Consensus Statement on Childhood Tuberculosis

WORKING GROUP ON TUBERCULOSIS, INDIAN ACADEMY OF PEDIATRICS (IAP)

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Justification: Revised National Tuberculosis Control Program (RNTCP) has focused on adults with smear positivity – a tool not so well used in children with tuberculosis. There is a need to redefine standardization of diagnosis and management protocols for childhood tuberculosis.

Process: Indian Academy of Pediatrics constituted a Working Group to develop consensus statement on childhood tuberculosis (TB). Members of the Group were given individual responsibilities to review the existing literature on different aspects of the childhood TB. The group deliberated and developed a consensus which was circulated to all the members for review. Efforts were made to ensure that the recommendations are standardized.

Objectives: To produce recommendations and standard protocols for reasonably accurate diagnosis and rational treatment of tuberculosis in children.

Recommendations: Fever and / or cough > 2 weeks with loss of weight and recent contact with infectious case should arouse suspicion of TB. Chest *X*-ray and trial with broad-spectrum antibiotic for 7-10 days is justified. In case of clinical and radiological non-response, Mantoux test and sputum or gastric aspirate for AFB is recommended. If AFB is positive, diagnosis is confirmed. If AFB is negative but chest *X*-ray is suggestive and Mantoux test is positive, it is a probable case and if these tests are negative, alternate diagnosis must be sought and referral made to an expert. Ideally it is recommended to use 1TU of PPD for Mantoux test but 2 or 5 TU may be acceptable (but less preferred). Cut-off point of 10 mms for natural infection may be used for test done with 1, 2 or 5 TU. There is no linear relation of reaction to tuberculin strength and so no more than 5 TU should be used. BCG test is not recommended. Diagnosis must not be made without an attempt to look for AFB in gastric aspirate or sputum, as it is possible to get AFB even in primary complex. Elisa and PCR tests for TB are not recommended. There is no place for trial of anti-tubercular therapy.

Lymphnode enlargement >2 cm with or without typical findings suggestive of TB and failure of antibiotic response demands FNAC for histopathology and bacteriology. Clinical suspicion of tubercular meningitis (TBM) should be confirmed by CSF examination and CT scan though none of these investigations are confirmatory and hence should not be considered in isolation. CSF tests for TB antibody and PCR are not recommended for routine use. Diagnosis of abdominal TB is made on circumstantial evidence and there are no standard guidelines.

For treatment, disease is divided into three categories. The Category I and III are recommended for different types of new cases i.e. those who have received treatment for not more than 4 weeks. Category III includes primary pulmonary complex, one site peripheral lymphadenitis and pleural effusion, while all other forms of TB are included in Category I, that corresponds to smear positive TB in adults. This is because AFB is often found in many Category I disease in children. Category II includes defaulters, relapses and failure cases irrespective of the site of disease.

Standard protocol is followed for each of these categories. Intermittent thrice weekly therapy with higher dose has been found to be equally effective as daily therapy and so is recommended in DOTS – Direct Observed Therapy Short term. Compliance of treatment must be ensured. Repeat chest *X*-ray is ideal at the end of therapy. Liver function tests are not routinely recommended. Recommendations are also made for special situations such as MDRTB, TB and HIV and neonate born to mother suffering from TB.

Key words: *Children, Diagnosis, Guildelines, Indian, Treatment, Tuberculosis.*

Tuberculosis is a single major infectious disease causing significant morbidity and mortality amongst all humans, including children. Three sets of guidelines related to the management of childhood tuberculosis have been produced by the various consensus groups of the IAP since 1997(1-3), with the last one coming out in 2004(3). Cases were classified into three cate-

gories, as per WHO and Revised National Tuberculosis Control Program (RNTCP) guidelines. These guidelines also addressed the issue of intermittent therapy and direct observation of therapy.

OBJECTIVES

In consonance with the decision of Indian Academy of Pediatrics to standardize and update the protocols for diagnosis and treatment of childhood tuberculosis, a meeting of IAP Working Group was held in Mumbai on 26th and 27th April 2008. Members of the Group were given individual responsibilities to review the existing literature on different aspects of the childhood TB and present the review to the Group. The Group deliberated in the light of presentations made by the members, based on literature reviewed, and developed a consensus for the topics covered.

The deliberations were than written as a draft document and circulated to all the members for review. The Group also informally interacted with the different national and international bodies that were also working on developing guidelines for TB management to incorporate the latest changes that were in the offing. Efforts were made to ensure that the recommendations are standardized for reasonably accurate diagnosis and rational treatment of childhood TB.

RECOMMENDATIONS

1. Pulmonary Tuberculosis – When to Suspect?

Fever and/or cough of recent onset lasting for >2 weeks should arouse suspicion of tuberculosis. It is important to document fever and not depend merely on impression. Fever can be of any type and the often-described evening rise of temperature is neither specific to this etiology nor commonly present. Cough can be dry or moist and may be severe. Cough persisting beyond 2 weeks, particularly as an only symptom in an otherwise healthy child can be due to viral infection and is often not due to TB. Such children, therefore, do not always warrant investigations. Recurrent symptoms with normal intervening period are less likely to be due to tuberculosis. Recent loss of appetite may be relevant but unexplained recent loss of weight can be an important pointer to the suspicion of tuberculosis. A static weight/not growing well are not significant pointers to this disease. History of contact with an infectious TB patient (smear positive) should always prompt detailed examination for likelihood of the disease. However, in a symptomatic child, contact with a person with any form of active tuberculosis within last two years may be significant.

Diagnosis is also more likely in presence of risk factors such as recent history of measles or whooping cough and immuno-compromised state including steroid therapy. Persistent lower respiratory infection not responding to antibiotic therapy may point to a probable diagnosis of tuberculosis. Significant superficial lymphadenopathy must be specifically looked for, as it may often coexist.

For a clinically suspected case, further investigations are necessary. Diagnosis of tuberculosis should never be made only on clinical features. The above-mentioned features in isolation or in combination should only make you suspect TB. Therapeutic trial with anti-TB drugs is, therefore, not recommended and instead, every attempt must be made to prove the diagnosis.

