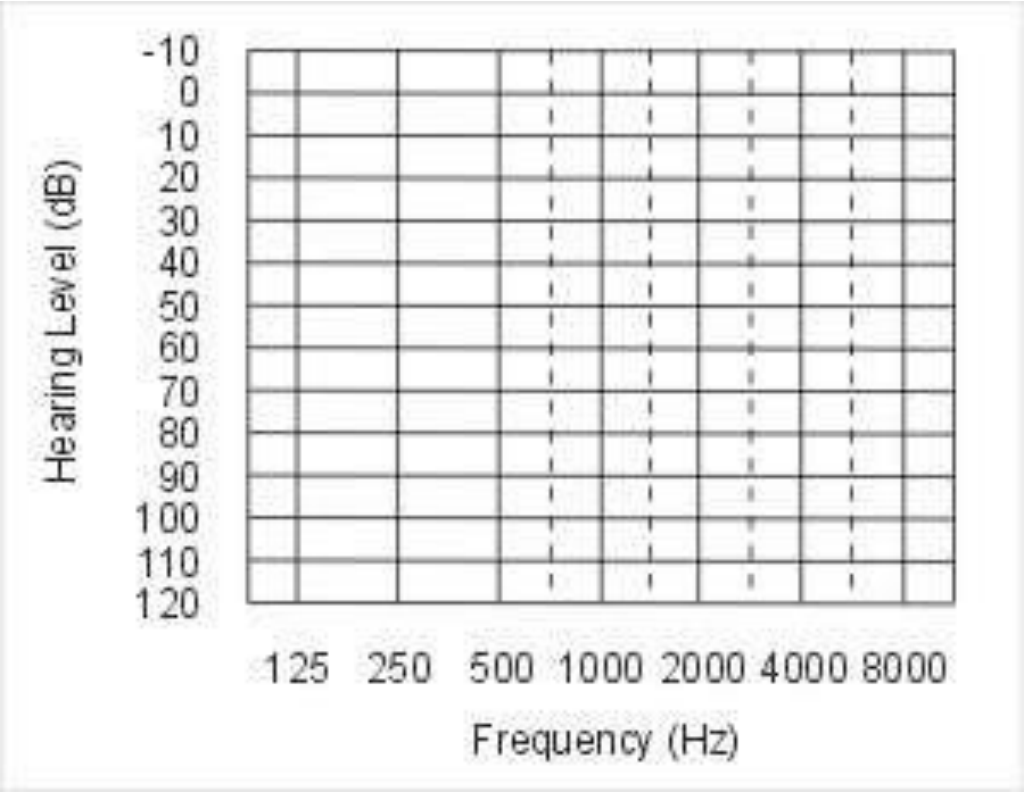


Fig 6. Audiogram graph

1) In the audiogram graph patient cannot hear area above the line.
2) Air conduction and bone conduction measured seperately
3) Air bone gap <10 db present in normal persons, SNHL
4) Air bone gap more than 10 db means conductive hearing loss

Common terminology criteria for adverse events (CTACE) was classified the drug induced hearing loss into 4 grades [19] as follows:

Grade 1 –threshold shift of 15 to 25db averaged at least two contiguous test frequencies in at least one year

Grade 2 - threshold shift of more than 25db averaged at least two contiguous test frequencies in at least one year

Grade 3- threshold shift of more than 25 db averaged at three contiguous test frequencies in at least one year

Grade 4 – threshold of more than 80 db at 2000Hz and above, corresponds to profound bilateral hearing loss.

Following figure 5 shows categorisation of hearing loss in the audiogram graph. Top of the graph shows normal audiometry pattern. Normal person hear the sounds less than 25db in all frequencies.

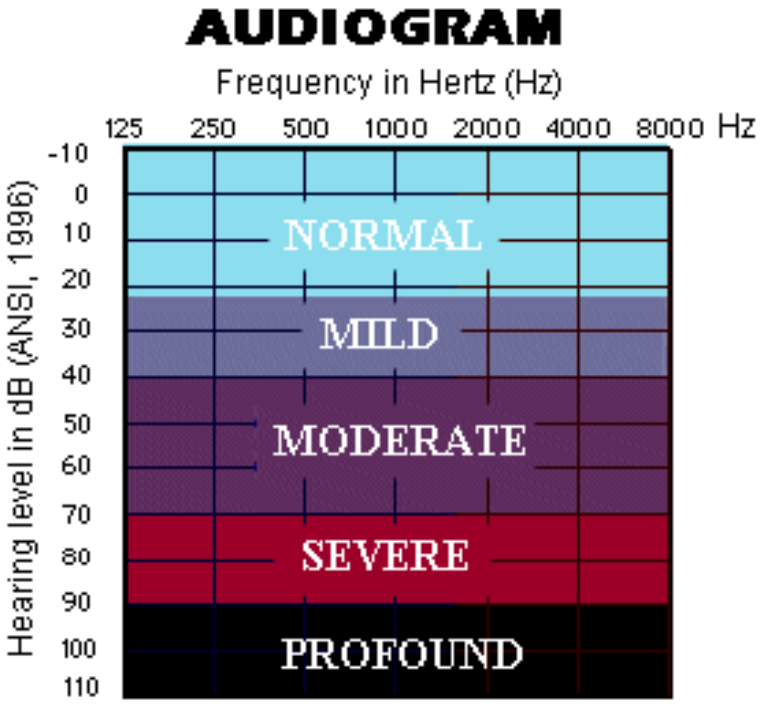


Fig 7. Classification of Hearing Loss

Figure 8 shows normal pattern of hearing , both ears shows 25 db hearing loss at 4000 Hz. Reported as normal

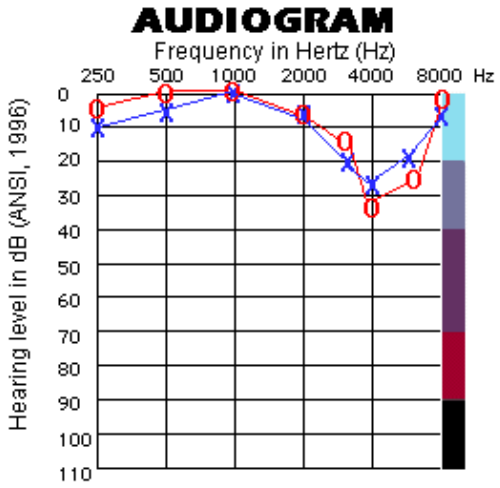


Fig 8. Normal

Figure 9 shows bilateral moderate hearing loss , started from 2000 Hz

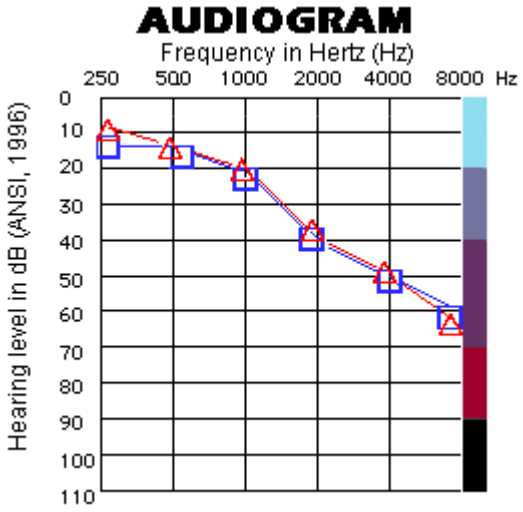


Fig 9. Moderate Hearing Loss Range Beginning at 2000 Hz

Figure 10 Normal pattern of hearing on left ear, right sided severe hearing loss according to WHO classification

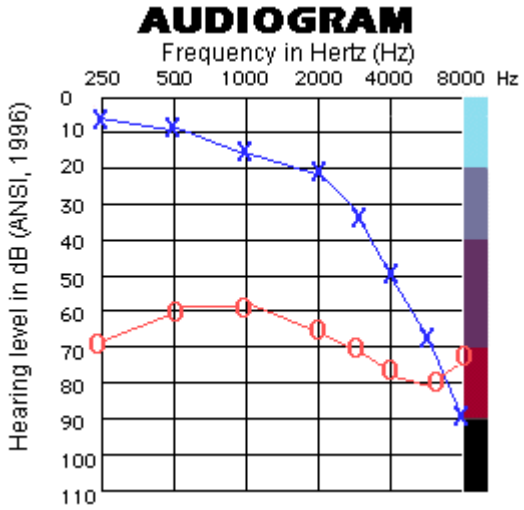


Fig 10. Left – Normal , Right Severe Hearing Loss

Figure 11 shows bilateral profound hearing loss involving the speech frequencies

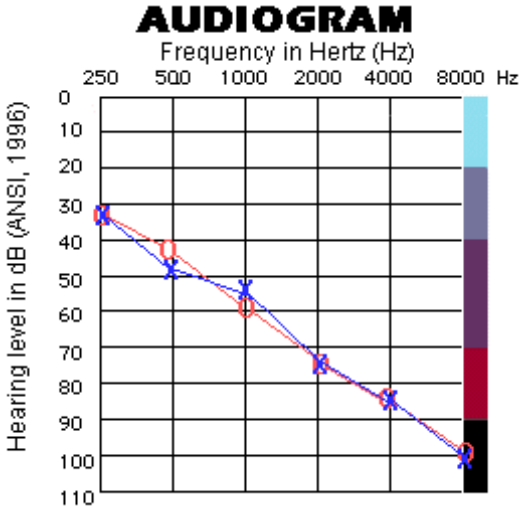


Fig 11. Bilateral Profound Hearing Loss

3.REVIEW OF LITERATURE

REVIEW OF LITERATURE

Ashishkumar C Zala et al [20] in department of pharmacology , government medical college , surat , conducted the study assessment of prevalence of kanamycin induced ototoxicity in MDR TB patients . In this prospective observational study 100 MDR TB cases were enrolled . Clinical and audiological examination was done in all patients at the initiation of DOTS PLUS regimen , and monthly for six months period in the intensive phase of the treatment. In this Study was conducted from January 2013 to may 2014 .

