

National Childhood TB Management Guideline



**Government of Nepal
Ministry of Health
Department of Health Service
National Tuberculosis Centre
Thimi Bhakatapur
2074**



Nepal Paediatric Society (NEPAS)



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Preface

Tuberculosis remains a public health problem in Nepal. TB is one of the Nepal's top health challenges. It is estimated that nearly 15 million populations, equals to almost half of the Nepal's total population are infected with TB. It is estimated that 44000 new cases of active TB occur in the country annually, but only 73% of the estimated cases in being notified currently. Among those notified cases the childhood TB is around 5-6% which is way below the estimation which should be around 10%.



The low case detection among children is identified as a key factor contributing for the overall low case detection. Tuberculosis in children has been relatively neglected, mainly due to challenges in the availability of effective diagnostic tools. In most settings diagnosis of pediatric TB is made on the basis of contact tracing, and very few attempts have been made for active case detection. This is mainly due to lack of a pathognomonic clinical presentation in pediatric TB and lack of sensitive diagnostic tools.

The National Strategic Plan for Tuberculosis Prevention and Cure (2016-21) has an objective to increase case notifications among children from 6.9% of total cases to at least 10% by 2020. The Plan will ensure that childhood TB is addressed in the NTC's policies and implementation, first by bringing national guideline on the management of childhood TB up to date. Childhood tuberculosis guidelines and training manual is essential for the effective and consistency for the diagnosis and management of childhood TB and capacity enhancement of health workers however currently, there is no Childhood Tuberculosis guideline in Nepal. This manual can be used by the trainers and later can be used by the trainees as reference for the management of childhood TB patients.

I would also like to take this opportunity to acknowledge the contributions by National and International consultants, NEPAS, my NTC team and experts and organizations engaged to develop this manual. My special thanks go to both Save the Children and KNCV for their financial and technical support for preparing this document.

If you have any suggestions for improving this manual, please write to:

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Preface

It gives me immense pleasure to write few words in this book of diagnosis and treatment of childhood tuberculosis. First of all I would like to congratulate director and entire team of Nepal Tuberculosis Center and Save the Children along with NEPAS team to write this manuscript for the use of medical persons in Nepal for the diagnosis and management of childhood tuberculosis.

The national childhood TB guideline is being produced in view of need in revision of guideline. We have been unable to identify existing 10% or more of childhood tuberculosis in the country. At the same time drug resistant tuberculosis is immerging rapidly. So this guide book will be helpful to all medical persons to make diagnosis and treatment of TB and be able to trace out the missed cases of childhood tuberculosis. The treatment has also been modified in view of immerging drug resistance. There has been great emphasis given in the use of IPT to children below 5 years with history of contact of tuberculosis. It has also been a guide of WHO childhood TB.

This book has been design with the practical approach in mind with algorithms along with concise test which can be consulted rapidly whenever and wherever it is necessary.

I am thankful to NTC and Save the Children for partnering with NEPAS not only in writing this manuscript but also in the training of childhood tuberculosis in future.

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Chapter 1: Tuberculosis in Nepal: Past, Present and Future

History: Building Block of the Present Success

Tuberculosis has been managed in Nepal for last 80 years. Over last 3 decades a significant improvement has been made with the efforts of Government and non-government sector. A short account of 80 years of TB achievements in Nepal is described below:

1937: Tuberculosis management in Nepal has begun seven decades back in 1937, through establishment of “Tokha Sanatorium” on the north of the Kathmandu city.

1951: Central Chest Clinic provided domiciliary services with the facility of diagnosis and treatment of TB

1952: Nepal Anti-TB Association (NATA) founded

1955: NATA established outpatient clinic

1965: Tuberculosis Control Program (TBCP) systematically organized through tripartite agreement with GoN, WHO and UNICEF

1966: GoN launched Tuberculosis, Leprosy and Small Pox Eradication Program

1970: Establishment of Chest Clinic

1989: National Tuberculosis Center (NTC) in Thimi, Baktapur and Regional Tuberculosis Center (RTC) at Pokhara established with support from JICA.