***Figure* 1** depicts the diagnostic algorithm for pulmonary tuberculosis in a child.

2. Tuberculin Test

The standard tuberculin test recommended for use is the Mantoux's test. Commercially available tuberculin in the country are 1, 2 and 5 Tuberculin Unit (TU) PPD (RT23 equivalent). It is important to raise a wheal of about 6 mm after the intra-dermal injection and the test is read 48-72 hours after an injection. Ballpoint or palpatory methods are used to read the induration.

The width of reaction (induration) in the horizontal plane is noted for interpretation (see *annexure* for details). Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more. This cutoff was recommended using a 1 TU PPD RT23.

Currently the laboratories more often use 5 TU PPD (RT23 equivalent), or sometimes even some other higher strengths or types of PPD are used. The standard cut off of 10 mm can actually not be justified for any higher strength of PPD used. The

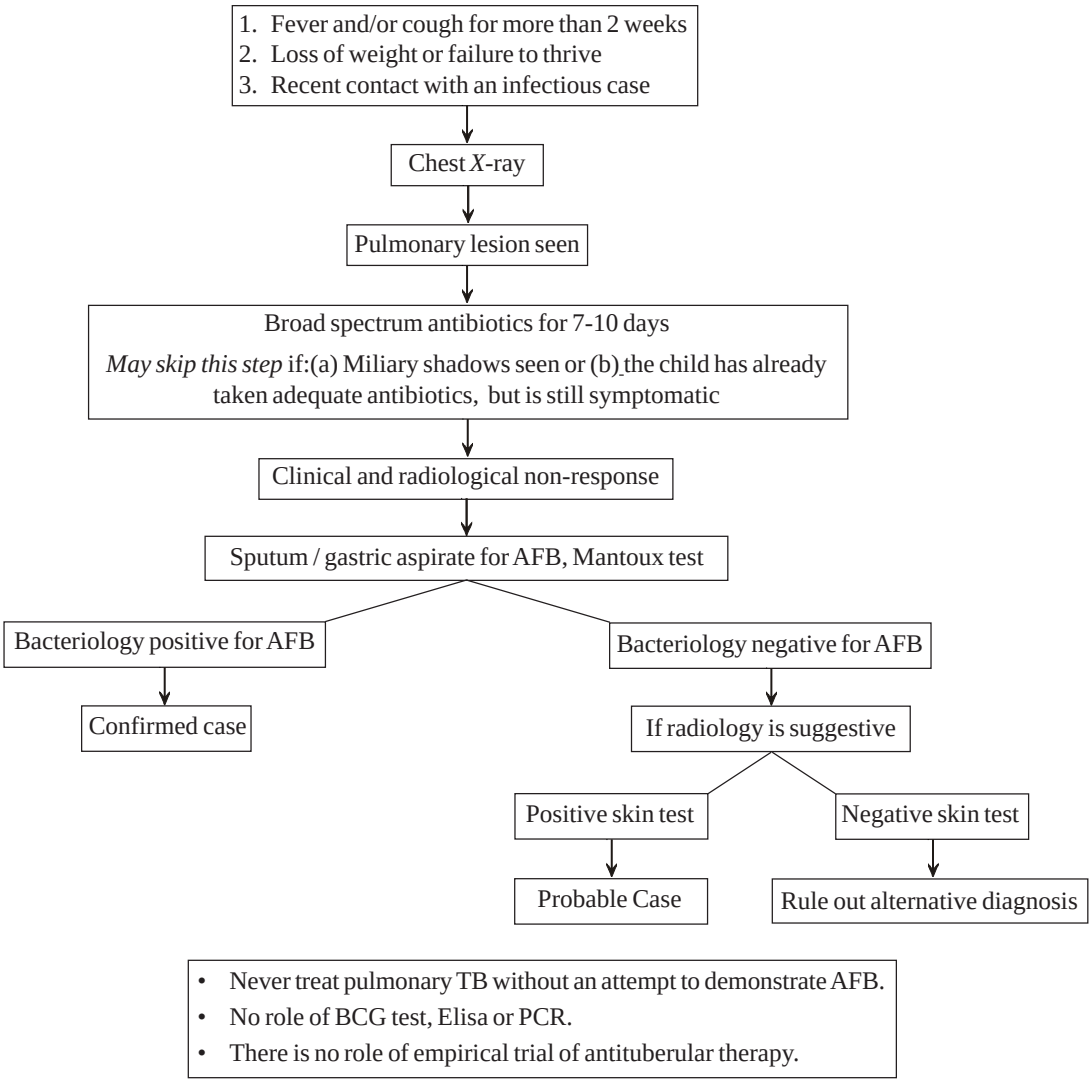

FIG. 1 *Algorithm for diagnosis of tuberculosis in children.*

reaction evoked is not only dependent on the amount of antigen given but also does not have a linear relationship with the increasing strengths. Therefore, the current practice may actually lead to an increase in false positive reactions using the 10mm cutoff with the higher strength of PPD. The Group recommends that the 10mm cutoff may be continued to use for strengths of PPD only up to 5TU. Efforts should be made to use only 1 TU PPD to decrease the false positives(4) and in no case strength higher than 5 TU should be used. Degree of reaction, including necrosis and ulceration, may not necessarily differentiate infected from diseased. Prior BCG vaccine has minimal influence on PPD reaction(5,6).

If the patient returns for reading beyond 72 hours but by 7th day, a positive test can still be read. A repeat test may be needed, if there is no induration and the suspect presents beyond the stipulated time for reading. Repeat tuberculin test when required should preferably be done on the other arm. The reading of the same should be interpreted as in any other individual.

3. BCG Test

BCG test is not recommended for diagnosis of tuberculosis(7).

4. Chest Radiograph

Chest radiograph merely localizes the site of

pathology and not etiology. There are no pathognomonic radiological signs of tuberculosis. In relevant clinical setting, certain radiological lesions may strongly suggest tuberculosis and they include miliary, hilar or paratracheal lymphadenopathy with or without parenchymal involvement and fibrocaceous cavitatory lesions. Rarely chest *X*-ray may be normal, such cases should be referred to an appropriate center for further detailed investigations if the clinical suspicion is high.