All newly diagnosed MDR TB patients was included in this study, at the time of initiation of drug treatment evidence of hearing loss and congenital deafness and infective pathology involving the ear like CSOM , meningitis , any surgical procedure in the ears , concomittent use of any ototoxic drugs are excluded. In this study 35 % patients develops mild to moderate bilateral sensory neuronal hearing loss , 65% patients without hearing loss during the six months period. During the Intensive phase of the CATEGORY IV REGIMEN 35% patients develops SNHL , among these 62.85 % (n=22) patients develops SNHL during the first month period , 11.4 % (n=4) during 2nd month of treatment , 2.85 % (n=1) developing SNHL 3rd month follow up period, 8.57 % (n=3) during 4th month , 8.57 % (n=3) on 5th month , 5.71 %(n=2) developed

SNHL on 6th month follow up period . In this study population diabetes and HIV status not mentioned.

Prahlad Duggal [21] et al in the year 2007 , conducted the study of audiologic monitoring of MDR TB patients getting aminiglycoside treatment with follow up was done a longer period. In this study 64 newly diagnosed MDR TB patients were included . They are divided in to three groups,

Group 1 - Thirty four patients administererd inj . Amikacin (dose is 15 mg / kg / day as a singleIM dose) , Group 2 - twenty six patients are received inj . kanamycin (dose is 15 mg / kg / day as a single IM daily dose) , and group 3 - four patients are using inj . capreomycin (dose was 15 mg / kg / day as a single IM dose). These drugs given for the period of six months . All patients in the study groups followed up for one year during the treatment, also after discontinuation of aminoglycoside for the next one year period . among them 18.75 % patients developed SNHL involving higher frequencies , and also 6.25 % patients hearing loss involved speech frequencies . after one year of discontinuation of aminoglycosides all patients were re-examined and found that all hearing loss are permanent also no threshold improvement . In Group 2 - four patients 15.4 % (n = 26) had hearing loss involving higher frequencies . Two patients 7.7 % (n = 26) had low frequency

hearing loss . total duration of the aminoglycoside use in this group 2 was 237 days +_ 34 days . In this study audiometry (PTA) was performed every month until the Completition of the treatment. Renal toxicity , diabetic status and , HIV status are not mentioned in the study .

Ann sturdy et al [22] conducted a retrospective study of DR TB treatment in the United Kingdom ; a study about aminoglycoside use and toxicity in DR-TB patients .This study was conducted in five DR - TB centres in UK between Jan 2004 and Dec 2009 , study about the incidence of ototoxicity for both clinically and audiometry testing and also factors contributed with hearing impairement were analysed. Outcome : 1) Total fifty DR-TB patients , 29 patients (58 %) received Inj. amikacin , 11 out of 50 patients (22%) received inj. capreomycin and 10 out of 50 patients (20 %) were administered inj. streptomycin or combination . 21 /50 patients (42 %) patients receiving basic audiological evaluation within two weeks of initiating treatment , and 16 out of 50 (32 %) had monthly audiograms , 12 / 50 (24 %) not receiving any audiological screening during the treatment . 2.) among the 50 patients , 14 patients (28 %) developed ototoxicity with 9 out of fifty patients (18 %) had permanant hearing impairement . Use of amikacin , increasing age decreased renal function were significantly associated

with ototoxicity .Nephrotoxicity was defined in this study was increasing creatinine values from baseline of more than 44 micomoles / litre at any time during treatment . In this study 7 (14%) patients developed nehrotoxicity during the treatment , 38 (76 %) normal creatinine values . among the fifty patients 5 (10%) patients HIV positive , 45 (90 %) HIV - non reactive

Mohammad Reza Javadi et al conducted the study in the year 2007 ,The Incidence of Amikacin induced Ototoxicity in DR-TB Patients was higher in men than in women . The hearing threshold values was significantly increased after the amikacin treatment in MDR-TB patients . incidence of the hearing impairment was significant in MDR –TB patients treated with inj.amikacin. In this study 41 patients received a fixed dose of IV amikacin (500 mg daily as 30 min IV infusion over 30 min) combined with the second - and third – line drugs for MDR – TB for six months period patient with pre treatment hearing problem like congenital deafness and congenital abnormalities and also patients with evidence of infective process involving the ear , previous history of meningitis , chronic otitis media) , surgical procedures and the ones using simultaneous use of ototoxic drugs were used as exclusion criteria for the study . Basic audiological evaluation Pure –Tone Audiometry (PTA) was done pre

and the post terament period . Total of 29 patients suffered from hearing impairement (70 . %) (Male :n = 18; Female : n = 20). Hearing impairment was bilateral in 18 patients (62.06 %) and unilateral in 11 patients (n = 6 right ear and n = 5 left ear) .

The severity of ototoxicity was varied widely from patient to patient (mild ototoxicity : about 44.83 % ; moderate ototoxicity : 17 . 24 % ; moderately severe ototoxicity : 24 . 14 % ; severe ototoxicity : 10 . 34 % ; profound ototoxicity : 3.45%) . In this study , age , cigarette smoking or drug abuse , do not significantly associate with the incidence and progress of cochleotoxicity

Tashneem harris [23] et al conducted a prospective cohart study about aminoglycoside induced hearing loss in HIV positive and negative pateint with MDR TB, result is 70% HIV positive patients developed hearing loss compared to HIV negative patients. HIV positive patients are at increased risk for developing hearing loss . In this study some patients developed severe hearing loss following single dose of kanamycin. This shows genetic susceptibility also plays important role for developing hearing loss.

In this study six MDR-TB patients had mitochondrial mutation involved in MT-RNR 1gene. This mutation involved aminoglycoside releated toxicity. In this study 70 % HIV positive patients developed hearing loss, no association found between degree of hearing loss with HIV status.

Elida mustikaningtyas [24] et al conducted a prospective observational study in Indonesia, to assessing the prevalence of hearing loss in MDR-TB patients in the year 2011. Study results was 36.6% of the patients are in between 31 to 40 years of age. 53.7 % patients developed asymptomatic hearing loss, 46.3% developed symptomatic hearing loss. Pure tone audiometry result showed 48% patients showed mild hearing loss, 24 % patients had moderate hearing loss.by using oto acustic emmison 54.87% had cochlear disease , 28.04% had normally functioning cochlea.

4. MATERIALS AND METHODS

Material and methods

Aim :

Audiologic monitoring and renal function monitoring for Drug Resistant patients under PMDT(programmatic management of drug resistant tuberculosis reatment) for six to nine months period in Tirunelveli Medical College Hospital DR-TB UNIT, from January 2014 to December 2014.

MATERIALS AND METHODS :

Total of 152 newly diagnosed DR-TB patients those registered in DR-TB centre , Tirunelveli medical college hospital from January 2014 to December 2014 were screened.

INCLUSION CRITERIA

All newly diagnosed DR-TB patients in tirunelveli, tuticorin, kanyakumari, virudhunagar districts in Tamilnadu state with normal baseline audiometry and normal serum urea and creatinine levels were included in this study

EXCLUSION CRITERIA

1. Pre treatment evidence of hearing loss in newly diagnosed DR-TB patient with baseline audiometry changes more than 25 db

2. Patient with prior history of audiological impairment, presbyacusis, any vestibulo-cochlear symptoms

3. Patients with age less than 10 year

4. Pregnant females

5. Patients not willing for routine follow up

6. Patients with elevated renal parameter at the time of initiation of the DOTS PLUS regimen.

7. Major psychiatric illness

Methods :

After getting the permission from the institutional ethical committee in Tirunelveli Medical College Hospital study commences, this prospective observational study was conducted from DR-TB unit in tirunelveli medical college . Informed Consent will be obtained from DR-TB patients admitted in DR-TB ward. This study starts after explaining the treatment regimen and probable adverse effects expected in the course of the treatment .

All newly diagnosed DR-TB patients admitted in DR-TB unit for DOTS PLUS regimen initiation in Tirunelveli Medical College were included in study group.

