IAP KERALA RESPIRATORY CHAPTER 2017

An Update on
PEDIATRIC TUBERCULOSIS

IAP KERALA 2017

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RESPIRATORY CHAPTER IAP KERALA 2017

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CB NAAT
A New frontier in TB Diagnosis

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Introduction

Tuberculosis in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis. This has made it difficult to assess the actual magnitude of the childhood TB epidemic, which may be higher than currently estimated. 70-80% of children with TB have the disease in their lungs (pulmonary TB). The rest are affected by TB disease in other parts of their body (extra pulmonary TB). Drug resistant TB is also a major issue in children.

Any child having signs and symptoms suggestive of TB including a cough for more than 2 weeks, and a fever for more than 2 weeks, significant weight loss, haemoptysis etc. and any abnormality in a chest radiograph should be evaluated to find out if they have TB.

Currently available tests to diagnose TB :

- Microbiological confirmation on sputum: All patients who have presumptive (that is are presumed to have) TB and who are capable of producing sputum, should undergo a sputum test for rapid microbiological diagnosis of TB.
- Chest X-ray as a screening tool: Where available chest X-ray should be used as a screening tool.
- Tuberculin skin test: Used as a complementary test along with history, symptoms, signs and radiology.
- Cartridge Based Nucleic Acid Amplification Test (CB NAAT): The CB NAAT also known as the GeneXpert, is the preferred first diagnostic test in children and people with TB and HIV co-infection.Serological tests for TB are banned and are not recommended for diagnosing TB.

Under the Revised National TB Control Programme(RNTCP), diagnosis of pulmonary TB includes collection of atleast 2 sputum samples (spot & early morning), followed by

sputum smear microscopy (both conventional Ziehl-Neelson staining/fluorescent staining), culture (on solid or liquid media using manual or automated machines like BacTAlert, MGIT), conventional PCR based line probe asssay (LPA for Mycobacterium Tuberculosis complex), and the Real time PCR based CB-NAAT.

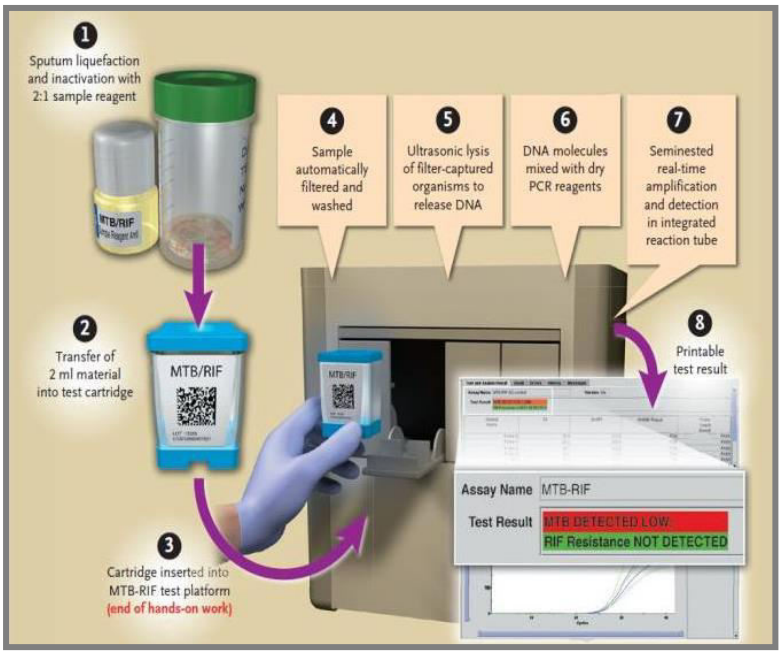
Sputum smear microscopy is inefficient due to its variable sensitivity particularly in patients with sputum smear-negative and/or extrapulmonary disease, and drug-resistant TB. Latest generation liquid culture diagnostics and molecular line probe assays are costly and cannot be performed in resource-limited settings, due to need for biosafety measures and specialised staff. Besides technical expertise and biosafety concerns, Lowenstein-Jensen (LJ) method, "the gold standard test", takes several weeks to produce result causing delayed onset of treatment.

In December 2010, WHO recommended use of a new Cartridge Based Nucleic Acid Amplification test (CB-NAAT), named GeneXpert system. The Xpert MTB/RIF assay employs five distinct nucleic acid probes each labelled with a differentially coloured fluorophore and responding to a specific nucleic acid sequence within the *rpoB* gene of *M. tuberculosis*. It can detect TB along with rifampicin resistance in less than two hours, directly from untreated sputum samples. RNTCP is currently using Xpert MTB/RIF to diagnose pulmonary TB, paediatric TB, extrapulmonary TB and rifampicin resistance and Multi Drug Resistance Tuberculosis in high risk populations like HIV positive as recommended by WHO under 2013 policy recommendations.

The Genexpert platform simplifies molecular tests by integrating four steps- 1)sample preparation(purification) 2)concentration, 3)amplification and 4)identification of targeted nucleic acid sequence in TB genome. Once loaded with specimen, DNA of bacilli is amplified and detected on real time.

Sample collection for pulmonary TB includes sputum(if obtained) in young children – gastric aspirate (preferably early morning before food since food particles can be inhibitory). It has been found to give good results with smear negative pulmonary TB. The results are not very good for extra-pulmonary TB with positivity rates lower than that for pulmonary TB. Samples like lymph node aspirate, cold abscess may give positive results, but pleural fluids, CSF have very low positivity rates. CB NAAT is not recommended on urine sample. Samples should be preferably not blood stained since blood is inhibitory. Bone marrow specimens cannot be dealt with due to the same reason. Multiple specimen increases the sensitivity, but WHO recommends a single sputum specimen due to resource implications. Minimum Bacilli needed for detection is 131/ml. Tissue samples should not be added with formalin before sending for

GeneXpert.



A minimum of 1 ml sample is required for the test. Most machines can take 4 samples at a time, but bigger machines with 8 samples per load are available. Though the average cost of doing the test may be upto Rs.2000/-per test, through RNTCP, it is available free of cost in Government Medical Colleges, District TB centres. Children, patients with HIV are given preference. It provides result from unprocessed pulmonary sample (Sputum) in 2 hours. Extra pulmonary samples takes approximately one more hour hands on technical time.

CB-NAAT determines the presence of Mycobacterium tuberculosis and also resistance to rifampicin in a rapid test. It can be incorporated at the point of care setting. There are less bio hazard concerns since contact with infective specimens is less. When compared with AFB smear it has a sensitivity of 89% and specificity of 99%. It has high sensitivity in case of HIV co-infection cases and children which has resulted in it being the preferential first test in these groups. Since bacterial load can also be detected, it indirectly indicates the infectivity of the patient. It may help in reducing the proliferation time of drug resistant strains by initiating an early detection. However, there are a few concerns which need to be addressed. Currently the running costs are quite high, but as the test becomes more widespread, this may be brought down.

Though the test needs just 2-4 hours for actual completion, due to the increased number of samples, there is a delay in the turn around time (TAT). This can be overcome by increasing the number of facilities doing the test. The test requires a stable and uninterrupted electrical power supply and a computer, a skilled technician. It requires an annual, expensive and specialized

calibration. The test identifies only Mycobacterium TB complex and cannot detect Non Tuberculous Mycobacteria(NTM) which still requires culture methods for identification. It detects resistance to rifampicin only, so monoresistance to Isoniazid if present alone cannot be detected. Since the test can not differentiate between live and dead bacilli, it can not be used as a follow up tool to know the response to treatment.

Diagnosing TB in children is difficult as children are less likely to have obvious symptoms of TB, and samples such as sputum are more difficult to collect from young children. Even when sputum can be collected, it may have very few TB bacteria in it (paucibacillary smear-negative disease).With the advent of CB-NAAT, the sensitivity and specificity of rapid diagnosis from sputum, has increased to approximately the levels seen in solid-media sputum culture, but the time scales, at just a few hours, are very much shorter with CB-NAAT.

Chest X-Ray in Pediatric Tuberculosis

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Tuberculosis is the second most common cause of death from infectious disease, being second only to HIV/AIDS. WHO reported that there is no single country in the world which has succeeded in reaching the point of control, ie less than 1% tuberculin positivity among children in the age group of 0-14years.

Unlike in adults, diagnosis of TB in children is difficult due paucibacillary nature of the disease, due to lack of characteristic complications like fibrosis and cavity lesion, etc. In children diagnosis is based on typical history(fever and cough of more than 2 weeks duration and weight loss of >5% in last 3months),history of contact, positive tuberculin test(with 2TU), X-ray features and if possible by isolation of the organism.