In clinical practice, non-resolving chest shadows despite adequate antibiotic therapy in a symptomatic child raises the possibility of tuberculosis. It is worth mentioning that all persistent radiological lesions are not necessarily due to TB. Asymptomatic patients may have persistent shadows due to parenchymal scarring, pleural thickening, and healed fibro-atelectatic changes. On the other hand, a child with bronchiectasis or an interstitial lung disease may have presence of non-resolving shadows with persistent symptoms.

Ultrasonography of chest is helpful to assess pleural fluid collection; although decubitus chest *X*–ray film may also reveal similar information. CT scan is rarely necessary and is not cost and radiation effective. Chest CT scan, however, may offer an opportunity for CT guided biopsy for tissue diagnosis.

5. Bacteriology

Demonstration of AFB from any body fluid or tissue is the gold standard of diagnosis of tuberculosis. Such a proof is often lacking in childhood tuberculosis because of difficulty in collection of sputum and due to paucibacillary primary disease in children. However, studies do report that the yield of a positive test in advanced cases may be as high as in adults.

Few studies have reported as high as 33% bacteriological positivity even in primary disease such as hilar adenopathy(8,9). Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected tuberculosis.

Early morning gastric aspirate is a preferred specimen for most young children with suspected TB for detecting AFB or isolating *M. tuberculosis*. The child is kept fasting for about 6 hours (at night) and an appropriate size intra-gastric tube is passed in the morning. Initially the aspirate is drawn from the stomach and then a further washing with 15-30 mL saline is taken. The contents so recovered are then immediately transferred to the laboratory. This specimen can also be collected as an ambulatory procedure after 4-6 hours fasting(10). Sputum collection is possible in older children with extensive and cavitatory disease, particularly if the patient has a wet cough. Induction of sputum by 3% nebulized hypertonic saline can be tried in older children (after the age of 4 months). The patient is pretreated with nebulized bronchodilators prior to induction. Following saline nebulisation, chest physiotherapy is done to loosen up the secretion and the samples are collected from the throat or nasopharynx(11). Whatever method one chooses to use, one needs to collect at least two, preferably three, samples.

Where the facilities are limited, these tests may be prioritized and atleast be done in all children with wet cough or children who have definite parenchymal lesion on chest skiagram. Experience with bronchoscopy and bronchoalveolar lavage (BAL) as a diagnostic tool is limited but it is often needed when evaluating persistent pneumonia. TB remains an important cause of persistent pneumonia in our country(9).

Ziehl-Neelsen stain can reveal AFB only if sample contains >10,000 bacilli per mL. Different culture methods are used, such as LJ medium, Radiometric (Bactec) and Non-radiometric (MGIT) can be used for confirming diagnosis in paucibacillary state. The newer methods are capable of giving faster results and may be used if available. Mycobacterial culture assumes special significance in case of suspected drug resistance.

6. Serodiagnostic Tests

As mycobacterial antigens overlap in different stages of infection and disease, there are no specific antigens that can confirm natural infection or active disease. Besides, antigen tests vary widely and are often negative in paucibacillary disease. Antibody tests share similar problems for interpretation and in addition cannot differentiate natural infection from BCG vaccine induced infection and active disease from old healed disease.

Thus both antigen and antibody TB ELISA tests are poorly sensitive and specific and are not recommended for diagnosis of tuberculosis(12).

7. Interferon Gamma Release Assays (IGRAs)

A newer generation of tests which measure the production of interferon gamma by the peripheral mononuclear cells have been developed to identify the patients with TB disease or latent infection. These use two antigens, early secretion antigen target (ESAT 6) and culture filtrate protein 10 (CFP 10), which are specifically present only in *Mycobacterium tuberculosis* and not in other mycobateria or the BCG vaccine strain. These tests though have a principle similar to skin test but do away with the need for a repeat visit by the patient for reading purposes(13). Quantiferon Gold and T spot are two of the commercially available IGRAs. These are being used in place of the skin test in low prevalence countries to detect latent TB infection. However, these expensive tests do not differentiate the TB infection from disease. Its exact utility in high burden situation is still not clear(14,15).

8. PCR Test

Nucleic acid amplification tests using polymerase chain reaction (PCR) cannot differentiate living from dead bacilli and so continues to be positive even after successful treatment. PCR is positive in 95% to 100 % of culture positive cases but only in 50% to 60% of culture negative cases. It may be false positive in 1% to 30% of cases. Thus, no decisions can be made only on the basis of PCR tests and hence these tests are not recommended in clinical practice(16).

9. Extra-pulmonary Tuberculosis

TB lymphadenitis

Clinical correlate of diagnosis includes progressive enlargement of lymph node for more than 2 weeks, firm, minimally tender or non-tender, fluctuating, further may get matted and develop chronic sinus formation.

Mantoux test is positive in a significant proportion. Fine needle aspiration cytology (FNAC) is usually adequate for accurate diagnosis and it correlates well with biopsy in >90% of cases(17,18). Histopathology, typically shows necrosis and epitheloid granuloma. It is important to look for AFB in FNAC specimen and it may be positive in 20-70% of patients. When FNAC is inconclusive, biopsy is necessary for confirmation of diagnosis. In children lymphadenopathy is common due to recurrent tonsillitis and upper respiratory tract infections. Reactive lymphadenitis may clinically mimic tuberculosis but do not warrant anti-TB drugs. Hence, anti-TB drugs should not be given unless the diagnosis of TB is confirmed by FNAC or histopathology. ***Figure* 2** depicts a diagnostic algorithm for tubercular lymphadenitis.

Pleural effusion

If chest *X*-ray is suggestive of pleural effusion, pleural aspiration should be performed for biochemical, cytological and smear examination by Ziehl-Neelsen stain to confirm the diagnosis. Typically, a tubercular effusion fluid is straw colored (pus, if aspirated, is very rarely due to TB etiology) has large numbers of cells (in hundreds; predominantly mononuclear), with high proteins (>3g/dL). ADA levels over 60 IU/L may be suggestive of tubercular pleural effusion but are not diagnostic of TB(19,20). Pleural biopsy may be performed, where available, particularly when the fluid aspirate findings are inconclusive.