1994-96: DOTS started

2001: “DOTS All Over” achieved

2006: Stop TB Strategy adopted by NTP

2011: DRS survey

2012: General Manual (Guideline on TB with a separate chapter on child TB), 3rd Edition Published by NTP

2016: Adoption of End TB strategy

1990-2016: Indicators of tuberculosis

| Criteria | 1990 | 2016 |
|---------------------------|------|------|
| Prevalence/100,000 | 460 | 215 |
| Incidence Rate/100,000 | | 156 |
| Death/100,000 | 43 | 20 |
| Case notification/100.000 | 32 | 112 |
| Treatment success rate | 50% | 91% |

Global epidemiology: TB and child TB

Though TB is declining at a rate 1.5% per year during MDG period yet, in 2015 total estimated TB in the world was 10.4 million. Among these total notified cases were 6.3 million, i.e. a gap of 4.3 million cases still exists. Children were estimated to be 1.0 million (10%) among the 10.4 million. Dodd PJ et al in 2014 stated it could be up to 22% in the high burden countries.¹ In the eight SAARC member states total TB case new cases reported was 2,181,285 in 2014, which is 36% of newly reported 6 million global TB cases. Among these 134,417 (6.16%) are children <15 years.

Situation of Childhood TB in Nepal:

Tuberculosis (TB) remains as a major public health problem in Nepal, as it is responsible for ill health among thousands of people each year. TB also ranks as the sixth leading cause of death in the country. It

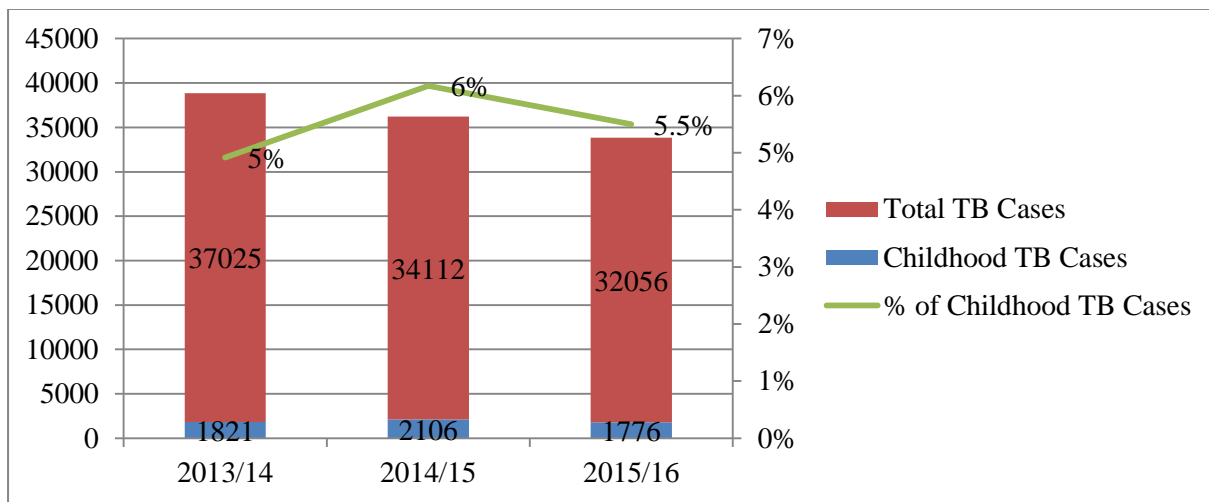
¹ Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014;2:453–59

is estimated that 44,000 new TB cases occur and 5000-7000 deaths each year. Despite the efforts there is unacceptable low rate of decline in incidence rate.

During 2015/16 reporting year, NTP registered 32,056 TB cases (all forms). Among them, 17,446 (54.4%) were new smear positive TB cases, 5850 (18.2%) were sputum smear negative and 8,760(27.3%) were extra-pulmonary TB cases. Out of total registered cases in NTP, there were 11,560 (36%) female and 20,496 (64%) male.² Among them 5.54% were childhood TB cases. TB program in Nepal was able to save 32,973 lives this year nationally, but still 978 deaths were reported among general TB cases.

The total number of notified TB cases is decreasing over the last 3 years. However, proportion of childhood cases has increased from 5% to 6% in 2014/15 and it decreased to 5.5% in 2015/16 which is less than WHO estimate of 10%.