Chest X-ray (CXR) is one tool most commonly used(and many times misused!) by pediatricians in diagnosing a case of TB. One have to keep in mind that one should never diagnose tuberculosis based on CXR alone, because there is no specific finding in X-ray that is diagnostic of TB .One may get hilar shadow in conditions like lymphoma, pneumonia, sarcoidosis, etc other than TB. Similarly, miliary shadow will also seen in bronchopneumonia, pulmonary edema, pulmonary infarction, interstitial lung disease, tropical eosinophilia, aspiration pneumonia, histocytosis, pneumoconoisis and hemosiderosis , but in a particular clinical context with help of other tests(eg: MTx), one can diagnosis tuberculosis with reasonable accuracy. Also one has to keep a high index of suspicion of TB in case “pneumonia” treated properly with sensitive antibiotics.

The type of radiological shadow depends up on the stage of the disease(Fig 1)

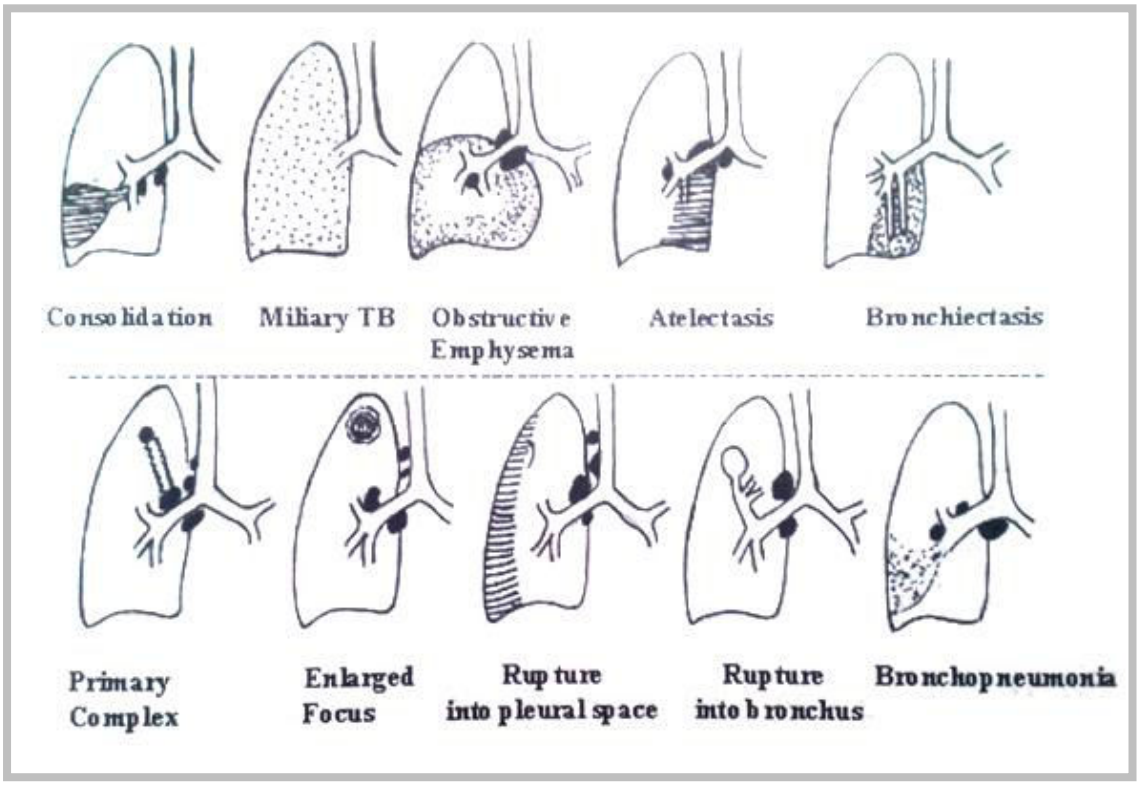

Fig 1: Progression of TB in children

Glandular element (hilar, para-tracheal and subcarinal) prominent in pediatric age group(Fig 2) , where as fbro-cavitory lesion is not common in this age group.

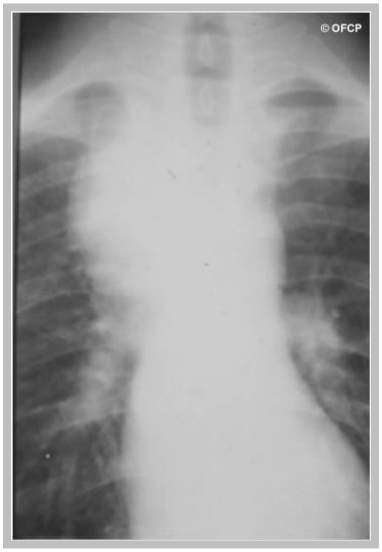

Fig 2: Para tracheal lymph node

Primary complex is one of the earliest radiological finding(Fig 3) appear.

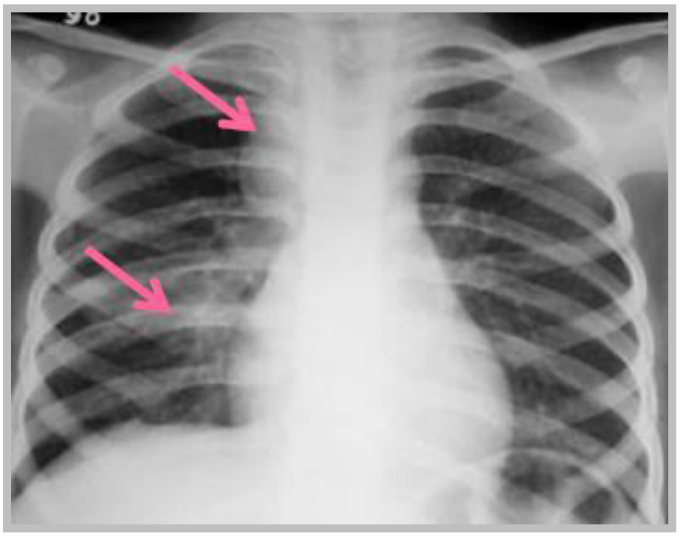

Fig 3: Primary pulmonary complex

The fate of primary complex is as follows:

I.Local spread:

a)Progressive pulmonary lesion like extended parenchymal involvement(Fig 4), pleural effusion(Fig 5) , pericardial effusion(fig 6) or bronchiectasis(Fig 7)

b)Bronchial obstruction resulting in collapse(Fig 8) or obstructive emphysema(Fig 8)

c)Brochial erosion resulting in spread of infection to various parts of the lung, the so called segmental(fig 9) or endobronchial TB