Tubercular meningitis

Children with tubercular meningitis (TBM) present with a longer (>1 week) duration of fever, with vague CNS symptoms such as behavior changes, irritability, drowsiness, headache, vomiting and seizures. Physical examination typically reveals global encephalopathy with focal deficits, hydrocephalus and movement disorder. Risk factors for TBM include age <5 years, contact with an adult suffering from tuberculosis, PEM grade III and IV, and HIV infection.

Typically CSF is clear, usually does not show very high cell count (under 500 cells/cumm) with lymphocytosis. Biochemical investigations reveal increased proteins and mild reduction in glucose. The typical CSF picture may, however, not always be seen. Furthermore, the typical CSF picture described above can also be mimicked by partially treated pyogenic meningitis. In such a situation, CSF can be

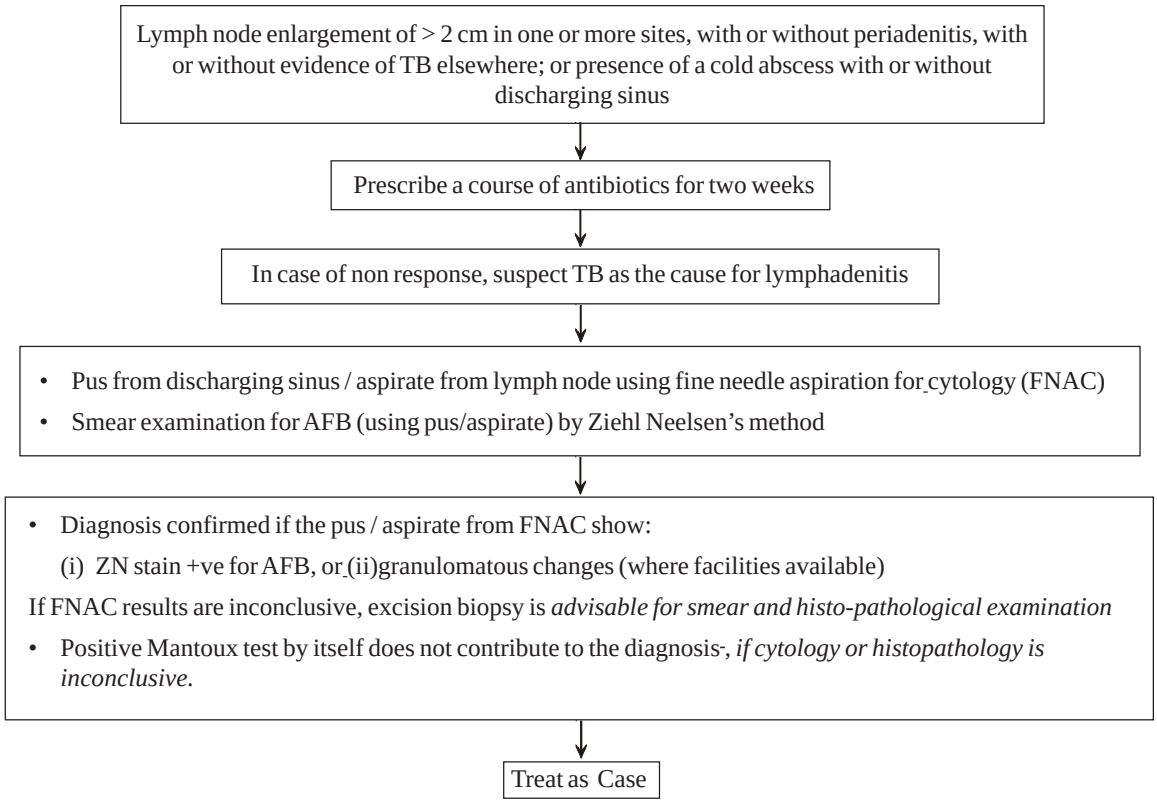

FIG. 2 *Diagnostic algorithm for tubercular lymphadenitis.*

repeated after 48-72 hours of treatment with a fresh set of broad spectrum potent antibiotics to evaluate change in clinical status as well as in CSF. During this time, efforts are made to establish the diagnosis by collecting more evidence using PPD, chest skiagrams, and bacteriological diagnosis from appropriate samples including CSF. Many a time concomitant TB lesions elsewhere in the body (say, pulmonary) co-exist and can clinch the diagnosis. Mycobacterial culture from CSF should also be attempted but CSF culture has poor sensitivity (16%) though specificity is high (90%).

Neuroimaging is an important diagnostic modality. It may reveal one or more of the following findings: basal meningeal enhancement; hydrocephalus with or without peri-ventricular ooze; tuberculoma(s); or infarcts may be seen in different areas, especially in basal ganglia.

Normal CT scan does not rule out TBM and in case of strong clinical suspicion of diagnosis, a repeat follow-up CT scan after few days may show newly developing lesions. CSF abnormalities in TBM may take variable time up to few months to return to normal. Besides routine CSF examination. CSF ADA is high in TBM. Various studies have a cut-off point between 7 and 11.3 IU/L for diagnosis. This may offer supportive evidence in favor of TBM but should not be taken in isolation(21). CSF antigen and PCR tests are neither routinely available nor reproducible. They are, therefore, not recommended. CSF antibody tests have poor sensitivity and specificity and hence are not useful.

Tuberculoma

Often seen in older children, it may present as a focal seizure in supra-tentorial cortical lesion or with symptoms and signs of raised intracranial tension with multiple localizing signs and hydrocephalus in posterior fossa lesion. It may sometimes also be seen as a part of TB meningitis.

Differentiation from other ring lesions, especially neurocysticercosis (NCC) is difficult in

cortical lesion. A ring enhancing lesion is not pathognomonic of tuberculoma. A larger lesion >20 mm, disc lesion or ring lesion with thicker rim with central nodule favors tuberculoma; while multiple, smaller, thin rim with epicentric nodule favor NCC. MR spectroscopy may help in diagnosis of tuberculoma as it shows lipid peak.