After using inclusion and exclusion criteria 51 eligible newly dignosed DR-TB patients were enrolled in this study .These patients were started on CATEGORY IV regimen according to weight basis. Pure tone audiometry was done in the ENT department in tirunelveli medical college.

AUDIOMETRY:

1. First Pure tone audiometry was done at the time of initiation of the CATEGORY IV regimen.
2. Second pure tone audiometry was done at third month of the treatment.
3. Third pure tone audiometry was done at sixth month of the treatment.
4. If patients develops tinnitus, vertigo, hard of hearing or any audiological impairement , pure tone audiometry was done in the intensive phase.

RENAL FUNCTION TEST :

1. Blood urea and serum creatinine was done at the time of initiation of treatment.
2. Follow up renal function test done at 3rd and 6th month period of the treatment.
3. If patient noticed facial puffiness, pedal edema, reduced urine output during the intensive period renal function test done at any time in between the treatment.

At the initiation of the CATEGORY 4 regimen for all DR-TB patients following investigation is required

- HEMOGLOBIN level,
- HIV status,
- DIABETIC screening for all patients

DURATION OF THE STUDY : 12 months(January 2014 to december 2014)

SAMPLE SIZE : 51

STUDY DESIGN : prospective observational study

SOURCE : MDR-TB Patients registered in DR-TB unit , Tiruneveli medical college hospital

WHO CRITERIA FOR CATEGORISING HEARING LOSS :

- Normal – amplitude less than 25 decibels
- Mild – amplitude 26 to 40 decibels
- Moderate- amplitude 41 to 55 decibels
- Moderately severe- amplitude 56 to70 decibels
- Severe - amplitude 71 to 90 decibels
- Profound - amplitude more than 90 decibels

5.RESULTS

ANALYSIS :

Total of 51 newly diagnosed DR-TB patients were included in this study. Pure tone audiometry and renal function monitoring was done and analysed as follows

AGE DIRSTRIBUTION :

- Out of 51 patients , 27 % (n -14) of the patients belongs to the age group of 41 to 50
- 24% of the patients (n-12)belongs to the the age group of 31 to 40 years
- 18% of the patients (n-9) belongs to the age group of 21to30 years
- 18% of the patients (n-9) belongs to the age group of 51to 60 years .
- 8% of the patients (n-6) belongs to the age group of 61 to70 years
- 6%of the patients (n-4) belongs to the age group of 11 to 20 years.

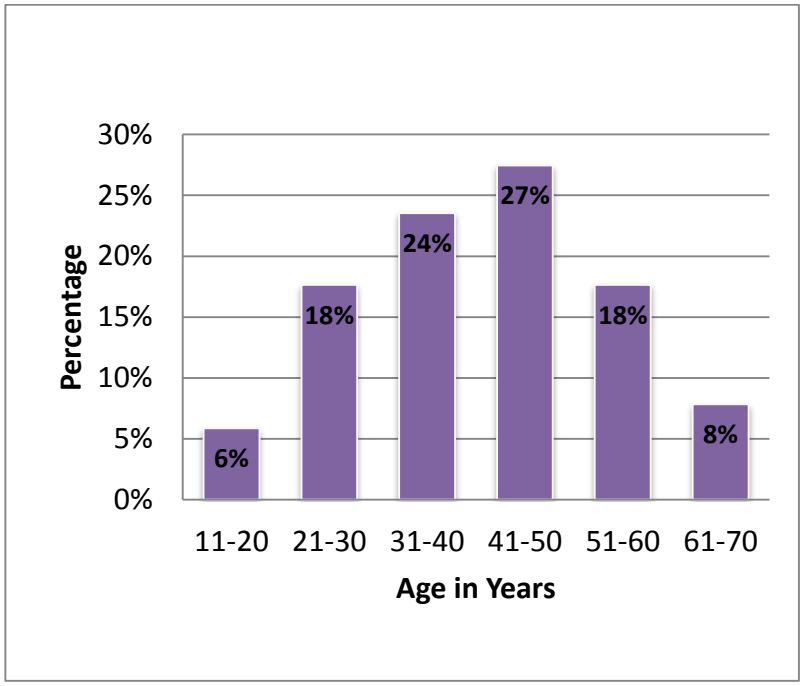


Fig 12. Age Distribution

Age	Number	Percentage
11-20	3	6%
21-30	9	18%
31-40	12	24%
41-50	14	27%
51-60	9	18%
61-70	4	8%

Table 1: Age Distribution

SEX DIRSTRIBUTION:

Out of 51 MDR-TB patients,82% (n- 42) patients are males,18% (n-5) are females

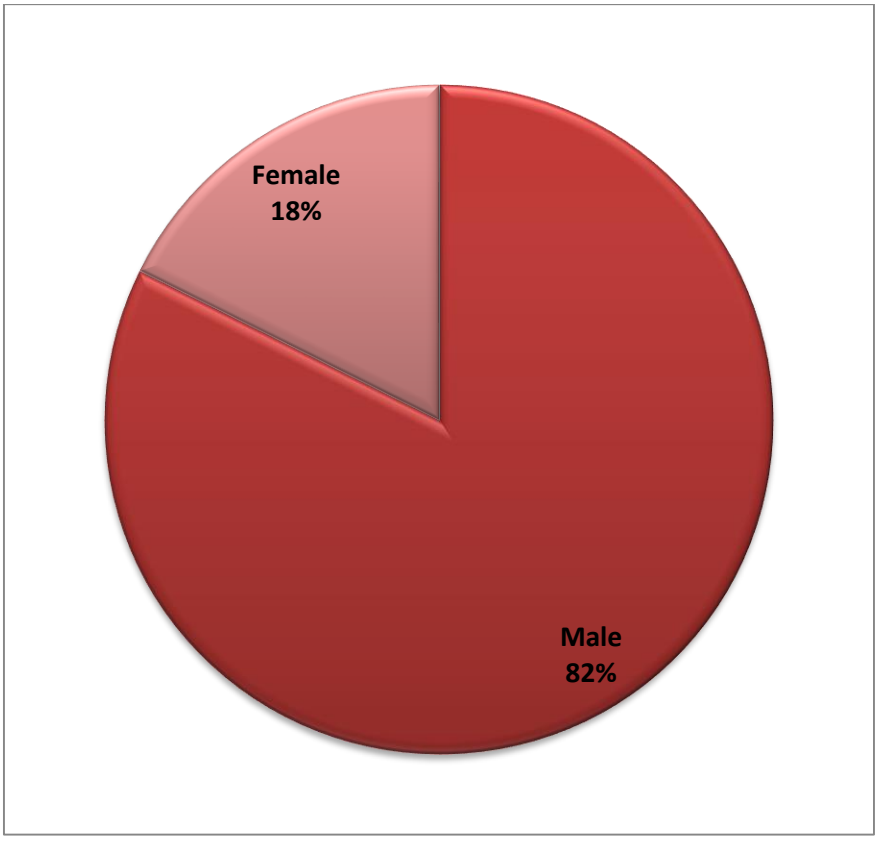


FIGURE 13; SEX DISTRIBUTION

Out of 51 MDR-TB patients 22 patients developed SNHL, among which 81% (n-18) are males ,18% (n-4) are females .

DIABETES MELLITUS

- Among the 51 patients 20%(n-10) patients are diabetic 80% (n-41) are non-diabetic.
- 70% of diabetic patients developed SNHL, Among these 86% (n-6) are males, 14% (n-1) are females.

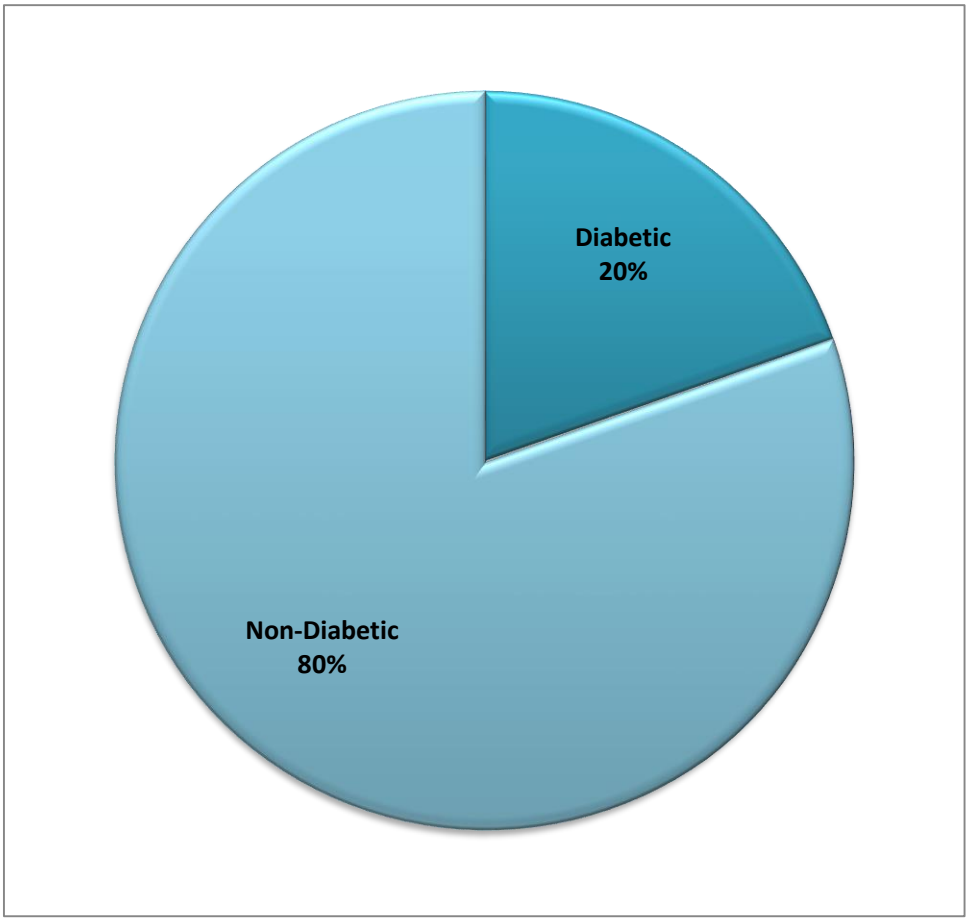


Fig 14. Diabetes in MDR TB

HIV SATUS :