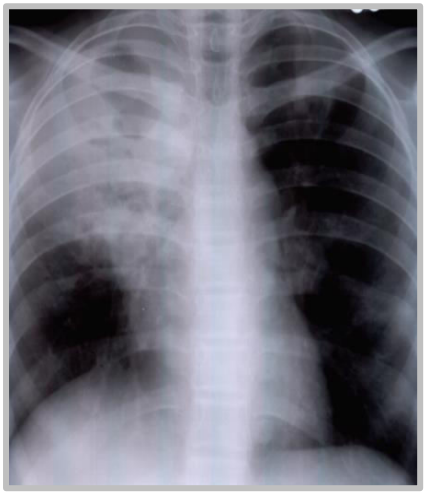

Fig 4: TB parenchymal involvement. Not responded to antibiotics

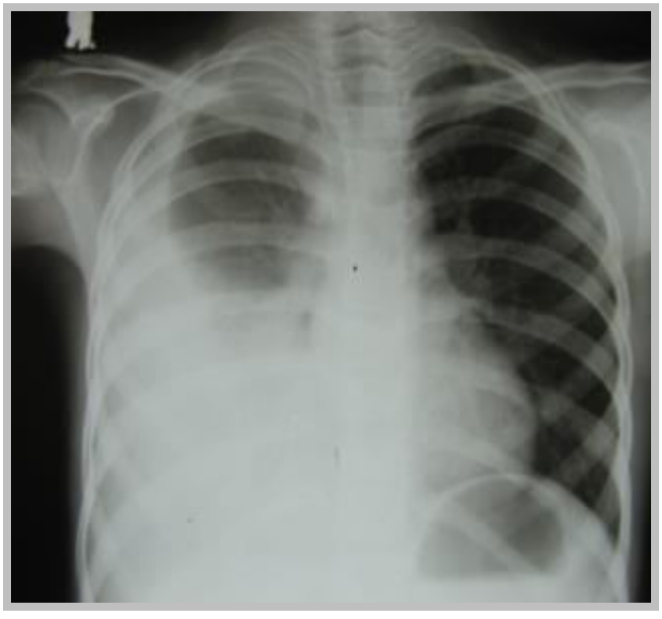

Fig 5: TB pleural effusion

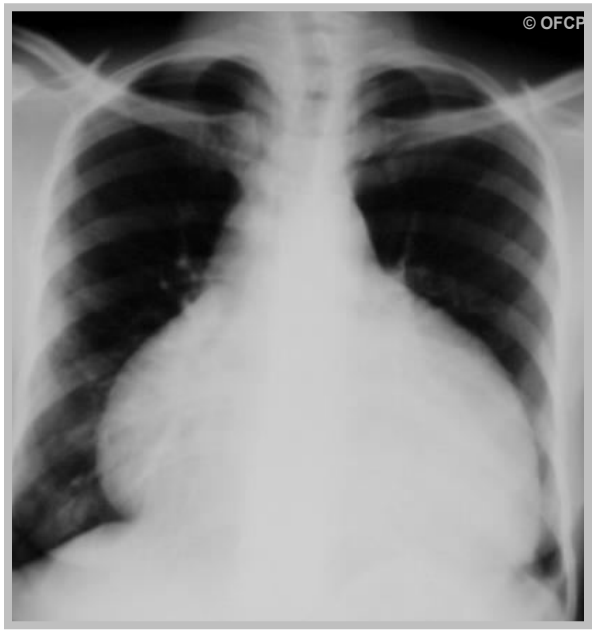

Fig 6: Pericardial effusion

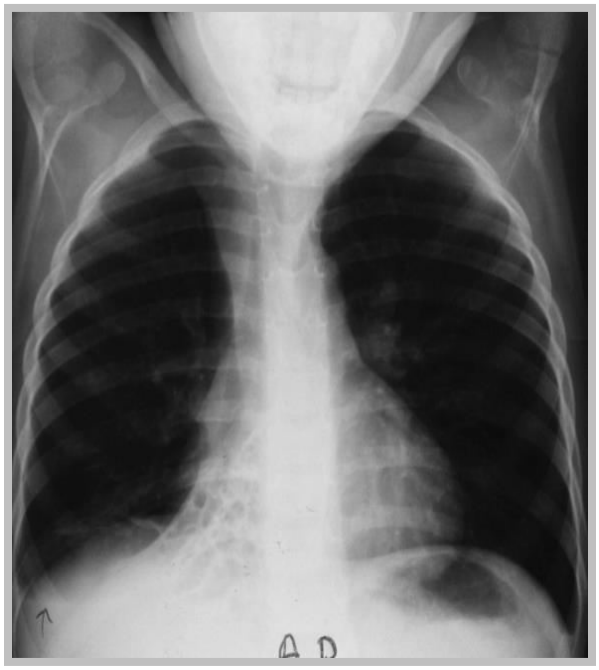

Fig 7: Bronchiectasis (Rt)

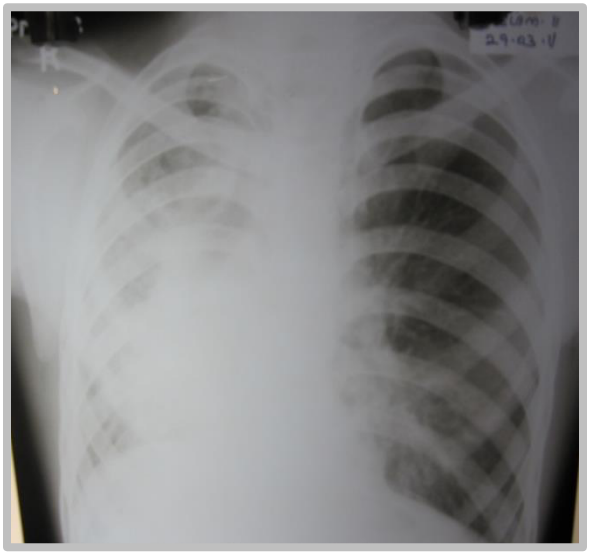

Fig 8: Right LL collapse

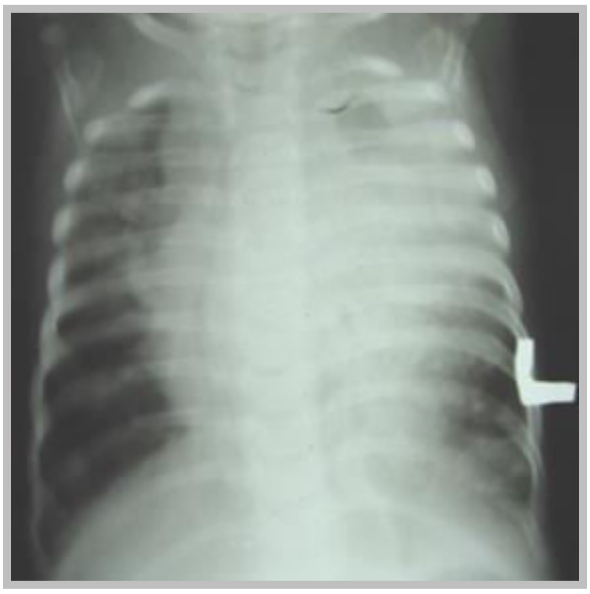

Fig 9: Paratracheal node (Rt) with lobar pneumonia(Lt)

II. Hematogeneous spread:

Due to the proximity of a minute lesion to intima of a blood vessel or rupture of caseous gland in to large vein. Blood dissemination may lead to extensive miliary mottling(Fig 10), involvement of other distant organ.eg: brain, bone, kidney, etc.

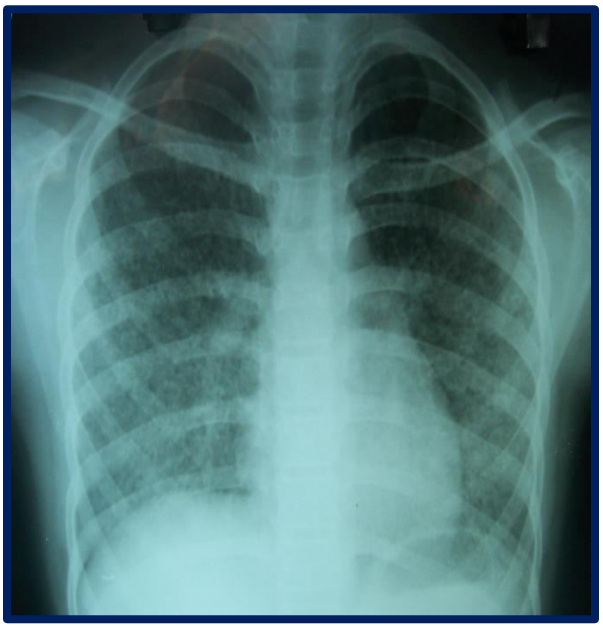

Fig 10: Miliary TB

Summary :

- Pulmonary TB diagnosis by means of CXR examination in a child, suspected of TB present a challenge. Physicians need to be trained on CXR interpretation.
- No specific shadow for tuberculosis.
- Diagnosis of TB never made with chest X-ray alone
- Be aware about TB mimicking shadow.
- Over or under diagnosis is possible , if the technical aspects are not fulfilled.

Essentials of Management of Childhood Tuberculosis

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Introduction

India contributes one fourth of total world TB cases. Forty percentage of Indian population is infected with TB. Pediatric cases represent 6-10% of TB burden of India. About 5.5 lakhs of new cases & 80000 TB related deaths occur annually in children. India also has a large burden of multi-drug resistant (MDR) TB and extensively drug resistant (XDR) TB. Though MDR-TB and XDR-TB are documented among children, there are no estimates of overall burden.

Unique aspect of TB in children is the imperceptible and often rapid progression of infection to disease. Risk of developing active disease is 43% below 1yr, 24% below 5 yrs and least in 5–10 year age group. The risk increases again during adolescence. In infants, the time between infection and disease is shorter than in older children, and the presentation may be more acute. Majority has paucibacillary disease. Extra pulmonary disease more commonly occur in children which represent 25 - 30 % of childhood TB. Adolescents develop an adult-like disease and could be infectious also.