Abdominal tuberculosis

It may present as localized disease such as mesenteric lymphadenopathy, intestinal disease, peritoneal involvement or systemic disseminated disease presenting as hepatosplenomegaly. Large matted lymph node mass may be clinically evident and ultrasound guided biopsy may help in confirming the diagnosis.

There are no standard guidelines for sonography diagnosis of abdominal tuberculosis. However, corroborative evidence includes: echogenic thickened mesentery with lymph nodes >15mm in size; dilated and matted bowel loops; thickened omentum, and ascites(22). Barium follow-through examination may be suggestive of intestinal disease but is not confirmatory. Exudative peritoneal disease presents as ascites that is often clinically evident. The ascetic tap should always be done in such situations and the fluid tapped is an exudate, typically showing lymphocytic predominant cellular response with high proteins (>3g/dL).

10. Treatment of Tuberculosis

Basis of pharmacotherapy

Choice of anti-TB drugs is based on several determinants such as bacillary and metabolic subpopulation, bacillary load, drug resistant strains, lag period of bacterial population, pharmacokinetic profile and pathological factors. There are different types of bacillary population in every case of tuberculosis and hence drugs are selected in a combination to attack entire (extra-cellular and intra-cellular, slow and rapidly growing) bacillary population for successful chemotherapy. Isoniazid (INH) and rifampicin (RMP) kill the fast growing bacilli, pyrazinamide (PZA) acts against intracellular organisms in acidic medium while extracellular slow growing bacilli are best killed by RMP. Thus every case of tuberculosis must be treated at least with these three drugs. The chances of naturally occurring mutants are higher if the bacillary load is more and therefore, such cases need more drugs in intensive therapy, say as in smear positive cases.

As dividing time of TB bacilli is about 21 hours, all the drugs are administered in such a way that they achieve peak concentration all at one time so as to hit bacilli hard. The drug concentration is poor in caseum and sequestrated tissue, so these should be removed surgically wherever feasible.

Mycobacterium tuberculosis when exposed to certain concentration of most currently used anti-TB drugs *in vitro* shows an inhibition of growth for 1 to several days. This suggests that the drugs can be effective even when used on an intermittent basis as a continuous high serum level of these drugs is not needed. This forms the basis of intermittent therapy. While RCTs in children using thrice weekly regime are awaited, RCTs from adults as well as observational studies including programmatic data in all age groups have shown that intermittent thrice a week therapy with higher dose is as effective as daily therapy with conventional dose and is an effective alternative(23). However, intermittent therapy is not safe when self-administered, as there is no margin for any error in taking medications. The directly observed therapy under DOTS takes care of the adherence issues and therefore uses thrice a week intermittent therapy.

Anti-tubercular therapy

The appropriate management of tuberculosis requires assessment of the patient correctly with respect to the site of disease, bacteriological status, treatment type of patient and the severity of disease. These definitions are detailed in ***Table* I.** After appropriately defining the disease, the patient is then categorized to receive appropriate anti- TB therapy (***Table* II**). The drug dosages are given in ***Table* III**.

The Group agreed to include all children with extensive pulmonary lesions (any thing beyond the primary pulmonary complex) under Category I because of the evidence and experience that a significant proportion of these turn out to be smear positive when diligent efforts are made. It is only

TABLE I DEFINITIONS FOR CATEGORIZING FOR TREATMENT OF PEDIATRIC TUBERCULOSIS

A. Case definitions for site

Pulmonary: Refers to disease involving lung parenchyma. Extra Pulmonary: Refers to disease involving sites other than lung parenchyma Both pulmonary and Extra pulmonary constitutes Pulmonary Extra- Pulmonary involving several sites is defined by most severe site.

B. Case definitions for severity

Pulmonary TB

Severe Pulmonary TB	***Less severe Pulmonary TB***
All other except PPC e.g.	• Primary Pulmonary complex (PPC)
o Progressive primary disease	
o Fibro-cavitatory disease	
o Miliary	

Extra-Pulmonary TB

Severe Extra-Pulmonary TB	***Less severe extra-pulmonary TB***
Meningitis Spinal or Bone or Peripheral joints	• Single Lymph node site
Bilateral or extensive pleural effusion	• Unilateral pleural effusion
Intestinal	
Genitourinary	
Peritonitis	
Pericarditis	
Adrenal glands	

C. Case definition for bacteriology

Smear positive- Sputum / Gastric aspirate /BAL/any other tissue or fluid

Any sample positive for acid fast bacilli on staining

Smear Negative- None positive

D. Type of patient as per history of previous ATT

New Case: A patient who has had no previous ATT or had it for less than 4 weeks.

Relapse: Patient declared cured/completed therapy in past and has evidence of recurrence.

Treatment Failure: Patient who fails to respond/deteriorates after 12 weeks of compliant intensive phase.

Treatment after default: A patient who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months and has active disease.

milder forms of the disease, also more likely to be paucibacillary, such as primary complex (mediastinal or hilar lymphadenitis with or without a parenchymal lesion, Single site peripheral lymphadenitis and unilateral pleural effusion that are treated as Category III(24).

In case of delayed response to assigned therapy, intensive phase may be prolonged by one more month in Category I and II. Similarly, continuation phase may have to be prolonged by 3 months for TB meningitis, miliary and spinal TB. There are studies to suggest that 6 months therapy may be adequate in these situations as well . Yet, the group felt that the prolongation of the continuation phase is justified in these situations as (*a*) the lesions may take longer to sterilize in such pathology, and (*b*) due to the risk of serious morbidity associated with relapse.