- In 51 DR-TB patients, 5 patients are HIV positive, 3 patients are males, 2 patients are females.
- One male patient developed right sided severe hearing loss during follow up period.

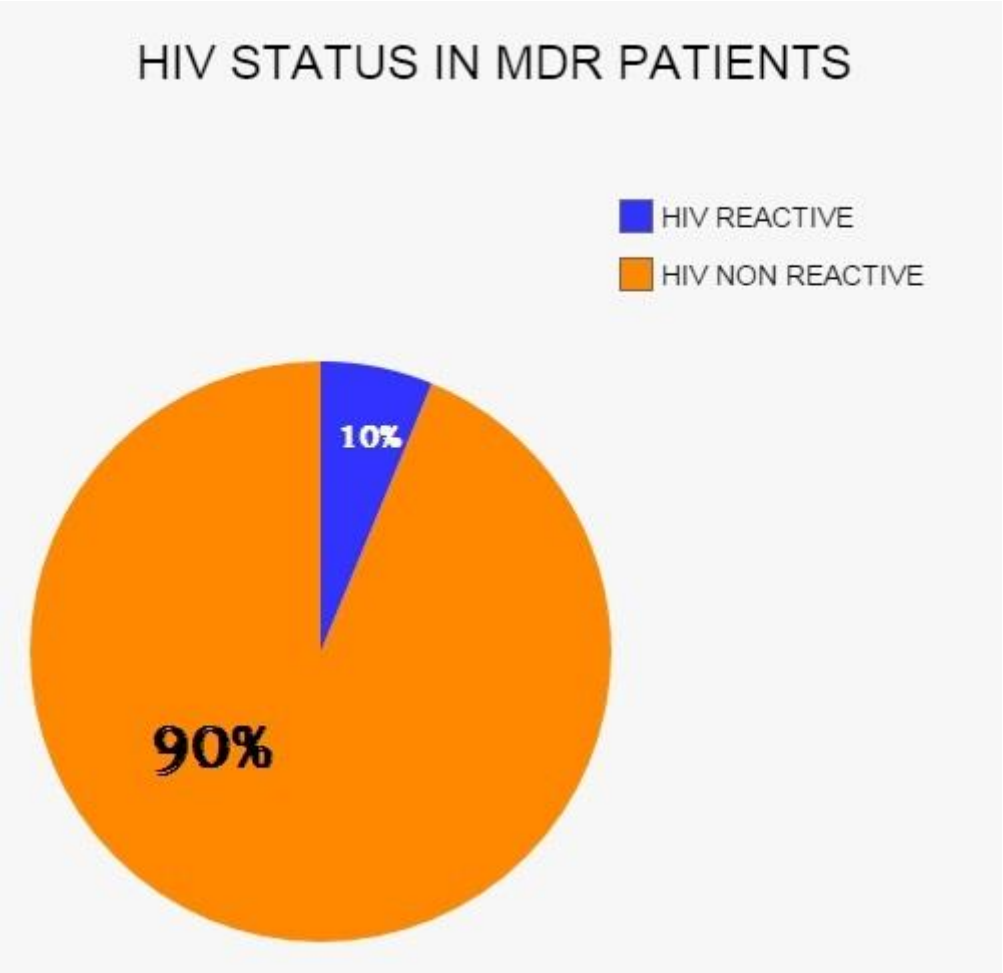


Fig 15. HIV in MDR TB

DEGREE OF HEARING LOSS

- **UNILATERAL HEARING LOSS :** TOTAL-8

- Total of 51 DR-TB patients, 8 patients (n-8) developed unilateral hearing loss.
- Among them 7 patients had mild hearing loss (male-6, female - 1), one had moderate hearing loss .

DEGREE	RIGHT	LEFT
MILD	4 (M 4 / F 0)	3 (M 2 / F 1)
MODERATE	1 (M 1 / F 0)	0
MODERATLY SEVERE	0	0
SEVERE	0	0
PROFOUND	0	0

Table 2 : Unilateral Hearing Loss

BILATERAL HEARING LOSS : T**OTAL** 14 (M 11 / F 3)

- Out of 51 patients , 14 patients (28ears) developed bilateral hearing loss, among these patients 11 were males, 3 were females,
- In this group 9 patients developed bilateral mild SNHL , 1 patient had severe hearing loss , one patient had right sided profound hearing loss and left severe hearing loss on 3rd month of follow up

DEGREE	RIGHT	LEFT
MILD	1	-
MODERTE	1	1
MODERATLY SEVERE	1	3
SEVERE	1	1
PROFOUND	1	0

Table 3 : BILATERAL SNHL

NUMBER OF PATIENTS DEVELOPED B/L MILD SNHL: 9

PERCENTAGE OF HEARING LOSS FOR USING WHO CLASSIFICATION :

Out of 22 patients who developed SNHL (44 ears) , 75% (33 ears) patients developed mild hearing loss, 9.1% (4 ears) patients developed moderate hearing loss, 9.1%(4 ears) patients developed moderately severe hearing loss, 4.5 % (2 ears) developed severe hearing loss, 2.3% (1ear) developed profound hearing loss.

CATEGORY	NO OF EARS	PERCENTAGE
MILD	33	75%
MODERATE	4	9.1%
MODERATELY SEVERE	4	9.1%
SEVERE	2	4.5%
PROFOUND	1	2.3%

FOLLOW UP OF HEARING LOSS :

During the follow up period in a 51 DR-TB patients, 3rd month follow up 27% (n-14) DR-TB patients had developed right sided SNHL, 20%(n-10) DR-TB patients had developed left sided SNHL .

In the 6th month follow up period DR-TB, 39% (n-20) patients had developed right sided SNHL , 27% (n-14)) DR-TB patients had developed left sided SNHL .

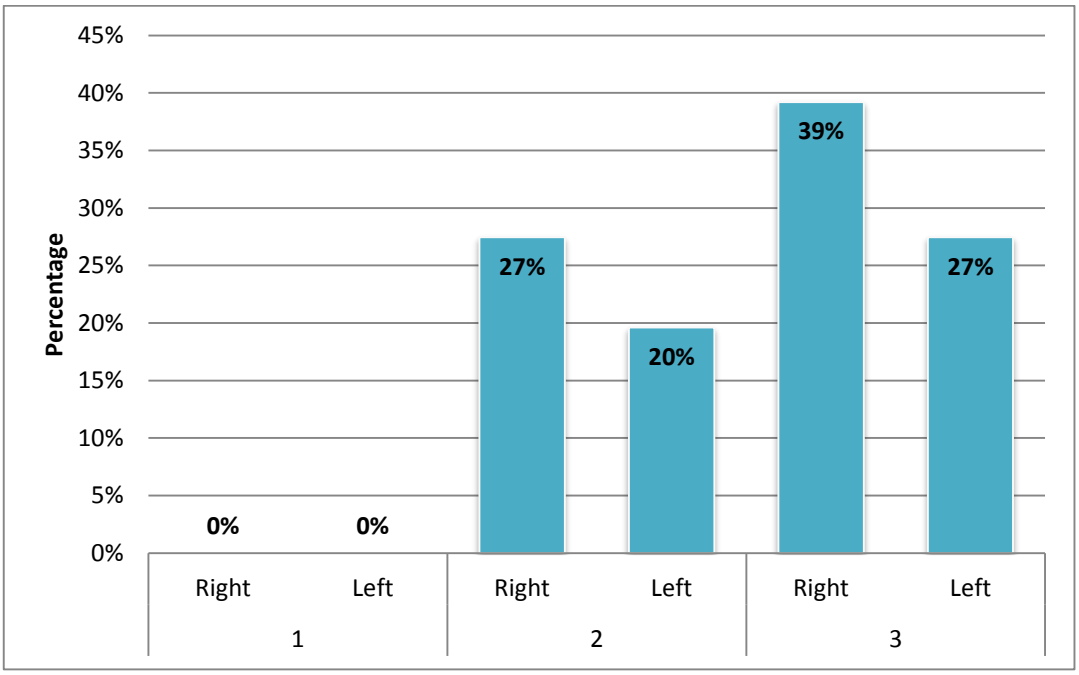


Fig 16 FOLLOW UP OF HEARING LOSS

FOLLOW UP VISITS	SIDE	NO OF PATIENTS	PERCENTAGE
1	RIGHT	0	0
	LEFT	0	0
2	RIGHT	14	27%
	LEFT	10	20%
3	RIGHT	20	39%
	LEFT	14	27%

Table 3: NO OF PATIENTS DEVELOPED HEARING LOSS DURING FOLLOW UP

RELATIONSHIP BETWEEN ONSET OF OTOTOXICITY AND DURATION OF THE TREATMENT :

Out of 51 DR-TB patients in this study, 22 DR-TB patients developed hearing loss. Of these 77.27% (n-17) patients had developed hearing loss during the first three month of the intensive period , 22.72% (n-5) DR-TB patients developed SNHL during the sixth month of the DOTS PLUS regimen.