Figure 1: Situation of childhood TB in Nepal



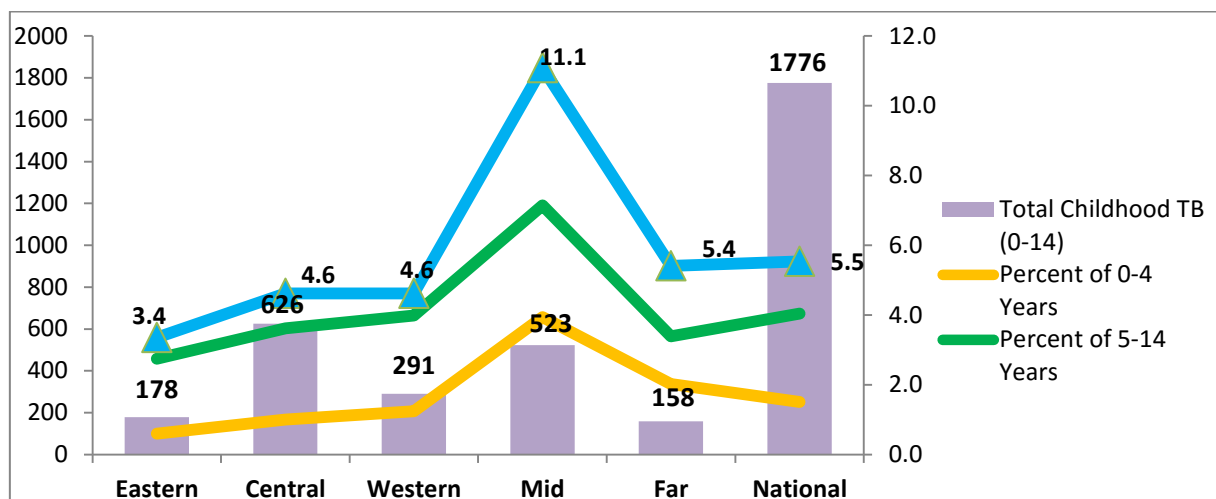
A total of 1776 childhood TB cases were notified in 2015/16. The highest number (626) of childhood TB cases was notified in central region and lowest number is notified in far western region. There is a wide variation in the proportion of childhood TB cases between the regions, being highest (11.1 %) in the mid-western region and lowest (3.4%) in the eastern region. There is a similar pattern on the proportion of 0-4 years and 5-14 years childhood TB cases across all the regions. Among the total notified childhood cases majority of the cases (72.2%) were aged 5-14 years and 27.8% aged 0-4 years.

As the population below the age of 15 years is 35% of total population: 0-4 years: 9.69%, 5-9 years: 12.10% and 10-14 years: 13.12%.³ WHO estimates 10% of childhood cases among total notified cases. The data above strongly suggest a marked under-representation of child TB cases, especially those in 0-4 years age group who cannot provide sputum, require a clinical diagnosis, and present with features that overlap with other common diseases in children such as pneumonia and malnutrition. The emphasis of NTP reporting has traditionally been on sputum smear-positive disease, and this is not uncommon in school-aged children and adolescents, and diagnosis and registration is as per adult suspect TB cases.

² Annual Report of National Tuberculosis Control Program Nepal, 2015/2016

³ Nepal population report 2016. file:///E:/Nepal%20Guideline/Nepal%20Population%20Report%202016.pdf

Figure 2: Percentage of childhood TB and regional distribution in 2015/16



Future- National Strategic Plan on TB: 2016-2021

With the goal and vision of SDG to end TB, Nepal has made its plan to reduce the TB burden and death from TB. In this plan, first objective is to increase case detection rate of childhood TB from 6% of 2015 to 10% by 2021 and a cumulative increase of 20,000 of total TB during the same period⁴.

The strategy aims to increase case notifications among children from 6.9% of total cases to at least 10% by 2020. The plan will ensure that childhood TB is addressed in the NTC's policies and implementation, first by establishing a childhood TB unit in the NTC. This revived unit will first bring national guidance on the management of childhood TB up to date. Treatment guidance will be revised with the advice from the 2014 WHO Guidance and the 2010 WHO Rapid Advice from WHO to develop dosage recommendations for the first-line drugs in children diagnosed with TB disease. Collaborations will be formed between the NTC childhood TB unit, paediatricians in hospitals, and those in the private sector as well as with Child Health programmes in the field, e.g. Integrated Management of Childhood Illnesses (IMCI), MCH, EPI, Well Baby and Sick baby clinics, Acute management of malnutrition. Children with HIV-associated TB will be addressed in an effort to coordinate between TB and HIV services.