Pulmonary parenchymal disease and intrathoracic adenopathy account for 60%–80% of pediatric TB. Lymphadenopathy is the most common(67%) extra pulmonary manifestations, followed by central nervous system involvement (13%), pleural (6%), miliary and/or disseminated(5%), and skeletal TB(4%). Disseminated (miliary) disease and TB meningitis are usually found in young (<3 years) and/or HIV infected children.

More than 95 % of children who progresses to disease, do so within the first 12 months of primary infection. Age < 3 years, HIV co infection & severe malnutrition are the 3 most important risk factors for progression.

In 2016 RNTCP has revised the management guidelines of TB which will be introduced in a phased manner from march 2017 onwards. Important changes will be discussed here.

Case finding and diagnosis

Identification of presumptive TB by a symptom based approach is the most important part of case finding.

Pediatric presumptive TB refers to Fever and / or cough > 2 weeks, loss of weight/not gaining weight and/or exposure to smear positive TB patient or significant superficial lymphadenopathy.

Presumptive DR-TB: Patients who failed treatment with first line drugs, who are contacts of MDR-TB or RIF resistant TB, previously treated TB and TB patients with HIV co infection are to be evaluated for drug resistant TB.

Symptom characterization: Very important in the evaluation to avoid over diagnosis and under diagnosis.

Fever: Should be persistent (>2weeks), unexplained, >38ºC, reported by guardian or recorded at least once.

Cough: should be **persistent** & **unremitting**. Cough and fever which is recurrent and, associated with cold is not a TB suspect.

Definitive weight loss or FTT: No weight gain in 3months or unexplained weight loss(more than 5% of the highest weight recorded in the past three months).

Lymph nodes: Maximum prevalence between 5 and 9 year and neck is the most common site (jugular, posterior triangular, supraclavicular). Nodes enlarge over weeks or months. Systemic symptoms are common. Lungs are usually the primary focus.

History of contact: In a symptomatic child, contact with a person with any form of active TB within *last 2 yrs* and in an asymptomatic child, exposure to a smear positive TB patient are considered as a positive contact history.

Contact: Any person who has been exposed to an index case. Two types of contacts.

Household contact: A person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods, during the 3 months before the beginning of current treatment episode.

Close contact: A person who is not in the household, but shared an enclosed space, such as a social gathering place, workplace, or facility, with the index case for extended daytime periods during the 3 months before the beginning of current treatment episode.

Diagnosis of Tuberculosis in children.

All efforts should be made to microbiological confirmation in every presumptive TB case.

Smear microscopy for AFB: Conventional Ziehl-Neelsen stain method and LED based Fluorescent microscopy(LED FM) are done under RNTCP. Even with concentration of specimen by centrifugation and use of fluorescent microscopy, the sensitivity remains less than 15%. So in children and Patients Living with HIV (PLWHIV), smear microscopy is now advised only if NAAT is not readily available.

Culture: Solid culture medium is Lowenstein-Jensen medium. Automated liquid culture medium are BACTEC-460TB, MGIT-960, Bacti Alert, Veratreck, etc. These are available in referral centers, medical colleges and regional TB research labs. Yield from culture varies from 30% to 50%. Liquid medium has an yield 10% more than solid media and reduced time to result from weeks to days. Solid cultures do not help in early diagnosis and are used only in DR TB, but liquid medium is recommended in the evaluation of cases in which routine tests are not helpful.

Nucleic Acid Amplification Test (NAAT) These are molecular diagnostic tests like PCR, Loop Mediated Isothermal Amplification Technology(LAMP), and Cartridge Based Nucleic Acid Amplification Test(CBNAAT). PCR and LAMP are used only in special situations or as a research tool.

Cartridge Based Nucleic Acid Amplification Tests(CBNAAT): Fully automated nucleic acid amplification that integrate sample preparation with real-time PCR amplification. Line Probe Assay and Xpert MTB/RIF are the two CBNAATs endorsed by the WHO. Line Probe Assay detects MTB complex, RIF & INH resistance. It is more accurate than GeneXpert and is mainly used for additional drug sensitivity tests in drug resistant TB cases. GeneXpert is the available Xpert MTB/RIF test under RNTCP. It detects tubercle bacilli and RIF resistance from sputum and also specimen from extra pulmonary sites Currently Xpert MTB/RIF is the first line bacteriological test recommended by RNTCP in suspected DR TB, presumptive TB in children, extra pulmonary TB and (PLWHIV).

Specimen collection:

Two samples are taken for tests other than GeneXpert. Method of collection depends on feasibility and individual case. Methods other than direct sputum collection needs supervision by paediatrician and always there is a risk of hospital acquired infections.

Gastric aspirate (GA): Routinely done as early morning aspiration of gastric content as an inpatient procedure, but now recommended on ambulatory setting also after fasting for 4-6 hours. Transport the sample immediately to the lab and process within 4 hours to prevent the killing action of acid in the gastric aspirate on tubercle bacilli. If delay is expected, neutralize using 1-2 ml of 10 % sodium bicarbonate solution depending on the volume of aspirate.

Induced sputum(IS) Can be done on ambulatory setting. No need of fasting, yield is less than GA.

Bronchial alveolar lavage (BAL): Used to evaluate persistent pneumonia. Yield is less than gastric aspirate & induced sputum, so may be used as an add on test only. Indicated in children with abnormal radiology & negative bacteriology in the setting of suspected DR TB, immunosuppression or HIV infection.

Chest radiography: Highly suggestive X-ray findings are miliary shadows, hilar or mediastinal nodes and fibrocavitory shadows. Consolidation, non homogenous opacities, ground glass appearance are other findings. Hilar node may appear either as sharply demarcated, loculated dense shadow or ill defined shadows with vague borders. Some times normal structures making up the hilum and mediastinum may obscure them. Occasionally it produce splaying of carina or indentation on tracheobronchial tree. A lateral view can pick up upto 12-19% of lesions missed by frontal view. It visualizes hidden areas like left lower lobe (hidden behind heart). Hilar nodes may be detected as Dough nut sign (lobulated densities posterior to bronchus intermedius) in a lateral view. In the absence of bacteriological evidence, after a careful clinical assessment TB can be diagnosed based on X ray findings alone which is termed as clinically diagnosed TB.

Contrast Enhanced CT: Useful to rule out TB in conditions like PUO & persistent pneumonia. Give better anatomical details, better description of nodes & hidden areas. It is recommended by RNTCP as a contributory investigation in selected cases.

Tuberculin skin test: Used as a complementary test along with history, symptoms, signs and radiology. Two preparations of PPD are available - PPD-S and PPD RT23. Two TU PPD RT23 with Tween 80 is equivalent to 5 TU of PPD-S. Current recommendation is to use 2 TU RT23. If it is not available 5 TU is acceptable, but there a risk of false positivity. Cut off for positive result is an induration of 10 mm. In HIV positive patients 5 mm is the cut off. Test is read between 48-72