Onest of Ototoxicity	**3rd month**	**4th month**	**5th month**	**6th month**
No of patients (n=22)	17 (77.27%)	0	0	5(22.72%)

Table 4. Onset Of Ototoxicity in MDR TB

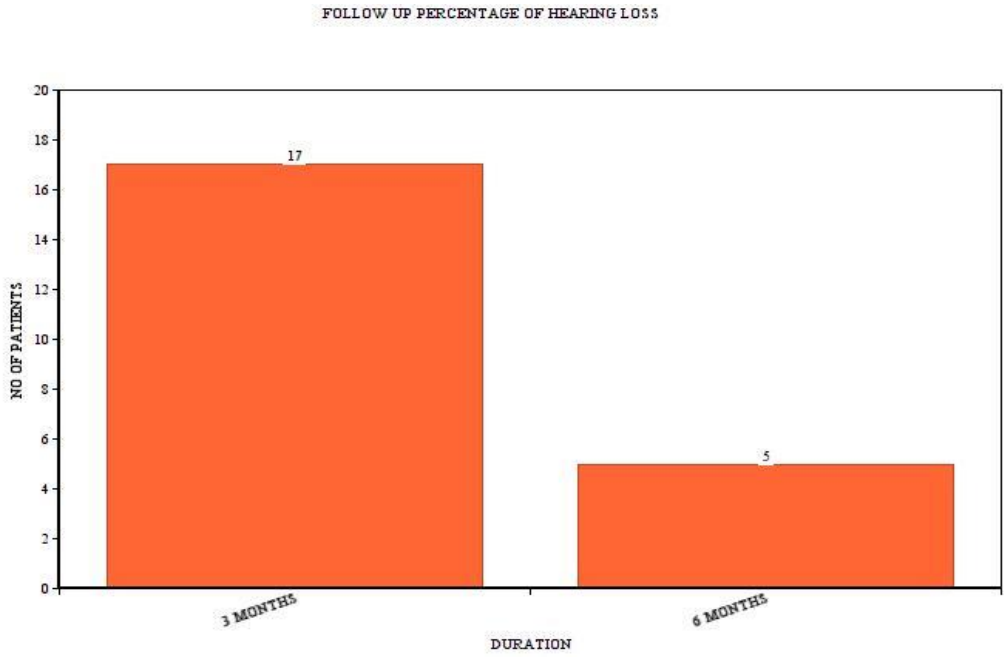


Fig 17. FOLLOW UP PERCENTAGE OF HEARING LOSS

STATISTICAL SIGNIFICANCE OF OTOTOXICITY :

During the follow up period of 51 DR-TB patients audiometry results were analysed by using ANNOVA TEST (analysis of variance) and Overall **p value is 0.002. T**his p value is statistically SIGNIFICANT . Hence injection kanamycin produce definite ototoxicity among the DR-TB patients receiving the CATEGORY 4 regimen .

	Follow up	**P Value**
PTA	All	0.002
Right Ear	1 and 2	0.24
	1 and 3	0.003
	2 and 3	1
Left Ear	All	0.003
	1 and 2	0.039
	1 and 3	0.003
	2 and 3	1

Table 5

SYMPTOMS ANALYSIS FOR OTOTOXICITY :

During the follow up 22 patients developed hearing loss , 36%(n-8) patients had vestibulo cochlear- symptoms like tinnitus , vertigo, hard of hearing, fullness of ear . Most common symptom noticed in this study is tinnitus (75%)

64% (n-14) patients NOT aware of the symptoms associated with hearing loss .

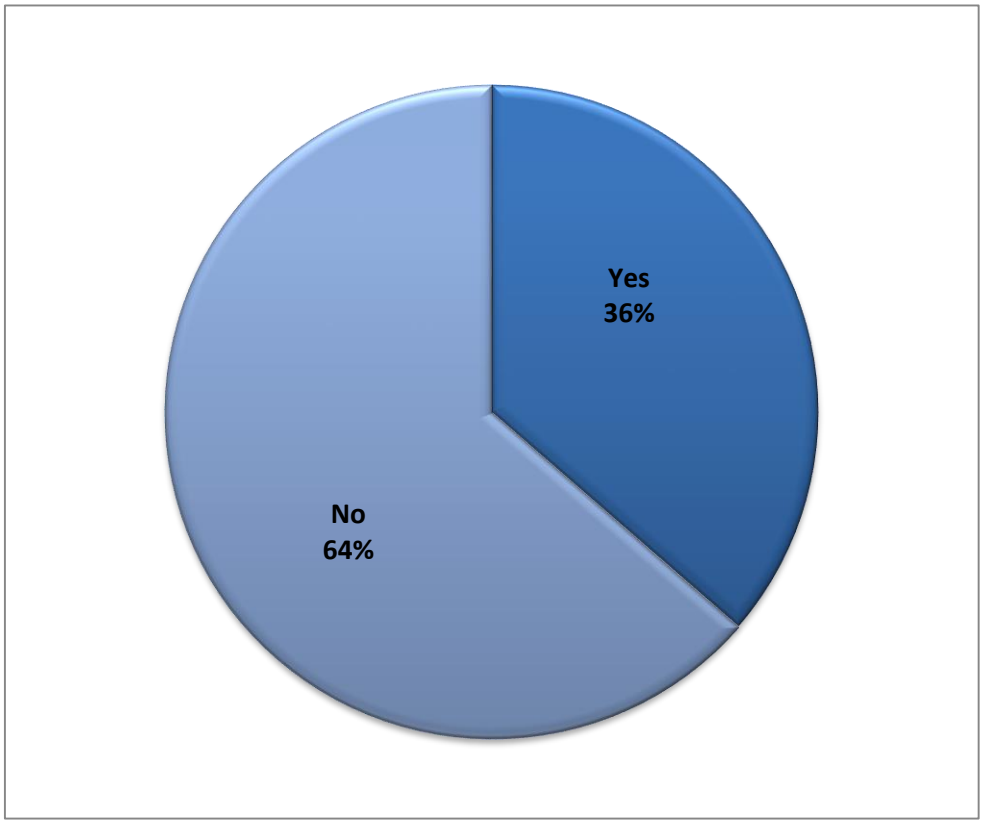


Fig 18. Symptoms Analysis For Ototoxicity

DIABETES AND DR-TB WITH SENSOY NEURAL HEARING LOSS:

Among 51 DR-TB patients , 10 patients found to be diabetic, in this sub group 7 paients developed SNHL (ototoxicity) during the follow up period .

		Ototoxicity	
		Yes	No
DM	Yes	6	4
	No	16	25

P value 0.295 Fisher's exact test

Table . 6

HIV positive AND DR-TB patients WITH HEARING LOSS :

Total of 51 patients , 5 patients were HIV – positive, 1 patient developed right sided mild hearing loss and left moderately severe hearing loss during the 3rd month follow up period.

NEPHROTOXICITY:

Total of 51 DR - TB patients, 4 patients (male-3, female-1) were found elevated renal parameters above the normal values. During the follow up period, 3rd month of the intensive phase 2%of patients noticed elevated urea and creatinine values above the normal range .

Sixth month follow up period 8% patients (n-4) had elevated blood urea levels above the normal range . 4% (n-2) patients had elevated serum creatinine levels above the nomal range.