⁴ National Strategic Plan for Tuberculosis Prevention, Care and Control 2016-2021. The Federal Democratic Republic of Nepal (Draft)

Chapter 2: General Concept on Childhood TB

As the symptoms are subtle and mimics other common childhood illness, diagnosing childhood TB is challenging. Clinical picture and diagnostic approach is not straight forward as adult TB (see the table below). A child usually gets the disease from an infectious adult hence the contact history is very important. Most of the cases in children are smear negative and paucibacillary. Moreover children below 6 years usually cannot expectorate sputum. While bacteriologic testing should always be attempted, the challenges with specimen collection at lower health care levels and the suboptimal accuracy of the present tools in children needs to be recognized. Therefore clinical diagnosis needs done based on high index of suspicion on the basis of contact history, risk factor and symptom analysis is needed.

Table I: Difference between adult TB and childhood TB

| Criteria | Adult TB | Childhood TB |
|-------------------|-----------------------------------|--|
| Symptoms | Suggestive | Non-specific |
| Physical signs | Easily elicited | Often subtle or absent |
| Sputum sample | Easy to obtain | Difficult to obtain |
| Sputum microscopy | Usually contains numerous bacilli | Often negative, sputum is paucibacillary |
| CXR | Easy to interpret | Difficult to interpret |

Contact with adult TB:

As the child mostly gets TB from an adult open case of TB, history of contact with an adult case is the most important point to be taken into consideration while diagnosing TB in children. Close contact with an open case increases the likelihood of TB by 35%⁵. A smear positive person expectorates 10^8 to 10^{10} bacilli daily or 10^6 to 10^7 bacilli/ml of sputum while a smear negative person expectorates $<10^3$ bacilli/ml of sputum⁶.

Contact Terminologies:

Contact screening: A systematic process for identifying contacts who have, or are at increased risk of developing TB. Contact identification and prioritization includes an interview with the index case to obtain the names and ages of contacts and an assessment of contact's risk of having or developing TB. This determines those who require clinical evaluation.

Contact: Any person who has been exposed to an index case.

Index Case: The initially identified case of new or recurrent TB, in a person of any age, in a specified household or other comparable setting in which others may have been exposed. An index case is the case, around which a contact investigation is centered (but is not necessarily the source case).

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

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 period during the 3 months before the start of current treatment episode.

Tuberculosis: Exposure, Infection and Disease

All the children who are exposed to an infected index case do not develop infection or disease. Certain risk factors make children more vulnerable to develop the disease.

⁵ Grzybowski S et al. Bull Int Union Tuberc. 1975

⁶ Sepkowitz KA. How contagious is TB? Clinical Infectious Diseases. 1996, 23:554-62

Exposure to TB bacilli:

A child is exposed to *M. tuberculosis* when he/she comes into contact with an infectious TB patient. The risk of inhaling the organisms and becoming infected is determined by the infectiousness of the source/index case, as well as the proximity or closeness and duration of contact. Children are most likely to become infected if the mother or another adolescent/adult household member has sputum smear-positive TB.

Infection with *M. tuberculosis*

A child becomes infected with *M. tuberculosis*, when he/she inhales the bacilli spread via tiny aerosol droplets that float in the air for prolonged periods of time. These tiny infectious droplets are mainly produced by adolescent and adult TB patients with cavities in their lungs. Inhalation of infected droplets into the lung leads to the development of primary parenchymal lesion (Ghon focus) in the lung with spread to regional lymph node(s). In most cases, the host immune response stops the multiplication of *M. tuberculosis* and contains the spread at this stage. However, few dormant bacilli may persist and give rise to disease later, at any stage of life, if immunity of the body becomes compromised.

Most young children become infected after household exposure to a patient with sputum smear-positive TB. In 2015/16, total number of new sputum smear positive cases detected in Nepal were 17,446. These patients are spreading TB infection in the community. Sputum smear-negative cases are less infectious, but may still transmit the infection if they have pulmonary TB (diagnosed on chest x-ray) especially when mother or primary caregiver of a young child has the infection. TB infection may also occur outside the household. Therefore, absence of household contact does not exclude TB.

Children with *M. tuberculosis* infection are not ill and do not have symptoms of TB disease unless the disease is active. Infection without symptom/signs of disease is also known as latent TB infection (LTBI).