Category II therapy utilizes all the first line drugs as it is used to treat relapsers, treatment defaulters and treatment failures who are more likely to have

TABLE II TREATMENT CATEGORIES AND REGIMENS FOR CHILDHOOD TUBERCULOSIS

Category of treatment	Type of patients	TB treatment regimens	
		Intensive phase	Continuation phase
Category I	• New smear-positive pulmonary Tuberculosis (PTB) • New smear-negative severe forms of PTB • New severe forms* of extra-pulmonary TB	HRZE (2 mo)	HR (4 mo)
Category II	• Smear-positive relapse, treatment failure or treatment after default • Cases who are smear negative but considered to have relapse, treatment failure or defaulted	SHRZE (2mo) +HRZE (1 mo)	HRE (5 mo)
Category III	• Less severe forms of pulmonary TB* • Less severe forms of extra-pulmonary TB*	HRZ (2 mo)	HR (4 mo)

*H=INH, R= Rifampicin, Z= Pyrazinamide, E= Ethambutol, S= Streptomycin; *Refer Table 1 for details of severity*

In patients with TB meningitis on Category I treatment, the four drugs used during the intensive phase can either be HRZE or HRZS. The present evidence suggests that ethambutol can be used in children; Continuation phase of treatment in TB meningitis, miliary and spinal TB with neurological complications should be given for 6 - 7 months, extending the total duration of treatment to 8 - 9 months. Under Revised National Tuberculosis Program (RNTCP) all patients shall be covered under directly observed intermittent (thrice weekly) therapy. While the supervised therapy is considered the most optimal treatment, this very same combination of drugs can also be used on a daily basis, for a similar duration, in case the treatment is being given unsupervised. It is important to ensure completion of treatment in every case put on treatment to prevent emergence of resistance, particularly to rifampicin.

TABLE III DOSAGE AND ADVERSE EFFECTS OF ANTI-TUBERCULOUS DRUGS

Drug (symbol)	Daily dosages per kg body weight	Maximum per day dose (daily regime)	Intermittent thrice weekly dosage as under RNTP per kg body weight	Maximum per day dose (intermittent regime)	Major side effects
Streptomycin*(S)	15-20 mg	1000 mg	20 mg	1000 mg	tinnitus
Rifampicin (R)	10 mg	600 mg	15 mg	600 mg	hepatotoxicity, gastritis, flu like illness
Isoniazid (H)	5-10 mg	300 mg	15 mg	600 mg	peripheral neuropathy, hepatotoxicity
Pyrazinamide (Z)	30-35 mg	2000 mg	35 mg	2000 mg	arthralgia, hepatotoxicity
Ethambutol (E)	20 mg	1000 mg	30 mg	1200 mg	oculotoxicity

drug resistance. It is generally considered to add two drugs to the failed regime till culture and drug sensitivity reports are available. However, this categorization can also mean addition of a single drug – Streptomycin – to a failed regime (say a Category I failure). Evidence suggests that most common drug resistance is limited to first line drugs singly or in combination, and the multidrug resistance with bacilli resistant to at least INH and rifampicin is relatively uncommon (<5%). Therefore, except for multidrug resistance, this regime would work well for most. Complete adherence to therapy being the key to achieving cure and decreasing the chances of development of resistance, this is imperative that the treating pediatrician makes all efforts to ensure compliance. DOTS provide, a great opportunity for the same. Patients who are non-responsive to a well-supervised category II are likely to have MDRTB and should therefore be referred to an appropriate facility.

The above definition, categorization and duration of therapy should be used for every child with TB whether the patient is under individual care or under the program. This protocol should form the current standard of care and should override all earlier recommendations.

Steroids in tuberculosis

Definite indications for concomitant steroid therapy include TBM and pericarditis. Steroids are routinely not indicated in lymphadenitis and pleural effusion. They may be used in endobronchial tuberculosis or mediastinal compression syndrome due to tuberculosis, pleurisy with severe distress and miliary disease with alveolo-capillary block. Predinsone 2-4 mg/kg/d or its equivalent is used for 2-4 weeks and then tapered over next 2 weeks.

Fixed drug combination (FDC)

These combinations contain 2 or more drugs in a single formulation and therefore simplify the prescription of drugs. More importantly, they limit the risk of drug-resistant tuberculosis arising as a result of inappropriate drug selection due to prescription errors or due to omission of some drugs by the patient. FDC is patient friendly but there are some relevant issues about them. Bioavailability of liquid formulations is not dependable. One of the problem with FDC is that it is "fixed" and makes titration of individual drug dosage difficult. While the combination of rifampicin and INH as a single formulation are still well accepted, the bioavailability of individual components, particularly rifampicin, may be affected in other 3 or 4 drugs FDC formulations. It is reported that in most situations, blood levels of the drugs are inadequate because of poor drug quality rather than poor absorption(25). Currently, there are several formulations available with varying combinations with confusing and similar sounding brand names. This could make the prescription not simplified but error prone. FDCs from standard manufacturers with proven bioavailability should only be used.

Control Program-RNTCP

TB is considered a global emergency and in countries like ours, despite effective chemotherapy, control has not been achieved due to poor therapeutic practices. The emerging threat of poorly treatable rifampicin resistant TB warrants that the first line drugs be used appropriately to give them longevity in the armamentarium. RNTCP has evolved to take care of these problems by using DOTS strategy(26,27). This includes quality diagnosis by sputum microscopy, supervised drug therapy (thrice weekly visits in intensive phase followed by weekly visit to the clinic during continuation phase when one dose is administered under supervision and two doses are given to the patient to be taken at home subsequently), regular drug supply, patient tracking (progress to be monitored till end of therapy) and administrative and political commitment. Each patient on diagnosis has an entire box of drugs allocated with his name on it, though not handed over, to ensure supervised uninterrupted therapy. The Indian program is the first program in the world to provide pediatric patient-wise boxes for childhood TB cases and the pediatricians should help their patients in using these facilities.

11. Chemoprophylaxis

It is estimated that in developing countries the annual risk of tuberculosis infection in children is 2-5%(28). The estimated lifetime risk of developing tuberculosis disease for a young child infected with *Mycobacterium tuberculosis* as indicated by positive tuberculin test is about 10%(29).

About 5% of those infected are likely to develop disease in the first year after infection and another 5% in rest of their lifetime. These rates increase in HIV infected individuals. Nearly 8-20% of the deaths caused by tuberculosis occur in children(30). The age of the child at acquisition of tuberculosis infection has a great effect on the occurrence of tuberculosis disease.

Approximately 40% of infected children less than 1 year of age, if left untreated, develop radiologically significant lymphadenopathy or segmental lesions compared with 24% of children between 1-10 years and 16% of children 11-15 years of age(31).