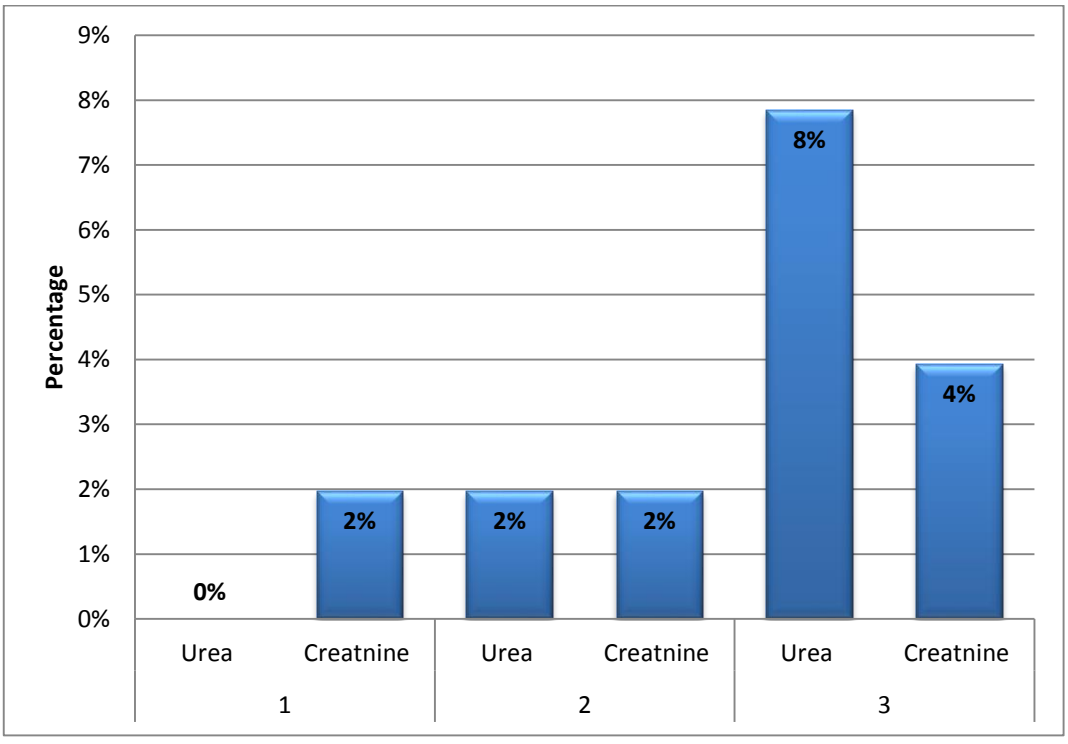


Fig 19.Onset of Nephrotoxicity

No of visit	Renal parameter	No of patients	%
1	Urea	0	0%
	Creatnine	1	2%
2	Urea	1	2%
	Creatnine	1	2%
3	Urea	4	8%
	Creatnine	2	4%

Table .7

STATISTICAL SIGNIFICANCE FOR NEPHROTOXICITY

During the intensive period of CATEGORY IV regimen, third and sixth month for urea level had significant p value <0.0001

	Follow up	P Value
Urea	All	<0.0001
	1 and 2	0.055
	1 and 3	<0.0001
	2 and 3	0.1

Table .7

During the intensive period of CATEGORY IV regimen, third and sixth month for serum creatinine level had significant p value 0.023

	Follow up	P Value
Creatnine	All	0.023
	1 and 2	1
	1 and 3	0.032
	2 and 3	0.09

Table .8

In this study overall statistically significant p values <0.05 obtained for 3rd and 6th follow up period for both elevated blood urea and serum creatinine values.

SYMPTOMS ANALYSIS FOR NEHROTOCITY :

Four patients (male-3, female-1) were elevated parameters are observed in this study.Most of the patients in this study noticed elevated renal parameters during 6th month follow up period. Patients are not aware of the symptoms of renal failure .

DIABETIS AND NEPHROTOXICITY:

10 diabetic patients are included in this study group , among them one patients had elevated blood urea and serum creatinine levels also ultrasonogram shows bilateral chronic medical renal disease at the 6th month of the intensive period .

Statistically no significant p values (0.357) obtained related to diabetes and nephrotoxicity among the DR-TB patients

		Renal toxicity	
		Yes	No
DM	Yes	1	9
	No	1	40

Table .9

OTOTOXICITY AND NEPHROTOXICITY :

In this study group total of 51 DR-TB (n-51) patients, 2 patients had developed both ototoxicity and nephrotoxicity ,there is no satistically significant p values (1.000)obtained for both ototoxicity and nephrotoxicity.

		Ren_toxi	
		Yes	No
oto_toxi	Yes	1	28
	No	1	21

P value 1.000 Fisher's exact test

Table .10

ANAEMIA :

Total of 51 DR-TB patients , 31 patients had Hb level less than 11gms%, among the 31 patients 17 patients developed SNHL

RESULTS :

In this study total of 51 DR-TB patients were included ,41%(n-22) patients were developed significant OTOTOXICITY ,2% (n-4) patients had NEHROTOXICITY, 2%(n-4) patients developed BOTH OTOTOXICITY AND NEPHROTOXICITY, remaining 55%(n-30) are ASYMPTOMATIC .

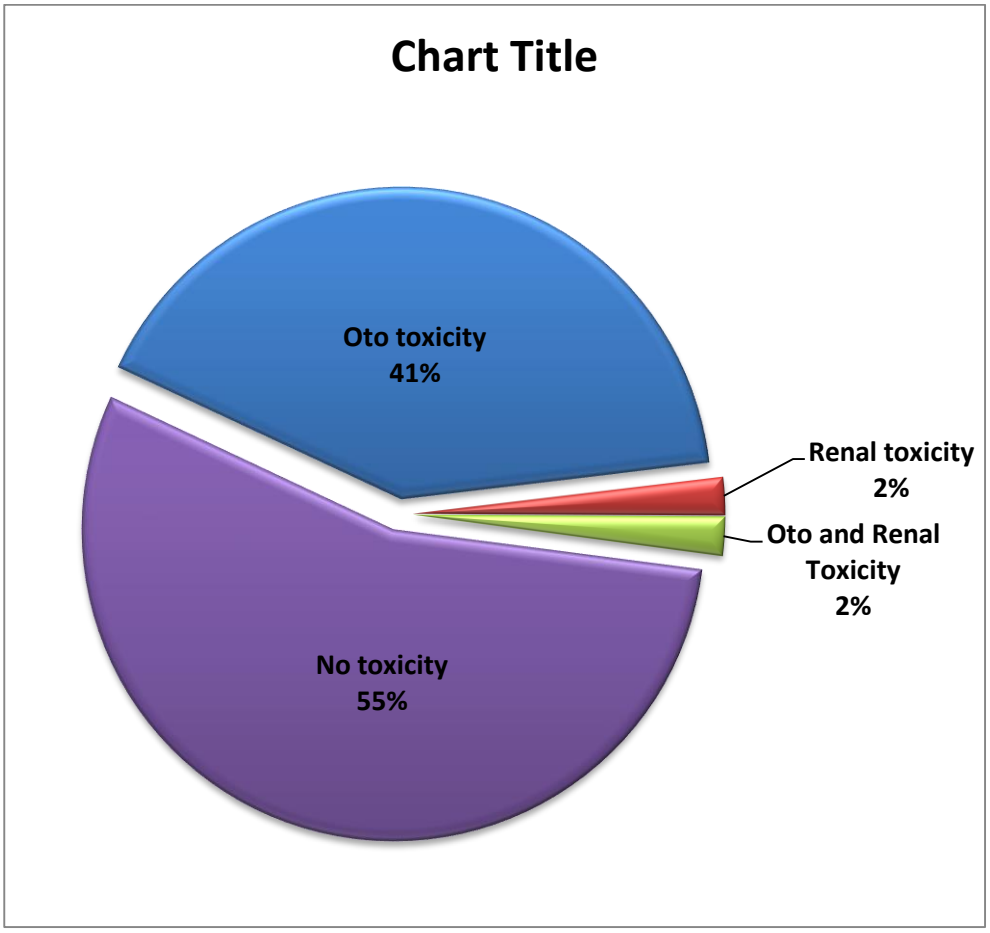


Fig 20. Over all Percentage of Kanamycin Induced Toxicity

6. DISCUSSION

DISCUSSION:

Injection kanamycin is the important bactericidal antibiotic drug used to treat the DR-TB patients during the intensive phase of the CATEGORY IV regimen. According to weight basis kanamycin is given as an intramuscular injection given for six days per week except Sunday dose. Kanamycin is the drug well known to produce ototoxicity and nephro toxicity.

Kanamycin induced ototoxicity is usually irreversible, because it destroys both inner and outer hair cells in the cochlea. kanamycin induced ototoxicity is dose dependent manner, initially it affects the higher frequencies, later it affects lower frequencies and also involves the speech frequencies and interfere with speech communication .

Kanamycin induce nephrotoxicity in a duration dependent manner, it is concentrated in renal cortex and produces well documented nephrotoxicity. If kanamycin is used in patients with poor renal reserves it will potentiate nephrotoxicity among them.

In our study incidence of injection kanamycin induced ototoxicity among the DR-TB patients was **43.13%.** Prahlad duggal et al reported prevalence of aminoglycoside induced ototoxicity of 47%, out of which 18.75% SNHL involving higher frequencies and 6.25% involving lower frequencies.

In our study 82% male , 18% females are included . Among these 63.63%(n-14) males, 36.36% (n-8) female patients were developed SNHL during the six months follow up period. In our study 69% (n-35) of the patients were in between 21 to 50 years of age group.