LTBI is usually indicated by a positive Montux Test (MT) test/IGRA. However, there are many limitations to both the MT and the IGRA (see TB diagnosis section). In HIV-infected and/or malnourished children, the MT may give a false negative result. After inhalation of TB bacilli, it takes minimum of 8 weeks to give a positive MT test result. It should be noted that during this window period, infected children the MT also not give a positive result (see TB diagnosis section). However, in young children < 5 years TB infection may progress rapidly into active TB disease before a MT conversion can be detected. This is the rationale for prompt chemoprophylaxis, with Isoniazid which will be mentioned in coming chapter.

Children rarely develop lung cavities and high bacillary loads. They are rarely infectious. However, older children (>8yrs of age) frequently develop sputum smear-positive TB and can also act as a source case.

TB Disease (Active disease)

Only a small percentage of children who inhale the TB bacilli develop active disease. A child is said to have TB disease (active disease) if-

1. infected with *Mycobacterium tuberculosis*, with
2. clinical signs and symptoms,
3. ± laboratory or radiologic evidence suggestive of TB

Certain groups are at far greater risk of developing active disease than others (Box-I). TB disease may manifest in many different ways, but is usually indicated by the presence of well-defined symptoms and/or radiological changes.

Risk factors for TB disease:

Certain groups of children are at increased risk of developing TB disease and the established risks are described in the following box.

Box 1: Key risk factors for TB disease in children⁷

1. Household or close contact with a smear positive or culture positive pulmonary TB- (parents, siblings, close relatives, caregivers, neighbors and teachers)
2. Age <5 years: The risk of developing TB disease is highest in very young children, who are immune immature
3. Severe malnutrition or other Immunosuppressive conditions
 - # Measles in the previous 3 months
 - # Whooping cough
 - # HIV infection
 - # Being on drugs like steroids, immunosuppressive drugs
4. The time since exposure or infection: the vast majority of children who develop TB disease do so **within the first year** after *M. tuberculosis* exposure or infection

NB : Other high risk factors are HIV/AIDS, diabetes, end-stage renal failure, cancer, connective tissue disease, silicosis, gastrectomy, solid organ transplantation and patients on prolonged steroid. Both type 1 and type 2 diabetes patient have the increased risk of having TB^{8,9}.

TABLE 2: Age-specific risk of progression to disease after primary infection with *M. tuberculosis* in immunocompetent children¹⁰

| Age at Primary Infection (yr) | Risk of Progression to Disease (%) | | |
|-------------------------------|------------------------------------|---|------------|
| | Pulmonary Disease | Disseminated disease or Tubercular Meningitis | No disease |
| < 1 year | 30-40% | 10-20% | 50% |
| 1–2 years | 10-20% | 2-5% | 75-80% |
| 2–5 years | 5% | 0. 5% | 95% |
| 5–10 years | 2% | < 0.5% | 98% |
| > 10 years | 10-20% | < 0.5% | 80-90% |

⁷ World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. Geneva: WHO. 2014.

[<http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf>]

⁸ Shen TC, Lin CL, Wei CC, Chen WC, Liao WC, Chen CH et al. Increased risk of tuberculosis with type 1 diabetes mellitus: results from a population-based cohort study in Taiwan. *Medicine (Baltimore)* 2014; 93(16) :e96 (Abstract)

⁹ Alladin B, Mack S, Singh A, C Smith B, Cummings E, Hershfield E, Mohanlall J, Ramotar K, La Fleur C. Tuberculosis and Diabetes in Gyana. *Int J Infect Dis.*2011; 15:e818-821

¹⁰ Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald P, Starke J.. Childhood Tuberculosis: Old wisdom and New Challenges. *Am J Resp Crit Care Med*, 173:1078-1090, 2008

Definition of TB in children^{6,11}:

WHO has revised the definition of different aspects of TB disease on 2013 (revised in December 2014). In a patient with symptomatic disease (due to *M. tuberculosis* infection), recognition of TB is made by clinical diagnosis or by bacteriological confirmation.

Presumptive TB: a patient who presents with the symptoms or signs suggestive of TB (previously known as *TB Suspect*).

Bacteriologically confirmed case: is a patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (e.g. Xpert MTB/RIF).

Clinically diagnosed TB case: is a patient who does not fulfill the criteria of bacteriological confirmation or smear not done but diagnosed as active TB by a clinician and decided to have a full course of anti-TB treatment. These cases are diagnosed as active TB on the basis of chest X-ray abnormalities or histology or extrapulmonary cases without laboratory confirmation.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to (i) Anatomical site of disease, (ii) Drug resistance, (iii) History of previous anti-TB treatment and (iv) HIV status. Beyond the diagnosis of TB disease, the type of TB should be defined clearly and completely to enable appropriate treatment and evaluate the outcome.