Six months of chemopropylaxis is recommended for all under 6 years age contacts of an infectious case, irrespective of their BCG or nutritional status. PPD positive children over 6 years of age and who do

not have any evidence of active disease but are planned for immunosuppressive therapy (e.g. children with nephrotic syndrome, acute leukemias, etc) may also be given the benefit of chemoprophylaxis. While there is evidence that HR combination can make the prophylaxis shorter (3 months) but the group does not recommend this due to the risk of misuse of rifampicin.

12. Follow-up

With correct evaluation of type of patient, site and severity of disease and compliant treatment, one can anticipate clinical and radiological improvement over a standard time frame. Symptoms of active disease such as fever, cough and loss of appetite usually disappear within 2-4 weeks. Weight gain is evident only if active disease had resulted in loss of weight. Children often do not loose significant weight and so would not show weight gain even after successful treatment.

The present evidence does not suggest any cost benefits of repeating *X*-ray chest at the end of intensive phase, if the clinical improvement is on expected lines. Few patients who have persistence of symptoms on therapy will need investigations for bacteriological and radiological response. They should be given the benefit of extension of intensive phase by 4 weeks provided alternative diagnosis and co-morbidities are ruled out.

At the end of stipulated therapy, patient must be shown to have achieved cure by demonstrating negative bacteriology. A chest radiograph at the end of treatment is desirable to document the radiological status. This may be helpful to diagnose any subsequent disease in this high-risk group.

Repeat chest *X*-ray may sometimes be considered early in case of unanticipated clinical progress. In the presence of clinical improvement but radiological persistence of lesion, it is best to wait for radiological clearance over time, as it may not signify active disease. The patient should be followed up every 3 months for at least one more year for a possible relapse.

Paradoxical upgrading reaction (PUR) – worsening of lesion on treatment or appearance of new lesion is often seen in TB irrespective of HIV co-infection. Immune reconstitution syndrome occurs in individuals on treatment with HAART.

Routine monitoring of liver transaminases in patients on ATT is not recommended though hepatitis is the commonest serious drug toxicity seen. As the anti-TB drugs are hepatic enzyme inducers, asymptomatic biochemical derangement without increase in billirubin level may be tolerated till the enzymes remain up to 5 times the normal range. However, if patient develops jaundice or other signs of liver dysfunction during therapy, it is prudent to stop ATT immediately irrespective of enzyme levels. The drugs are withheld till the serum bilirubin becomes normal and the enzymes also start touching the normal range. Although many patients with drug-induced hepatotoxicity can be success-fully rechallenged, this is best done in a place where liver function can be carefully monitored. The drugs should be re-introduced in sequential order starting with rifampicin, followed by isoniazid and then pyrazinamide. We add the first drug and reassess for its impact on liver enzymes. If the enzymes remain within the acceptable range, then only the subsequent drugs are added in the given sequence every 5-7 days. Some experts prefer building up the doses of each of the drug; starting with half the dose and then increasing to full dose after 3-4 days, and then adding the next drug in half the dose and continuing the same way till all the drugs are re-introduced. Drugs causing severe intolerance on reintroduction are best avoided and substituted with other drugs. If the period without drugs is likely to be prolonged, and the patient is sick and requires treatment, at least two other drugs (*e.g.* streptomycin, ethambutol, floroquinolones) should be given until it is determined whether the offending drug can be resumed. All patients who require alteration from the standard regimen should be referred to experienced pediatricians.

Efforts should be made to ensure drug adherence in every patient. If the patient is under non-DOTS treatment, then the treating pediatrician should monitor adherence to therapy and followup. At each visit a pill count or prescription review should be done with the patient or the caregiver. It is very important to realize that the emergence of multidrug resistant TB (MDR TB) is always a man made

problem and failure of the patient to complete the prescribed course completely and adequately is one of the major reasons. When you have a patient who has returned after a break in therapy, further management becomes difficult. ***Table* IV** details the guidelines for treatment after a period of interruption in therapy. Whenever treatment is interrupted for more than 2 wks, the child should be reassessed clinically and radiologically, with bacteriological examination, wherever possible. In all such cases the resumption of treatment must be preceded by evaluation for activity and investigating the causes for non-adherence. The pediatrician should not merely restart the treatment but also enable the completion of treatment by addressing issues related to non-adherence in the first instance. Addressing issues like side effects of the therapy (real or perceived), cost involved as well as educating about the need for a complete treatment even after the symptoms abate may help adherence. Both the child as well as the caregivers must be involved in decision making for re-initiating treatment.

13. Special Situations

When to suspect MDRTB

It may be suspected prior to starting therapy in case of contact with proven MDRTB. It is also likely in a child who has had one or more courses of ATT in the past or had been non-compliant with prescribed therapy. Persistence of positive sputum or symptoms after extended intensive phase (3 months) in spite of compliant therapy should alarm you to the possibility of drug resistant TB and all necessary cultures should be sent while the patient is put on Category II therapy. The patients who are non-responsive to a well-supervised Category II are likely to have MDRTB and should therefore be referred to an appropriate facility.

Multi-bacillary lesions are more likely to be drug resistant than paucibacillary. HIV infection by itself does not predispose to MDRTB but the MDRTB prevalence is higher in such cases due to several factors. Malabsorption of anti-TB drugs in such patients may lead to suboptimal concentration of drugs in spite of compliance. Due to frequent hospital visits, they may also come in contact with MDRTB.

The treatment of MDRTB should only be done by experts. The details of the management of MDR TB in children are beyond the scope of this consensus guidelines.

When to consider HIV testing

Clinical markers of HIV infection such as oral thrush, chronic diarrhea, clubbing of nails, herpes infection, failure to thrive, require HIV testing. Beside these, history of HIV infection in parents and past history of blood transfusion justifies HIV testing. In case tuberculosis in a child does not respond as anticipated to compliant treatment, HIV infection may be one of the causes. HIV testing may be considered, especially if there is no other cause for poor response to treatment.