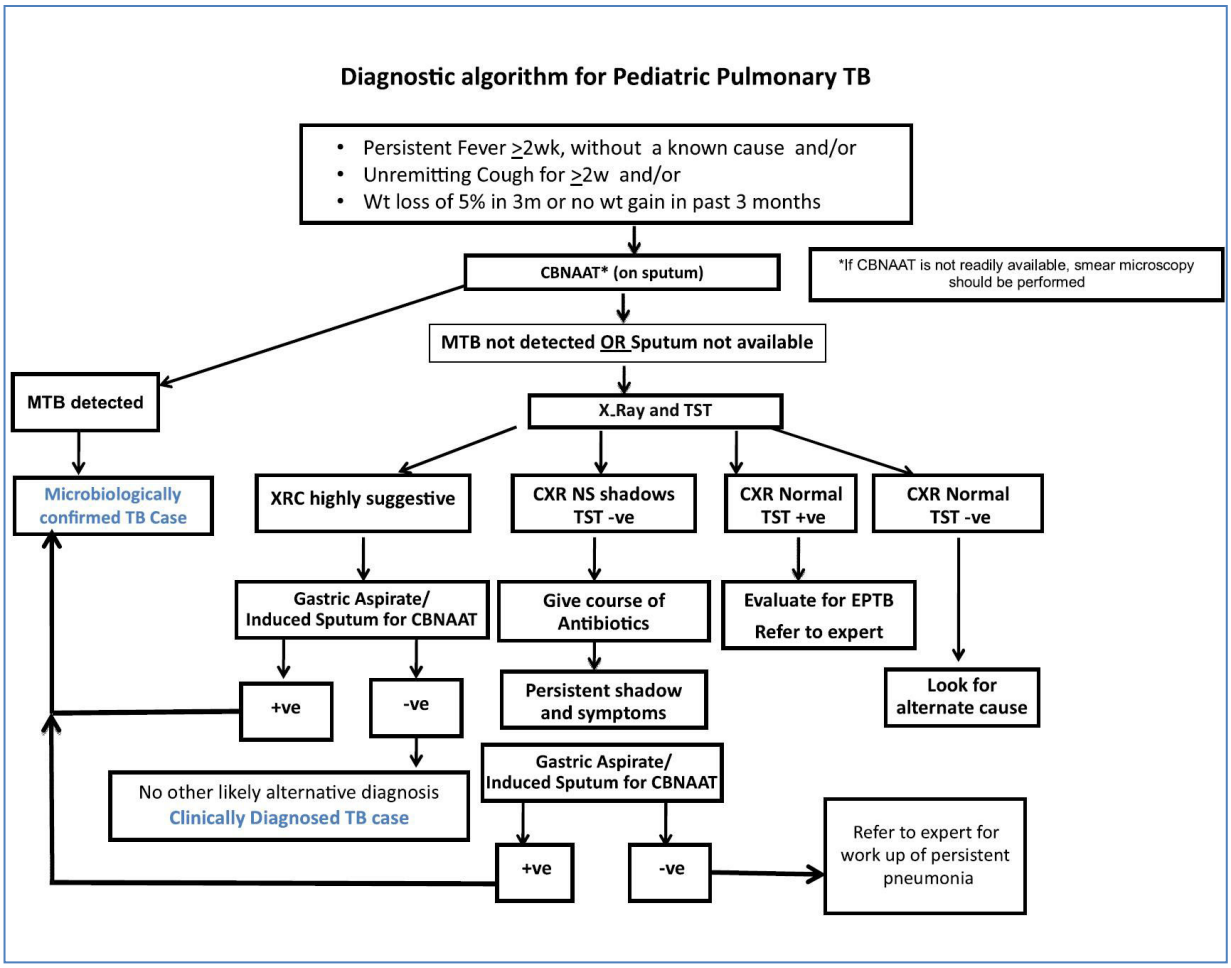
hours. If patient reports after 72 hours it can be read upto 7 days. If still positive it can be taken but if negative test is repeated. If child is reporting after 7 days, test is repeated irrespective of induration. Repeat test is done on opposite forearm. Record the induration in millimeter in the horizontal plane. No induration result is recorded as 0 mm. Erythema alone may be due to subcutaneous injection of PPD in which case it is repeated on opposite side.BCG vaccination has minimal influence on PPD reaction which wanes after 2 to 3 years.Degree of reaction, including necrosis and ulceration, may not necessarily differentiate infection from disease. A negative TST does *not* rule out infection with *M. tuberculosis*. Severe form of TB, HIV infection, severe malnutrition and recent infection are important causes of false negative results.

Interferon Gamma Release Assays (IGRAs): Do not distinguish between active disease and latent TB infection. Used in low prevalence countries to detect latent TB infections. Not recommended in children either by RNTCP or by IAP.

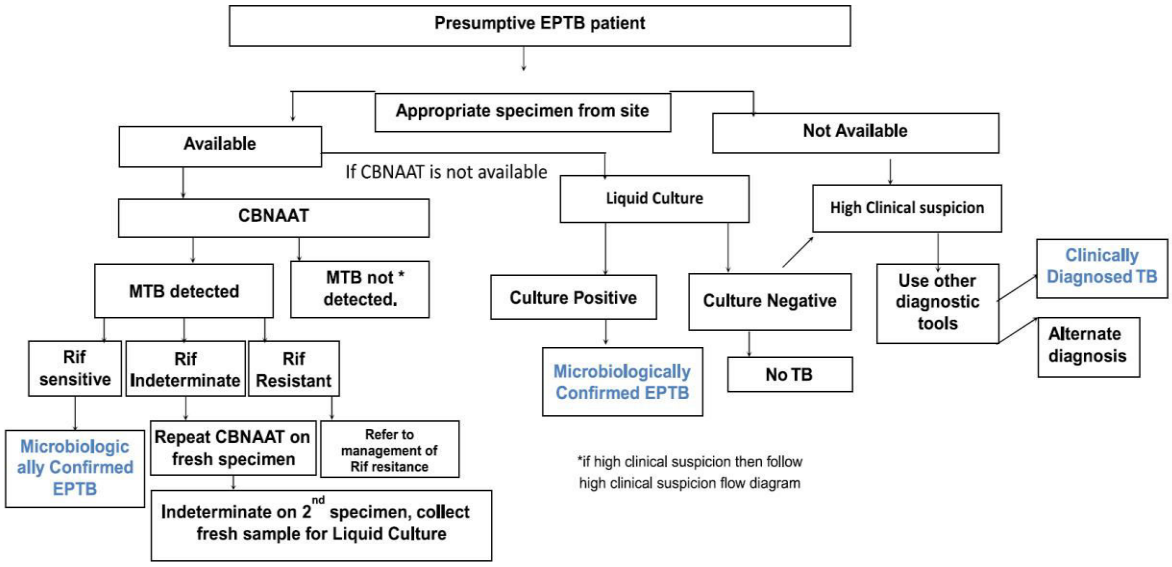
Serologic tests: Not useful in detection of TB in children and these tests are banned in India.

Diagnosis of lymph node TB: Either FNAC or biopsy is needed. Specimen should be sent for cytology (for granuloma) and bacteriological tests like AFB smear, AFB culture and GeneXpert. Now GeneXpert is the preferred test. Lymph node TB should not be treated without a tissue or bacteriologic diagnosis. CXR may show findings in 5-40% of cases and TST positivity in > 70% of cases.

According to RNTCP all diagnosed cases of TB should be offered HIV testing after counselling.



Diagnostic Algorithm for Extra Pulmonary TB



Treatment

Principles of treatment: More drugs are used during the initial stage of high bacillary load and less drugs once bacillary load reduces considerably. Different drugs acts on different metabolically active bacillary populations. INH, Rifampicin, Streptomycin and Ethambutol are active against intra cellular and extra cellular rapidly multiplying organisms. INH and Rifampicin are also effective against extracellular slowly multiplying bacilli, while PZA alone is effective against intracellular slowly multiplying (semi dormant) populations. Some bacilli remain metabolically inactive (dormant) and no drugs acts on them. Dormant forms and few semi dormant populations survive the treatment which can later cause relapses or reactivation. Due to the paucibacillary nature of disease, chances of drug resistance are less in children.

For the purpose of treatment patients are defined into different types based on various criteria.The programme plans standardized regimens for defined patient groups.

Case definition: Microbiologically confirmed and clinically diagnosed. Clinically diagnosed TB is the disease, diagnosed in the absence of a positive bacteriological test.

Based on anatomical sites classified into **Pulmonary (PTB) and Extrapulmonary (EPTB)**

Based on previous treatment

New cases**:** Cases not taken treatment prior or taken treatment for less than 1 month.

Previously treated cases: Classified into **Recurrent TB** (previously successfully treated case again developing bacteriological confirmed TB), **Treatment after failure**(patients declared failure of treatment at the end of treatment) and **Treatment after lost follow up** (cases who lost follow up after 1month of treatment, later presenting with bacteriologically confirmed TB).

Depending on drug resistance

Mono resistant TB: Resistant to any one of the first line drugs
Poly resistant TB: Resistant to more than one first line drugs other than INH and RIF
MDR TB cases: Resistance to INH and RIF with or without resistance to other first line drugs.
XDR cases: MDR TB plus resistance to any fluoroquinolones and at least one of the three second-line injectable drugs (capreomycin, kanamycin or amikacin).

Drug regimen for TB.

RNTCP has been adopting thrice weekly regimen till now.In 2010 WHO recommended daily dosage wherever feasible for new patients throughout the course of therapy, and also to add Ethambutol during intensive & continuation phase in countries with high levels of isoniazid resistance and/or in high HIV-prevalent setting. It also recommended formulations of anti-TB drugs as fixed-dose combinations (FDC). And also, based on recent pharmacokinetic data, WHO 2010 Rapid advice revised dosage of anti tuberculus drugs.