Intrathoracic TB: Bacteriologically confirmed or clinically diagnosed cases of TB involving the lungs or extrapulmonary sites should be classified as following:

Table 3: Classification of Intrathoracic TB⁶

| Anatomical involvement | Pulmonary TB (PTB) | Extra-pulmonary TB (EPTB) |
|--|---------------------------|----------------------------------|
| Lung parenchyma | Yes | No |
| Tracheo-bronchial tree | Yes | No |
| Miliary | Yes | No |
| Pleural (effusion) | No | Yes |
| Intrathoracic lymphadenopathy (mediastinal/hilar/subcarinal) | No | Yes |
| Both Extra-Pulmonary and Pulmonary TB | Yes | No |

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheo-bronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs too.

There are standards for the optimum number of specimens for smear microscopy¹².

PTB, smear-positive

- ☒ One initial sputum smear examination positive for acid-fast bacilli
- or

¹¹ World Health Organization. Definitions and reporting framework for Tuberculosis-2013 revision (updated December 2014)

¹² TB CARE I. International Standards for Tuberculosis Care. Third edition. The Hague: TB CARE I; 2014

- ❑ Smear negative but culture or Xpert-positive for *M. tuberculosis*.

PTB, smear-negative-

A case of pulmonary TB that does not meet the above definition for smear-positive

PTB. Such cases include cases without smear results/smear not done. It is frequent in children. For good clinical and public health practice, diagnostic criteria for sputum smear-negative PTB should include:

- ❑ At least two sputum specimens negative for acid-fast bacilli
and
- ❑ Have diagnostic features strongly suggestive of Pulmonary TB
and
- ❑ Decision by a clinician to treat with a full course of anti-TB chemotherapy.

Extra-pulmonary tuberculosis (EPTB)

EPTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs outside the lung parenchyma and bronchial tree (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

Children with TB outside lung parenchyma and trachea-bronchial tree are labeled as extra-pulmonary TB. For example, TB in pleura is regarded as EPTB. Publications from tertiary hospitals of Nepal showed EPTB to be between 46.3% to 78.3% among children^{13,14}, while in African countries it was found to be 30%¹⁵. Note that children who have both pulmonary and extra pulmonary TB are classified under the case definition of PTB.

Classification based on treatment history:

New patient: Has never been treated for TB or taken TB drugs for less than *one month*. INH preventive therapy is not considered as previous treatment

Previously treated patient: Has received 1 month or more of anti-TB drugs in the past. This group further sub-classified to relapse patient, treatment after failure patients, treatment after loss to follow-up patients and others.

Relapse- A patient whose most recent TB treatment was cured or treatment completed, and he/she is subsequently diagnosed with a bacteriologically confirmed episode of TB(based on smear microscopy, Xpert MTB or culture).

Treatment after failure- are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow-up- A patient who had previously been treated for TB and was declared loss to follow-up at the end of most recent course of treatment (previously called as 'treatment after default').

¹³ Shrestha S, Bicha RP, Sharma A et al. Clinical profile of tuberculosis in Nepal. Nepal Med Coll J 2011; 13(2): 119-122

¹⁴ Sreeramareddy C, Ramakishnareddy N, Shah R et al. BMC Pediatrics 2010, 10:57
<http://www.biomedcentral.com/1471-2431/10/57>

¹⁵ Harries AD, Graham SM, Weismuller MM, Claessens NJM, Meljnen S, Hargreaves NJ, Mwansambo C, Kazembe PN, Salaniponi FM.. Childhood Tuberculosis in Malawi: caseload, diagnostic practices and treatment outcomes Malawi Medical journal 2005 December;17(4): 119-124

Others- e.g. sputum smear positive with unknown previous outcome; sputum smear positive patients who received treatment other than standard first-line treatment regimen(possibly in a private sector); previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.

Classification based on drug resistance:

Drug-resistant TB

Drug-resistant TB is a laboratory diagnosis i.e. based on drug susceptibility test (DST). Children are susceptible to drug-resistant as to drug-sensitive TB. However, drug-resistant TB should be suspected if any of the features below are present:

1. Features in the source case suggestive of drug-resistant TB:

- ☒ Contact with a known case of drug-resistant TB.
- ☒ Remains sputum smear-positive after 3 months of treatment.
- ☒ History of previously treated TB.
- ☒ History of treatment interruption.