In our study of 51 DR-TB patients 22 patients developed hearing loss. During the 3rd month follow up period out of 22 patients, 77.27% (n-16) patients developed SNHL, 22.72 % (n-6) patients developed SNHL at the 6th month follow up period. **Aasishkumar et al** conducted a study in govt surat medical college, overall incidence of ototoxicity is 35%, of which during the 1st month follow up 62.85% , 2nd month follow up 11.4% , 3rd month follow up 2.8% , 4th 5th and 6th month results are 8.57%,8.57%,5.71% respetively developed SNHL .

Kanamycin induced ototoxicity initially involve higher frequencies. At that time most of the patients are not aware of the symptoms of ototoxicity, at this time if the patients was not diagnosed . Later it will involve lower and speech frequencies , patient may land up with audiological symptoms,at this time hearing loss will be permanent. Detection of the hearing loss in the later stages may not be beneficial to the patient by stopping the inj. kanamycin. Hence strict audiogical evaluation is mandatory in DR-TB patients at the time of initiation of CATEGORY IV regimen, also every month follow up period till

completion of inj.kanamycin, thereafter every three months till end of the treatment for early detection and prevention of ototoxicity .

In our study majority 64% (n-14) of patients were unable to recognised the symptoms of hearing loss, 36% (n-8) patients noticed symptoms of hearing loss like tinnitus, hard of hearing, fullness of the ear and vertigo. In a symptomatic patients most common symptom noticed is tinnitus (75%) , then hard of hearing (16%) , least symptoms noticed were fullness of the ear and vertigo.

In our study incidence of nephrotoxicity was found in 2% , four patients developed statistically significant (p values urea <0.0001, for serum creatinine 0.023) nephrotoxicity during the follow up period of CATEGORY IV regimen , none of them were aware of the symptoms associated with nephrotoxicity.

In our study simultaneous development of ototoxicity and nephrotoxicity found in 2% of patients.

In our study population 20% (n-10) patients were found to be diabetic, in this group 70% (n-7) patients had SNHL during the follow up period, among this group 86% of patients were male, 14% patients were female. None of these patients had associated with nephrotoxicity. In our study diabetic patients with irrespective of glycemic control, none

of these patients were developed statistically significant symptomatic ototoxicity and nephrotoxicity.

In our study , 9.8% (n-5) of patients had HIV positive , in this group 20% (n-1) patients developed otoxicity , none of them developed nephrotoxicity during the intensive phase period. Tashneem harris et al study shows 57% of HIV positive patients developed high frequency SNHL, when compared to HIV negative MDR-TB patients. Co-existence of HIV positive status would not increase the nephrotoxicity and ototoxicity, which was statistically insignificant.

7.CONCLUSION

CONCLUSION :

1. In this prospective observational study, during the intensive phase of CATEGORY IV regimen 43.3% patients developed statistically significant OTOTOXICITY , 2% patients developed NEPHROTOXICITY and 2% of patients developed BOTH OTOTOXICITY AND NEPHROTOXICITY.
2. **OTOTOXICITY-** 63.63% patients developed bilateral hearing loss and 36.36% patients developed unilateral hearing loss. among the patients with ototoxicity 75% patients had mild hearing loss, and mostly during first three months period of the intensive phase.
3. In our study 64% patients with hearing loss are asymptomatic and 36% patients noticed symptoms associated with hearing loss and the most common symptom being tinnitus (75%) .

4 . In our study 64 % of asymptomatic hearing loss cases were picked up by using pure tone audiometry. Early detection of the hearing loss among these patients shall improve adherence to the treatment. hence pure tone audiometry to be done as a pre treatment evaluation for all MDR-TB patients at the initiation of the treatment, every month for the first six months, then every three month till completion of the treatment.

7. BIBLIOGRAPHY

REFERENCES:

1) Global Tuberculosis control 2014,WHO, Geneva, 2014 www.who.int/tb/ publications/ global report.
2) TB India 2012, Revised national TB control programme annual status report,New Delhi2012.www.tbcindia.nic.in/documents.html
3) Lambregts-van Wezenbeek CSB, Veen J. Control of drug-resistant tuberculosis. Tubercle and lung disease1995:76;455-458.
4) Ramachandran R, Nalini S, Chandrasekar V, Dave PV, Sanghvi AS, Wares F, Paramasivan CN, Narayanan PR, Sahu S, ParmarM, Chadha S, Dewan P, Chauhan LS. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int J Tuberc Lung Dis* 2009: 13(9); 1154-1160.
5) Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *Int J Tuberc Lung Dis* 2001: 5(1); 40 45.
6) *Global tuberculosis control: surveillance, planning, financing. WHO report 2004*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.331).
7) Laserson KF et al. Speaking the same language: treatment outcome Definitions for multidrug-resistant tuberculosis. *International*

Journal of Tuberculosis and Lung Disease, 2005, 9(6):640–645. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313)

8) Akula SK, Aruna, AS et al. Cycloserine-induced Stevens-Johnson syndrome in an AIDS patient with multi drug resistant tuberculosis. Int J Tuberc Lung Dis 1997; 1(2): 187-90.

9) J.M.Walker, R.A.Wise the pharmacokinetics of amikacin in volunteers: a comparision of individual differences, journal of antimicrobial chemotherapy, vol.5, no.1,pp.95-99,1979.

10) J.M. Aran and J.Darrouzet, observation of click evoked compound VIII nerve responce before, during,after seven months after kanamycin treatment in a guinea pig, Acta oto-laryngologica, vol.79, no1-2,pp 24-32,1975

12) Chaulk, C., Chaisson R., Lewis, J., et al. Treating multidrug-resistant-tuberculosis: compliance and side effects. Journal of the American Medical Association 1994; 271(2): 103-104.

13) Furin JJ et al. Occurrence of serious adverse effects in patients receiving

community-based therapy for multidrug-resistant tuberculosis. *International*

Journal of Tuberculosis and Lung Disease, 2001, 5:648–655

14)TB/HIV: a clinical manual. Geneva, World Health Organization, 2003 (WHO/HTM/TB/2004.329).

15) S.A.Fausti et al. High Frequency Audiometric Monitoring For Early Early Detection of Aminoglycoside Ototoxicity . Journal Of Infectious Diseases, vol.165, no.6, pp.1026-1032,1992.

16) J.E.Hawkins And L.G.Johnson, Histopathology Of Cochlear And Vestibular Ototoxicity, S.A.Lerner et al, pp.327=339.1981.

17) British Society Of Audiology.Pure Tone air-bone conduction threshold Audiometry . Reading ,British Society Of Audiology 2004. Www.Thebsa. Org. Uk/ Docs /Recpro/Pta.Pdf

18) Goodman A . Reference Zero Levels For Pure Tone Audiometry Asha 1965; 7: pp.262-263.

19) National Cancer Institue, National Institue of Health, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Available at http://evs.nci.nih.gov/ftp1/CTCAE/ CTCAE_4.03_ 2010- 06-14_ QuickReference_5x7.pdf (accessed 26.1.12). 2009.

20) Ashiskumar C Zala et al, Assessment Of Prevalence Of Kanamycin Induced Ototoxicity In MDR-TB Patients In Tertiary Care Hospital, India EJPMR,2(4).Pp 995-999.

21) Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BMC Ear Nose Throat Disorder* 2007; 7: 5.

22) Sturdy A, Goodman A, Jose RJ, Loyse A, O'Donoghue M, Kon OM, Dedicoat MJ, Harrison TS, John L, Lipman M, Cooke GS. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a studyof injectable use and toxicity in practice.
J Antimicrob Chemother 2011; 66: 1815-1820.

23) Tashneem Harris Et Al, Aminoglycoside Induced Hearing Loss In HIV Positive And HIV Negative Multi Drug Resistant Tuberculosis Patients, The South African Medical Journal, vol.102. no.6.2012.

24) Elide Mustikaningtyas Et Al Hearing Disorder In MDR-TB Patients At The Outpatients Unit, Pulmonary Department, DR. Soetomo Hospital, Surabaya, Folia Medica Indonesiana Vol.49, No.4,pp 263-264, 2013.

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

DEPARTMENT OF THORACIC MEDICINE

NAME: **AGE/SEX** **IP NO:**
DATE:

ADDRESS:

CONTACT NO:

1.Any previous history of Psychiatric Illness: Yes/No

2.Previous H/O hearing loss : Yes/No

3.Willing for audiometry test : Yes/No

4.Base line(first) audiometry date & result

5.Followup audiometry at 3 months and 6 months

DATE	AUDIOMETRY DONE	RESULTS
1		
2		
3		

6.Any history of hearing problem during this period: Yes/No

If yes – detailed h/o

Tinnitus/HOH/Fullness of ear/Vertigo/Giddiness/Ataxia

FOLLOWUP	UREA	CREATININE
1.		
2.		
3.		