Table 1. Recommended daily doses of first-line anti-TB drugs for children

Drugs	Dose in mg/kg/day	Maximum dose
Isoniazid	10 (7-15)	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	–
Ethambutol	20 (15–25)	
Streptomycin	15 (12-18 mg/kg)	

**The higher end of the range for isoniazid dose applies to younger children; as the children grow older the lower end of the dosing range becomes more appropriate.*

India is a high HIV prevalent country and INH resistance in India is ≈ 5%. Considering these RNTCP is introducing daily regimen for the treatment of drug sensitive TB in PLWHIV and pediatric TB in entire country and all TB patients in 104 selected districts from march 2017 onwards. This will be scaled up across India by the end of 2017 and also extended to the private sector in a phased manner over the next 5 years. It also introduces daily regimens as fixed drug combinations (FDC).

For new cases intensive phase includes 2 months daily doses of INH, Rifampicin, Pyrazinamide and Ethambutol. During 4 months of continuation phase INH, Rifampicin and Ethambutol will be given as daily dosages.

For previously treated cases intensive phase is 3 months and streptomycin is given additionally during the initial 2 months. All the drugs will be provided as FDC. Each dose will be given as observed dose. Mother or a responsible family member will be counseled as an effective DOTs provider.
In severe form of TB like CNS TB, disseminated TB or skeletal TB, the continuation phase is extended 12-24 weeks more. Ethambutol can be safely used in TBM instead of streptomycin.

There is no added advantage of SM over EBM and injection related problems can be avoided, more over SM can be preserved for resistant TB.

Table: 2 Treatment regimen for drug sensitive TB

Type of Patient	Intensive Phase	Continuation Phase
New	**2HRZE**	**4HRE**
Previously Treated	**2HRZES + 1HRZE**	**5HRE**

Prefixed number denotes months.

Ethambutol in children: It is a bacteriostatic drug primarily used as a fourth drug which will lower the risk of treatment failure, by ensuring at least three effective drugs in the intensive phase, if there is INH resistance. Earlier EMB was not given below 6yrs.In 2004 it was included for Cat I patients and later recommended for all pediatric patients. Initially recommended during intensive phase only, now RNTCP recommends during continuation phase also. The concern with EMB was that it might cause optic neuritis and children may not report the early visual symptoms, which could lead to irreversible blindness. The toxicity is dose-related and it is negligible if recommended dosages are adhered to. It was reported that *visual symptoms* of ethambutol toxicity are more sensitive than objective clinical ophthalmological *signs*. So a regular ophthalmologic screening is not necessary, but a baseline test for vision may be performed in all patients.

Fixed Drug Combinations (FDC): This will reduce the pill burden and prescription errors. Pharmacokinetics in children shows that infants and young children have lower peak serum levels than older children or adults. Currently available FDC, which will be withdrawn in a phased manner, has an INH/RIF ratio 1:1. Some commercially available FDC is also having 1:1 ratio (60 mg INH : 60 mg RIF). INH, RIF ratio in the newly recommended FDC is 2:3. It has INH 50, RIF 75 and PZA 150 per pill with a dose per kg ratio of 10:15:30 mg/kg. If commercially available FDC is used, better choose a preparation with 2:3 INH/RIF ratio.

Table: 3 Fixed Drug Dosage & Pediatric weight Bands for Children

Weight category	Number of tablets (dispersible FDCs)		
	Intensive phase		Continuation phase
	HRZ	E	HRE
	50/75/150	100	50/75/100
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25-29 kg	3 + 1A*	3	3 + 1A*
30-39 kg	2 + 2A*	2	2 + 2A*

A = Adult FDC for IP - HRZE=75/150/400/275 ; A*for CP - HRE= 75/150/275

Adjuvant therapy in TB.

Steroids: Interaction between TB bacilli & host immune system can lead paradoxical worsening of illness due to release of pro inflammatory markers like IL 2 and gamma interferon. Corticosteroids may be used for the management of some complicated forms of TB, e.g. tuberculous meningitis, miliary TB , tuberculous pericarditis, endobronchial TB, airway obstruction by TB lymph nodes, and plural effusion with severe distress. Prednisone is used, in a dosage of 2 mg/kg daily (increased to 4 mg/kg daily in most seriously ill children), with a maximum dosage of 60 mg/day for 4 weeks. It is tapered and stopped over 1–2 weeks.

Pyridoxine supplementation: Isoniazid may cause neuropathy in children with severe malnutrition and retro infection on ART. Supplemental pyridoxine (5–10 mg/day) is recommended by the WHO in these cases.

Treatment response and follow-up:

Serious adverse events with the use of recommended treatment regimens are very low. Ideally, each child should be assessed at least 2 weeks after the start of treatment, at the end of the intensive phase, and every 2 months until completion of treatment. Follow-up chest X-rays are not routinely required in children who are improving with treatment. A child who is not responding should be referred for the possible drug-resistant TB, an unusual complication of pulmonary TB, a lung disease from another cause or problems with treatment adherence.

ALT monitoring: Routinely not necessary. Monthly monitoring is indicated in disseminated TB, concurrent or recent hepatic disease, receiving higher dose of INH (>10 mg/kg/day), especially in combination with rifampicin and/or pyrazinamide.

ATT induced hepatitis: Asymptomatic transient elevation of liver enzymes up to five times the normal values is not an indication to stop treatment. Drug induced liver injury (DILI) is diagnosed when any of the following is present. 1) Rise of ALT and/or AST more than 5 times the upper limit of normal in an asymptomatic child, 2) ALT more than 3 times in a symptomatic child, 3) serum bilirubin more than 1.5 mg/dl. *Red flag signs of hepatotoxicity are anorexia, nausea, vomiting, abdominal pain, jaundice, unexplained fatigue, new onset hepatomegaly and bleeding.* In the event of hepatitis, stop ATT. In severely ill patients, give modified ATT **(**non-hepatotoxic regimen with streptomycin, ethambutol and a fluoroquinolone) and in not severely ill patients, stop ATT and do weekly liver enzyme till it reaches twice the normal level. Restart Rifampicin first, next INH and lastly Pyrazinamide. Some Pediatricians do not restart PZA if the patient is tolerating INH and Rifampicin. If Rifampicin is implicated, **2HES** plus **10 HE** is given and if INH is implicated, 6–9 months **RZE** is given. In pyrazinamide toxicity, **9 HR** is recommended.

Prevention of TB:

Contact screening: As per WHO routine assessment of exposed contacts does not require CXR or TST. These tests have limitations and are often not readily available or possible in low- and middle-income settings. In the absence of TST or CXR, clinical assessment alone is sufficient to decide whether the contact is affected or not.

Indications for contact investigation:

Household or close contacts are investigated when the index case has any of the following characteristics.

1. Sputum smear-positive pulmonary TB
2. Proven or suspected MDR-TB or XDR-TB
3. Person living with HIV
4. Children <5 years of age.

Isoniazid preventive therapy (IPT) or Window prophylaxis

Indications of preventive therapy in children are

1. Children less than 6 years of age who had an exposure to an infectious TB case
2. All HIV infected children (regardless of age) who had an exposure to an infectious TB case
3. All TST positive (>=5 mm induration) children who is HIV positive with no exposure to TB
4. All TST positive children who are receiving immunosuppressive therapy *e.g:* nephrotic syndrome, acute leukemia, *etc*.

Isoniazid 10 mg/kg (7-15 mg/kg) with maximum dose 300 mg/day) daily for 6 months is started after excluding active disease Follow-up should be carried out at least every 2 months until treatment is completed. There is no risk of isoniazid resistance developing in children receiving IPT, even if the diagnosis of active TB is missed.

Management of neonate born to mother with tuberculosis.

First line anti tuberculosis drugs except streptomycin, given in pregnancy including during first trimester are safe for the fetus. Miliary and meningeal TB in mother are the high risk factors for congenital TB. Vertical transmission does not occur in maternal pleural effusion or lymph node TB. Mothers who have completed ATT before delivery or have received ATT for at least two weeks duration before delivery are less likely to transmit the disease to the newborn.

Previously INH prophylaxis was recommended in neonate only if the mother is smear positive or has received treatment for <2 wk. But present recommendation is to give INH prophylaxis (10 mg/kg) for 6 months to all the babies born to a mother who was diagnosed to have active TB during pregnancy, after delivery or exposed to any case of active disease after delivery. Rule out congenital TB before starting INH and closely follow up these babies for any TB symptoms.