TABLE IV MANAGING PATIENTS WITH INTERRUPTIONS IN TREATMENT

Duration of therapy	Duration of interruption	Decision
Upto 4 weeks	<2 weeks	Resume original regime
	> 2 weeks	Reassess and start treatment again
4-8 weeks	<2 weeks	Resume original regime
	2-8 weeks	Extend intensive phase by 1 month more
	>8 weeks	Category II if diagnosis is still TB
> 8 weeks	<2 weeks	Resume original regime
	>2 weeks	Review activity • continue same treatment if no active disease • Category II therapy for active diseases

Management of a neonate born to a mother with tuberculosis

Prophylactic INH is recommended for newborns born to mother with tuberculosis after ruling out congenital tuberculosis. Modern chemotherapy is so efficacious that separation of the mother and infant is no longer considered mandatory, once the mother's therapy is started. Separation should occur only if the mother is ill enough to require hospitalization, if she has been or is expected to become non-adherent to her treatment, or if she is infected with a drug resistant strain of *M. tuberculosis*. INH therapy should be continued in the infant at least until the mother has been shown to be non infectious (culture negative) for 3 months. The infant should receive INH for a total of 6-9 months. Vaccination with BCG appears to decrease the risk of tuberculosis in exposed infants, but the effect is variable. The mother can continue to breast feed the baby. The ATT excreted in the milk has no therapeutic or adverse effect on the baby. Appropriate cough hygiene should be observed by the mother.

14. Gaps in Knowledge

The group identified the following key research areas which can provide answers to some of the unresolved issues.

1. Feasibility and utility of induced sputum in children.
2. Tuberculin test and redefining cutoff values for diagnosis of infection with the different strengths and formulations available.
3. Role of gestric aspirate in ambulatory setting.
4. Role of Interferon gamma release assays in diagnosis and assessment of activity in children.
5. Possibility of shorter duration of ATT for CNS/ renal and bone and joint TB by RCTs.

Finally, in conclusion we submit that the current guidelines have been developed keeping in mind the earlier guidelines of IAP, the National program guidelines and the International standard for TB care. We hope that these guidelines will henceforth form the basis of childhood TB management in the country in both public and private sectors.

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Annexure

Tuberculin test

Purified protein derivative (PPD) solution must be kept refrigerated at 2-8°C and to avoid fluctuations in temperature, never store in the refrigerator door. The vial should be discarded if it has been open for more than 30 days or the expiration date has passed. Select a well-lit area for administering the test.

Administration of Skin Test

The patient's forearm is exposed with the palm-side-up and slightly flexed at the elbow. The injection is to be given about 2 to 4 inches below the elbow avoiding areas of skin with veins, sores, rashes, scars, or excess hair. Using standard precautions for injection safety, the injection site is cleaned with alcohol swab, using circular motion beginning in the center and working the way outward.

The 1mL tuberculin syringe is loaded with PPD just prior to administration ensuring that all air and excess solution is expelled from the syringe, leaving exactly 0.1 mL of tuberculin solution in the syringe.

The skin is stretched taut over the injection site to provide a surface that is easy for the needle to penetrate. The syringe is held between thumb and index finger with the needle bevel facing up and the syringe parallel to the forearm. With the needle against the patient's skin, the needle is inserted slowly at a 5- to 15-degree angle, just below the surface of the skin (one should be able to see the bevel of the needle just below the skin surface).Once the bevel of the needle has fully entered just beneath the superficial most part of the skin, the stretched skin is released holding the syringe in place. The tuberculin solution is then injected slowly forming a 6 to 10 mm wheal (pale, raised area with distinct edges; has orange peel appearance and does not disappear immediately). If no wheal forms or if it is less than 6 mm in diameter, the test should be repeated about 2 inches from the original site or on the opposite arm.

After a successful injection the needle is removed without massaging or pressing the area.Sometimes there may be minor bleeding which can be dabbed with a 2x2 gauze pad or cotton ball till oozing of blood stops. There is no need to cover the site with an adhesive bandage. The patient can get mild itching, swelling, or irritation which is normal and usually goes away within 1 week. The patient is advised to avoid scratching the site, keeping the site clean and dry and is also advised to return within 48 to 72 hours for reading of the test result.

Reading the Mantoux Tuberculin Skin Test

The site of injection on the forearm of the patient is located. The fingernails of the reader should be short and should not extend beyond the fingertip. The induration may not always be visible, Therefore palpation of the area with fingertips to determine induration at the injection site is needed. The area is touched lightly with the pads of fingertips and the fingertips are lightly swept in 2-inch diameters from the injection site in all four directions to locate the edges of the induration. Alternatively, one can use a zig-zag, feather-like touch to palpate the area for margins of induration. Some times a margin of induration may be confused with a margin of muscle on the forearm. In such a case a repeat palpation with the patient's arm raised to a 45-degree angle is done.

Once the outer edge of the induration is reached rest one fingertip firmly against the induration margin on one side before marking the margin. The fingertip should remain in contact with the skin at all times. A ball point pen is used to mark the margin lightly with a fine dot at the widest edge of the induration. The procedure is reported on the opposite margin on the other side of the induration. It is ensured that the induration was marked correctly by a repeat palpation. If needed, the dots are altered on repeat measurement.

Alternatively the induration may be detected by the Ball point method. In this technique, a medium-point ballpoint pen is used to draw a line starting 1 to 2 cm away from the skin reaction and moving toward its center. When the pen reaches the margin of the induration, an increased resistance to further movement is felt and the pen is lifted. The procedure is repeated on the opposite side of the skin reaction. The distance between the ends of the opposing lines at the margins of the induration is measured.

Usually a millimeter ruler is used to measure the widest diameter of the induration perpendicular to the long axis of the forearm. Only the margins of the induration are relevant for measurement and the redness should not be measured. Reactions to the tuberculin skin test at the injection site vary and if there is blistering, the induration should be palpated gently as it may be painful. Sometimes the margins are not equally clear all the way around the induration but it is still necessary to mark the margins on each side of the induration. For irregular margins of induration, mark and measure the longest diameter across the forearm. The exact measurement in millimeters of induration should be recorded and not the interpretation of the results aspositive or negative along with the date and time the test was read. If there is no induration, this measurement should be recorded as 0 mm of induration.