2. Features in a child suspected of having drug-resistant TB:

- ☒ Contact with a known case of drug-resistant TB.
- ☒ Not responding to the anti-TB treatment regimen despite adherence.
- ☒ Recurrence of TB after adherence to treatment.

Chapter 3: Diagnosis of TB in Children: Choice not challenge

Diagnosis of TB in children is not as straight-forward as in adult TB patient. It requires careful and thorough assessment of all the data derived from a careful history, clinical examination and relevant investigations e.g. mantoux test (MT), chest X-ray (CXR), smear microscopy, gene-Xpert and other investigations. PTB is a common form of TB in children although bacteriological confirmation through sputum microscopy is not always possible for young children. In this group sputum induction and gastric aspiration have been documented to be an effective method for collection of specimen. Every attempt to collect sputum should be sought whenever possible. Sputum sample collection is strongly encouraged for the children who are able to produce a sputum sample.

Also, child with fever of unknown origin, failure to thrive, whooping cough, severe malnutrition and/or other immunosuppressive conditions such as measles in the previous 3 months, PLHIV, AIDS or being on medication like steroids or unexplained lymphadenopathy should be evaluated for TB. Any child with pneumonia, pleural effusion, or a cavitary or mass lesion or other abnormality in the lung that does not improve with standard antibacterial therapy should also be evaluated for TB. Common differential diagnosis like asthma, bronchiectasis, lymphoma, non-tubercular mycobacterial diseases etc. should be kept in mind.

Diagnosis of TB in children is often difficult for several reasons:

1. Symptoms are often non-specific particularly in young children and often mimics common childhood illness.
2. Childhood TB is paucibacillary & a microbiological diagnosis is often not possible.
3. It is difficult to obtain sputum or other respiratory specimen for bacteriological confirmation.
4. The Mantoux Test (MT) or Tuberculin Skin Test (TST) is often negative in malnourished children or in children with overwhelming TB. Moreover, a positive MT cannot differentiate active TB disease from infection.
5. CXRs are often non-specific and prone to variable interpretation.

Despite these difficulties, even in an OPD settings of remote Nepal, an accurate diagnosis of childhood TB can still be made in the majority of presumptive children from careful history, clinical examination and relevant investigations. To increase case detection rate in childhood TB from the community, both active and passive case-finding strategies have to be adopted with intensified case-finding among the high-risk groups (both clinical and population-based high risk groups).

A trial of treatment with anti-TB medicine is not recommended as a method to diagnose or rule out TB in children.

Box 2: Recommended approach to diagnose TB in children^{6,11}

1. Careful history (including history of TB contact and symptoms suggestive of TB)
2. Clinical assessment (including serial weight monitoring/growth assessment)
3. Investigations
 - 3.1 Mantoux test
 - 3.2 Chest X-ray and other radiological evaluation
 - 3.3 Bacterial confirmation whenever possible: Smear microscopy, Xpert-MTB RIF, culture of respiratory sample / gastric lavage
 - 3.4 Investigations relevant to suspected PTB/EPTB
 - 3.5 HIV testing

HISTORY

HISTORY OF THE INDEX CASE

Most important part in the diagnosis of TB in children is history. It includes presenting symptoms and signs, history of contact with a known case of TB and medications taken by patient and the source/index case. Children usually acquire the disease from a sputum-positive, usually adult/adolescent, index case. Hence the household contact and other close contacts are to be sought in all presumptive TB cases. Particularly young infants, who stay at home (less mobility and remain on the lap and stay longer in close proximity to infectious adult/adolescent) are more likely to have contracted TB at home^{11,16} Children below 5 years and with conditions of immunosuppression (e.g. HIV, on anti-cancer medication) should be evaluated by a competent physician for possible TB disease or infection. Conversely, if a child is diagnosed with TB, active search should be made to find household contacts/cases with active TB (reverse contact tracing)¹⁷. If a child is diagnosed with TB all the contacts must be sought and screened.

It is also important to document whether the suspected index case is responding to TB treatment or not (cured, not cured, dead). While taking history, if an index case is found not to be responding or poorly responding to treatment, it points that the index case may be a case of drug-resistant TB and the child contact (if diagnosed as TB) is most likely to also have drug-resistant TB. This is an important consideration in the diagnosis and treatment of the child.