Usual practice is to give BCG vaccine, 2 weeks after completion of INH prophylaxis (as per WHO). *But for practical purpose RNTCP recommends BCG vaccination at birth even if INH chemoprophylaxis is planned.* Mothers receiving INH and their breast fed babies may be advised pyridoxine supplementation (dosage for neonates is 5 mg/day).

Breast feeding of babies:

All efforts should be sought to continue breast feeding in newborns of mothers having tuberculosis. First line ATT is secreted in milk in small quantity and causes no adverse effect..Isolation of baby is indicated only if mother is having a smear positive MDR TB. Isolation may be considered when mother is sick, non adherent to therapy, received ATT for less than 2 weeks or suspected to have DR TB. Barrier nursing, using face mask and appropriate cough hygiene are advised for all the mothers.

Prophylaxis in contacts of drug-resistant TB: There is no recommend preventive therapy for contacts of DR-TB patients even though a combination of EMB, PZA and Flouroquinolone has been suggested. They should be screened for active disease and followed up every 2-3 months for the first 6 months and then 6-monthly for at least 2 years)

Sources

1.Revised National TB Control Programme Technical and Operational Guidelines for Tuberculosis in India 2016,Central TB division:www.tbcindia.gov.in.

2.Treatment of tuberculosis, Guideline, Fourth edition, Geneva, World Health Organization 2010. WHO/HTM/TB/2009.420.

3. Guidance for national tuberculosis programmes on the management of tuberculosis in children, Second edition, Geneva,World Health Organization 2014.WHO/HTM/TB/2014.03.

4. Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

5. Soumya Swaminathan and Banu Rekha,Pediatric Tuberculosis: Global Overview and Challenges, Clinical Infectious Diseases, 2010; 50(S3):S184–S194.

6. SK Kabra,et al, Recent advances in diagnosis of tuberculosis,Pediatric Infectious Disease 2012; April–June.Volume 4, Number 2; pp. 45–50.

7. Ethambutol efficacy and toxicity:literature review and recommendations for daily and intermittent dosage in children, Geneva, WHO. 2006. WHO/HTM /TB/ 2006.365.

8. B.J.Marais, et al, The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era, INT J TUBERC LUNG DIS 8(4):392–402,2004

9. S.M. Graham, The background and rationale for a new fixed-dose combination for first-line treatment of tuberculosis in children, 2015 The Union, INT J TUBERC LUNG DIS 19(12):S3–S8

11. Ashok kumar,et al, Updated National Guidelines for Pediatric Tuberculosis in India, 2012, Indian pediatrics 301 volume 50;march 16, 2013.

12. Joint Tuberculosis Committee Guidelines 1999. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax,*2000;**55**:210-8.

13. National Strategic Plan for Tuberculosis Elimination 2017–2025. march 2017; Central TB Division, Directorate General of Health Services, Ministry of Health with Family Welfare, Nirman Bhavan, New Delhi – 110 108

Drug Resistant Tuberculosis in Children

Dr. Bindu. G.S
Professor,
Dept. of Pediatrics, GMC Idukki

Anti tuberculous drugs have been used for decades and resistance to them is now widespread. These drug resistant strains pose a serious threat to the efficacy of TB control programme. India is striving hard to implement the End TB strategy from 2016 with the vision to attain a world free of TB. Hence early identification and effective treatment of these cases is of vital importance to achieve our goal of ending global TB epidemic.

According to WHO in 2015, globally there were an estimated 480,000 new cases of MDR TB and an additional 10,000 people with Rifampicin resistant TB. Drug surveillance data shows that the prevalence of MDR / RR TB is 3.9 % in newly diagnosed cases and 21 % in previously treated cases . About 9.5 % of MDR TB cases have additional resistance to second line drugs and they are called Extensively drug resistant cases or XDR TB. Community based surveillance data from India shows a prevalence of 3 % in new cases and 12 – 17 % in retreatment cases. There is very limited data of drug resistant TB in children.

Types of drug resistance

1. Monoresistant TB - TB caused by strains that are resistant to only one of the first line anti TB drugs

2. Polydrug resistant TB – TB caused by strains resistant to multiple first line drugs but not to both INH and Rifampicin together.

3. Multidrug resistant TB - TB caused by bacilli that do not respond to INH and Rifampicin with or without resistance to other first line drugs.

4. Extensively drug resistant TB – This is a form of MDR TB that is resistant to a flouroquinolone and a second line injectable drug

   Resistance is also classified as primary and secondary . Primary resistance refers to infection with mycobacteria which are resistant to drugs from the outset prior to anti TB treatment. Secondary resistance is the resistance acquired during treatment with anti TB drug due to poor adherence or sub optimal treatment.MDR TB in children is usually acquired from adults.

Drugs used in treatment of TB

Group	Drugs
Group 1 – first line oral drugs	INH,Rifampicin,Ethambutol,Pyrazinamide,Rifampicin
Group 2 – Injectable agents	Kanamycin, Amikacin, Capreomycin, Streptomycin
Group 3 - Flouroquinolones	Moxifloxacin, Levofloxacin, Ofloxacin
Group 4 – oral bacteriostatic 2nd line agents	Ethionamide, Protionamide, Cycloserine, PAS
Group 5 – Agents with unclear efficacy	Clofazimine, Linezolid,Amoxicillin/Clavulanate, High dose INH, Clarithromycin

Mechanism of drug resistance

Mycobacteria have natural defences against some drugs and can aquire resistance through genetic mutations. These spontaneous mutations can alter the bacterial proteins which are the targets of drug, making bacteria drug resistant. Initially the mutant bacteria are present in low numbers in the mycobacterial population but with continued administration of the drug, it suppresses the replication of susceptible bacilli but allows the drug resistant mutants to replicate. Later the drug resistant mutants may outnumber the drug susceptible bacilli and become the dominant bacilli.

Genetic sites for drug resistance have been identified and they can be detected by Line probe assay or CBNAAT.

Eg: 1. Rifampicin normally acts by inhibiting mycobacterial transcription by targeting DNA dependant RNA polymerase. Mutation in a well defined region of the gene that encodes the beta subunit of RNA polymerase ' rpo B ' causes resistance to Rifampicin. So detection of rpo B mutation helps in rapid detection of Rifampicin resistance.

2. INH resistance mutations – 2 main types are mutations in inh A and Kat G genes.

Mutation in inhA gene replaces aminoacids in NADPH binding sites of inhA and thus prevents the inhibition of mycolic acid synthesis in mycobacteria.

Mutation in Kat G gene makes the enzyme catalase – peroxidise unable to convert INH to its biologically active form. Hence INH becomes ineffective and bacteria is resistant.

When to suspect drug resistant TB in children?

Presumed case of drug resistant TB (DRTB)is a child with TB who is a

1. Contact of an adult with MDRTB
2. Defaulter – received TB treatment for 1month or more and then discontinued treatment for more than 2 months and found to have active disease
3. Recurrent TB - declared cured after treatment and now has bacteriological or clinical evidence of recurrence

4. Non responder – if the child fails to have bacteriologic conversion to negative status or fails to respond clinically or deteriorates even after 12 weeks of compliant treatment.
5. HIV with TB coinfection

Diagnosis of Drug Resistant TB

Drug resistant TB is a laboratory based diagnosis and is performed in the specimen by either of the following methods:

1) Phenotypic DST (Drug Susceptibility Testing) using solid (LJ)medium/ liquid culture (MGIT)
2) Genotypic Test – by LPA/CBNAAT

Genotypic testing is faster than phenotypic methods, as these are not growth based tests.

DST results by solid L J medium has a turn around time of upto 84 days,liquid culture(MGIT) upto 42 days , LPA upto 72 hours and CBNAAT 2 hours.

Under RNTCP, either CBNAAT or LPA should be used for diagnosis of DRTB. For CBNAAT a single specimen and for LPA two specimens should be sent.

If Rifampicin resistance is confirmed by CBNAAT or LPA

1. Start standardized regimen for MDR TB

2 .Perform Liquid culture DST at base line to Levofloxacin and Kanamycin & if facilities are available DST to Moxifloxacin, ,Capreomycin,Ethambutol,Ethionamide, Linezoid and Pyrazinamide.

3. LPA for detecting INH resistance on sample or culture isolate – reported as Kat G or inhA mutation to decide on use of INH

If resistance is detected to any second line injectable and/or fluoroquinolones,extended DST is performed for PAS and Clofazimine and treatment modified accordingly.