Any H/O Oedema/Oliguria/Abdominal Pain : Yes/No

S.No	PMDT NO	NAME	AGE	SEX	PTA 1-R	PTA 1-L	PTA2-R	PTA2-L	PTA3-R	PTA3-L	UREA1	CREATININE1	UREA2	CREATININE2	UREA3	CREATININE3	OUTCOME	OUTCOME	Hb	DM	HIV	PTA Symptoms
1		Dharshini	22	F	23.3	30	24	26.4	24	26.4	16	0.8	18	0.9	24	0.9	3B	U/L SNHL-L	12.4	NO	NR	NO
2	132/14	SHANMUGA SUNDARAM	34	M	18.3	18.3	18.3	18.3	20	20	22	0.7	26	0.9	28	0.8	1	Normal	13	NO	NR	
3	81/13	MAYANDI	33	M	20	21.6	76.6	64.6	76.6	64.6	26	1.1	28	1.4	47	1.6	2 & 4	B/L SNHL / F	10	NO	NR	YES
4	137/14	MASANAM	45	M	20	21.6	35	25.6	35	25.6	25	0.8	27	0.7	33	0.7	2	B/L SNHL	11.3	NO	NR	NO
5	104/14	PARAMASIVAM	33	M	23.3	20	23	18	15	15	16	0.9	24	0.8	26	0.8	1	Normal	8	NO	REACTIVE	
6	131/14	SUNDARAM	68	M	20.4	21	38	40	38	40	16	0.8	16	0.8	24	1	2	B/L SNHL	12	YES	NR	NO
7	130/14	MOHAMAD ASKAR	23	M	16.6	20	16.6	16.6	18	20.4	16	1	18	0.9	18	0.9	1	Normal	11	NO	NR	
8	128/14	JEBAKANI	22	F	21.6	20	18.4	18.4	18.8	20.4	16	0.8	24	1	22	1	1	Normal	8	NO	REACTIVE	
9	91/14	murugan	50	M	18.8	20	33.3	25	33.3	25	19	0.9	24	0.8	22	1	2	B/L SNHL	10	YES	NR	YES
10	57/14	SHAKEELA	30	F	20	18	18.6	24	20	21.4	20	0.7	18	0.8	24	1	1	Normal	11	YES	NR	
11	21/14	REJINA	49	F	20	20	23	20	23.3	23.3	20	0.8	24	0.8	32	0.8	1	Normal	10	NO	REACTIVE	
12		SIVARAJAN	40	M	20	20	18.4	20	20	21.4	22	0.8	28	0.6	42	0.8	4	Normal	8	NO	NR	
13	117/14	DURAISAMY	46	M	20	20	34	32.6	34	32.6	21	0.6	21	0.8	34	1	2	B/L SNHL	9	YES	NR	YES
14		GURUSAMY	38	M	18.3	20	21.4	20	20	20	24	0.9	22	1	24	0.8	1	Normal	10	NO	REACTIVE	
15	114/14	JAINSIRANI	35	F	20	20	22	22	58.3	51.6	25	0.8	26	0.9	29	1	2	B/L SNHL	10	NO	NR	YES
16	39/14	SUBBAIAH	50	M	21	21	90	85	90	85	28	0.8	40	1	40	1	2	B/L SNHL	9	NO	NR	YES
17	16/14	karupasamy	45	M	25	20	21	20	18	20	21	1	24	0.8	22	0.9	1	Normal	8.6	NO	NR	
18		BALAKRISHNAN	45	M	21.6	18.3	21.6	20	22	20	22	1	34	0.8	34	0.9	1	Normal	12	NO	NR	
19	69/14	RAMESH	25	M	18	21	55	20	55	20	22	1	32	1	28	1	3A	U/L SNHL R	11	NO	NR	YES
20		SHANMUGA SUNDARAM	34	M	18.3	23.3	21.4	20	18	20.4	22	0.8	24	0.8	24	0.9	1	Normal	11	NO	NR	
21	73/14	HYDER ALI	51	M	18	20	20	21.3	46	60	28	0.9	42	1	44	1	2	B/L SNHL	10	NO	NR	YES
22	136/14	SUNDARA RAJAN	45	M	18	18	20	21.3	20	20	24	0.8	26	0.9	34	1	1	Normal	8	NO	NR	NO
23	112/14	SARASWATHI	51	F	20	20	21.3	24	38.6	33.3	24	0.8	34	0.9	34	0.9	2	B/L SNHL	10	YES	NR	
24	13/14	GANESAN	43	M	18	18	18.3	16.6	20	20	34	1	36	1	28	0.9	1	Normal	10	NO	NR	
25	86/14	AMBIGAI SELVI	23	F	15	16.6	18	18	18	18	19	0.9	21	0.9	18	0.9	1	Normal	9	NO	NR	NO
26	106/14/	SELVARAJ	40	M	23.3	18.3	20	20	21.3	18.3	25	0.8	25	0.8	28	1	1	Normal	11	NO	NR	
27	104/14	PARAMASIVAM	33	M	20.3	21	23.3	20	18.4	21	16	0.9	24	0.9	22	0.9	1	Normal	11	NO	NR	
28	152/14	LAXMANAN	67	M	21	21	20	18.3	16.6	18	18	0.7	24	0.9	80	2.1	4	RENAL	8	YES	NR	NO
29	319/14	S M RAHMAN	45	M	21.6	20	20	21	25	20	19	0.8	16	1.1	18	0.9	1	Normal	12	YES	NR	
30	133/14	MURUGAN	14	M	20	20	26.6	20	26.6	20	18	1.2	17	0.8	18	0.6	3A	U/L SNHL R	10.4	NO	NR	NO
31	142/14	SUDALAI ANDI	68	M	20	20	21.6	23.3	20	25	22	0.8	18	0.7	24	1.1	1	Normal	12	NO	NR	
32	49/14	DEVARAJA SINGH	68	M	21.4	20	43.3	50	43.3	50	33	1.3	34	1.1	36	1	2	B/L SNHL	10.6	NO	NR	
33	114/14	BALASUBRAMANIYAN	34	M	22	18	20	20	28.3	21.4	34	0.7	28	0.9	34	0.7	3A	U/L SNHL R	10	NO	NR	NO
34	67/14	MANI	36	M	18.3	18.6	19.2	18.3	18.3	18.3	16	0.6	24	0.8	18	0.8	1	Normal	11	YES	NR	
35	14/15	CHELLADURAI	55	M	21.6	20	24	21.4	28.3	21.6	18	0.9	18	0.9	21	0.9	3A	U/L SNHL R	10	YES	NR	NO
36	100/14	MUTHIAH	60	M	18.3	21.6	18	20	18.3	21.6	19	0.9	18	0.9	18	0.8	1	Normal	12	NO	NR	
37	30/15	MUTHU RAKKU	43	M	18	19.6	33.3	60	33.3	60	22	0.9	34	0.8	24	0.9	2	B/L SNHL	10	NO	REACTIVE	YES
38	139/14	MUTHU PANDI	41	M	20	20	18	20	20	20.4	18	1.1	24	1.2	32	1.1	1	Normal	12	NO	NR	
39	147/14	MARIMUTHU	28	M	22.4	20	24	24	18	20	24	1	34	1.1	26	1.1	1	Normal	12	NO	NR	
40		SAROJA	50	F	18	20	21	24	25.6	26.6	18	0.9	22	0.9	24	1.1	2	B/L SNHL	10	NO	NR	NO
41		VELUSAMY	60	M	22	18	30	21.6	30	21.6	24	0.9	36	1	34	0.8	3A	U/L SNHL R	10	NO	NR	NO
42		RAJASEKAR	53	M	18	20	28.3	23.3	28.3	23.3	34	1	28	0.9	36	1.1	3A	U/L SNHL R	10	NO	NR	NO
43	70/13	BOOPATHI	53	M	18	20	21.4	20	21.6	20	24	0.6	28	0.8	22	1	1	NORMAL	12	NO	NR	
44	006/15	SANKARASAMY	54	M	24	18	38.3	38.3	38.3	38.3	24	0.8	18	0.6	34	1	2	B/L SNHL	8.6	NO	NR	NO
45	141/14	VELMURUGAN	31	M	22.3	18	22	18	20	21	24	0.9	36	0.8	26	1	1	Normal	11	NO	NR	
46	111/14	MOTCHAM	59	M	20	20	26.4	28	26.4	28	26	0.9	34	1	34	1.1	2	B/L SNHL	12	YES	NR	NO
47	19/14	RAVI	19	M	24	20	19	20	20	20	28	0.9	24	0.6	24	0.8	1	Normal	11	NO	NR	
48	103/14	JEYAPARVATHI	24	F	21	21	24	18	24	21	26	0.9	24	0.5	38	1.1	1	Normal				
49		DHONI	11	M	21	21	25	38.3	25	38.3	18	0.9	24	1	32	1.1	3B	U/L SNHL-L	12	NO	NR	NO
50	29/14	KARUPPAIAH	50	M	21	18	18	20	20	24	24	1	34	1	36	0.8	1	Normal	11	NO	NR	
51	75/14	RAJA	27	M	21	18.4	20	20	20	20	34	0.9	34	1.1	28	0.9	1	Normal	11	NO	NR	