If Rifampicin sensitive is detected by CBNAAT among presumptive DRTB cases

1. Continue treatment with first line drugs
2. Send sample for LPA to detect INH resistance
3. Liquid culture DST for Ethambutol, Pyrazinamide, Kanamycin & Levofloxacin.
4. If resistance is detected to 2nd line injectable and / or fluoroquinolones, perform DST for remaining second line drugs.

Principles of treatment of Drug resistant TB

1. Treatment should be started in consultation with an expert
2. The treatment regime must include at least 4 – 6 bactericidal drugs to which the strain is susceptible.

3. Treatment should be given for at least 12 months after Mycobacterial cultures have become negative.
4. With HIV infection or cavitatory lesions it is extended to 24 months.

Drug regimen

Type of TB	Intensive phase	Continuation phase
MDR TB	Kanamycin,Levofloxacin,Ethionamide, Cycloserine,Pyrazinamid & Ethambutol for 6 – 9 months	Levofloxacin,Ethionamide,cycloserine & Ethambutol for 18 months
XDR TB	Capreomycin,PAS,Moxifloxacin,High dose INH,Clofazimine,linezoli & Amx/Clv for 6 – 12 months	PAS, Moxifloxacin, High dose INH,Clofazimine,Linezolid,amx/Clv for 18 months

The drugs should be taken daily and patient closely monitored for side effects.

Drug dosage

Drug	Daily dose – mg/kg
Kanamycin/ Capreomycin	15 - 20
Lfx/ Mfx	7.5 - 10
Ethionamide	15 - 20
Cycloserine	15 - 20
Ethambutol	25
Pyrazinamide	35
PAS	150

With the available data, the success rate of MDR TB was estimated to be 52 % and that of XDR TB 25 %.

RESPICON KERALA 2017

10th
ANNUAL
STATE
CONFERENCE OF
RESPIRATORY CHAPTER
INDIAN ACADEMY OF PEDIATRICS
KERALA STATE BRANCH

Venue: HOTEL ELITE PALAZZO, ANGAMALY

SUNDAY 7th MAY 2017

Time: 9.00 AM to 4.30 PM

Scientific Programme

8.30 AM : Registration / Break Fast (will be served till 9 am only)

9.00 AM : Inauguration

9.30 -10.40 AM : SESSION I

1. Choosing rational antibiotic in respiratory infection:
   Dr. Sushil K Kabra (Professor of Paediatric Pulmonology and Critical Care, All India Institute of Medical Sciences, Delhi)
2. "Cough is the watch dog of the lung…"- Persistent cough an evaluation:
   Dr. H. Paramesh (Paediatric Pulmonologist, Environmentalist, Bengaluru)
3. Role of Immunological Tests & Allergen Immunotherapy in Respiratory allergies
   Dr. Krishna Mohan (Paediatrician & Paediatric Allergist, Kerala Health Service, Kozhikode)

10.40 AM-10.50 AM : Tea

10.50 AM-12.00 AM : SESSION II (Asthma)

1. Childhood Asthma - Early diagnosis:
   Dr. Sushil K Kabra (Professor of Paediatric Pulmonology and Critical Care, All India Institute of Medical Sciences, Delhi)
2. Long term management of Asthma:
   Dr. H. Paramesh (Paediatric Pulmonologist, Environmentalist, Bengaluru)
3. Management of Persistent Difficult Asthma:
   Dr. Gowri Shankar (Paediatric Pulmonologist, Chennai)
4. Acute Severe Asthma:
   Dr. H. Paramesh (Paediatric Pulmonologist, Environmentalist, Bengaluru)
5. Drug delivery system in Asthma-practical tips:
   Dr. T.U. Sukumaran (HOD, Paediatrics, Pushpagiri Medical College, Thiruvalla)
6. What is new in Asthma:
   Dr. Jayakumar C (HOD, Paediatrics, Amritha Institute of Medical Science, Kochi)

12.00 N – 1.25 PM : SESSION III (Rapid Fire)

1. Controversies in Diagnosis of Childhood Tuberculosis:
   Dr.Gowri Shankar (Paediatric Pulmonologist, Chennai)
2. Child with Acute Strider-Management:
   Dr. Jayakumar C (HOD, Paediatrics, Amritha Institute Of Medical Science)
3. Bronchiolitis - Management:
   Dr. H. Paramesh (Paediatric Pulmonologist, Environmentalist, Bengaluru)
4. Allergic Rhinitis - Management:
   Dr. Ramesh Kumar (Consultant Paediatrician, N.S.S. Mission Hospital, Panthalam)
5. Latest guidelines for T.B. Management & MDR Tuberculosis:
   Dr. Gowri Shankar (Paediatric Pulmonologist, Chennai)
6. Nocturnal Cough:
   Dr. T.U. Sukumaran (HOD, Paediatrics Pushpagiri Medical College)
7. "Block Paediatric Pneumonia"- Pneumococcal & Influenza Vaccine
   Dr. Jayakumar C (HOD, Paediatrics, Amritha Institute of Medical Science)

1.15 PM-2.00 PM : LUNCH

2.00 PM – 3.20 PM : SESSION IV

1. "He is always sick with recurrent chest infection…" - Case discussion
   Panellist: Dr. Sushil K Kabra, Dr.T.U.Sukumaran, Dr.Gowri Shankar, Dr.H.Paramesh
2. Interventional Pulmonology - an overview
   Dr. Arun Nair (Chief interventional pulmonologist, Amritha Institute of Medical Science, Kochi)
3. Interpretation of Paediatric Chest X-Rays:
   Dr. Ananda Kesavan (Professor, Dept. of Paediatrics, Medical College Thrissur)

3.20 – 4.30 PM : SESSION V

1. Congenital Respiratory Anomaly - Diagnosis and management:
   Dr. Naveen Viswanath (Professor, Dept. of Paediatric Surgery, Amritha Institute of Medical Science, Kochi)
2. Bronchectasis - Clinical approach and management:
   Dr. Susil K Kabra (Professor of Paediatric Pulmonology and Critical Care All India Institute Of Medical Sciences, Delhi)
3. Recurrent and Persistent Pneumonia - Clinical approach and Management:
   Dr. Gowri Shankar (Paediatric Pulmonologist, Chennai)

4.30 PM : Valedictory Function

Organising Committee

Scientific	: Dr. Rafeeq A.K. Dr. Bipin Jose
Finance	: Dr. M.R. Nair
Souvenir	: Dr. Ashok Kumar P.
Registration	: Dr. Thomas Thachil
Food	: Dr. M.A. Thomas
Transportation	: Dr. V. M. Kartha
Stall	: Dr. Sunny Paul
Venue	: Dr. Muraleedharan
General Convener	: Dr. Shimmy Poulose

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Dear Doctor,

I.A.P. Madhya Kerala has immense pleasure in inviting you to the "RESPICON KERALA 2017", the 10th Annual State Conference of Respiratory Chapter, Indian Academy of Pediatrics, Kerala State Branch, on Sunday, 7th May, 2017, at Hotel Elite Palazzo, Angamaly. We are planning an academic fiesta you definitely not want to miss. Experts from inside and outside the state will deliberate on various current developments in the field of pediatric practice, especially related to respiratory medicine. We promise you a fruitful experience and opportunity to interact with stalwarts in this field .

We are expecting CME credit hours by TC medical council.

Looking forward to interact with you at RESPICON KERALA 2017.

Dr. M. A. Sajith
Chairman
Organising Committee

Dr. K.J. George
Secretary
Organising Committee

Dr. V. Balagopal
Treasurer
Organising Committe

Dr. M.N. Venkiteswaran
President, IAP Kerala State

Dr. Riaz I
Secretary, IAP Kerala State

Dr. M.E. Sugathan
President
Respiratory Chapter
IAP Kerala State

Dr. Krishnamohan
Secretary
Respiratory Chapter
IAP Kerala State

Registration Tariff

	Upto 30.04.2017	01.05.2017 onwards & spot
PG Students	1000	1500
IAP Member	1500	2000
Non IAP Member	2000	2500

PG Students should produce certificate from HOD'S

Registration form along with Demand Draft / Cheque drawn in favour of IAP MADHYA KERALA BRANCH payable at ALUVA, (please add Rs. 50/- for out station cheques) should be sent to:

Dr. K.J. George
Org. Secretary
Kaithayil House, Opp. Municipal Office,
Pump Junction, Aluva - 683101
Ph: 0484- 2623283 (R), 2623890 (O), 9895188747
Email: george.kaithayil@yahoo.co.in

Helpline: **Dr. Shimmy Poulose - 9895272071**


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WORLD TB DAY MARCH 24