Young children living in close contact with a source case are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is in close proximity with prolonged exposure and the source case has sputum smear-positive PTB. Source cases that are sputum smear-negative but culture-positive are also infectious, but to a lesser extent.

If no source case is identified, but someone else in household is found to have chronic cough upon further inquiry, assessment of that person for possible TB is warranted as soon as possible to prevent further transmission and re-exposure.

Children usually develop TB within 2 years after exposure and most of them (90%) within the first year. Therefore, history of close contact with a patient (adult or adolescent or even a child) with PTB within the recent past (especially last one year) is the most important clinical clue.

To increase the case detection among children and prevent further transmission and re-exposure, all close contact (including household contact) should be asked/checked for common TB signs and symptoms. Although the best way to detect TB infection is the MT and PTB is a CXR, symptom-based screening has been found to be a good tool in case detection in resource-limited countries¹⁸. These tests can be done, if available, to screen exposed contacts.

¹⁶ Del Castillo-Barrientos H, Centeno-Luque G, Untiveros-Tello A, Simms B, Lecca L, Nelson AK, Lastimoso C, Shin S. Clinical presentation of children with pulmonary tuberculosis: 25 years of experience in Lima, Peru. *Int J Tuberc Lung Dis* 2014, 18(9):1066-73.

¹⁷ Puryear S, Seropola G, Ho-Foster A, Arscott-Mills T, Mazhani L, Firth J, Goldfarb DM, Ncube R, Bisson GP, Steenhoff AP. Yield of contact tracing from pediatric tuberculosis index cases in Gaborone, Botswana. *Int J Tuberc Lung Dis* 2015, 17(8):1049-55.

¹⁸ Jerene D, Melese M, Kassie Y, Alem G, Daba SH, Hiruye N, Girma B, Suarez PG. The yield of a tuberculosis household contact investigation in two regions of Ethiopia. *Int J Tuberc Lung Dis* 2015 Aug 1; 19(8): 898-903

Clinical assessment of presumptive TB case

Symptoms suggestive of TB

TB in children commonly presents with fever and failure to thrive. But these symptoms are non-specific¹⁹. In most cases, children with symptomatic TB develop chronic unremitting symptoms (symptoms persisting for >2 weeks even after appropriate treatment). Hemoptysis or coughing up of blood (a common symptom in adults) is rare in children with TB, but may occur in adolescents.

TB in many cases present as acute pneumonia. Hence cough for 2 weeks or more may delay the diagnosis. TB disease can be more severe and of rapid onset in infants and young children.

For EPTB, symptoms depend on the organ involved (enlarged lymph nodes with/without sinus formation, spinal deformity and seizures). Children particularly those <3 yrs of age, severely malnourished and living with HIV pose the greatest challenge for clinical diagnosis. WHO criteria has a high specificity (84%) and low sensitivity(40%) in diagnosing TB in children²⁰.

TB in Severe Acute Malnutrition-

Severe Acute Malnutrition (SAM) has been recognized an important risk factor for the development of TB disease and enough evidence has been generated. Impaired cell mediated immunity, mucosal immunity and lack of vitamin D are postulated to be the reasons for TB in SAM children²¹. NDHS 2016 data shows 10% children <5 years are wasted²². The clinical picture of TB in children with SAM is different.

In SAM children under 5 years of age, cough and/or fever of <2 weeks have been demonstrated to be symptoms of TB in many parts of the world. This high-risk group of under 5 children, presenting with severe pneumonia, accounted for 23% TB cases in Bangladesh²³. Similarly studies done in India²⁴ and Ethiopia²⁵ showed the incidence of TB in SAM children to be 13% and 6.6% respectively.

¹⁹ Blount RJ, Tran B, Jarlsberg LG, Phan H, Thanh Hoang V, et al. (2014) Childhood Tuberculosis in Northern Viet Nam: A Review of 103 Cases. PLoS ONE 9(5): e97267. doi:10.1371/journal.pone.0097267

²⁰ Chisty MJ et al. Diagnosis of Tuberculosis Following World Health Organization–Recommended Criteria in Severely Malnourished Children Presenting With Pneumonia. Global Pediatric Health Volume 4: 1–4

²¹ Jaganath D and Mupere E. Childhood TB and malnutrition. The Journal of Infectious Diseases 2012;206:1809–15

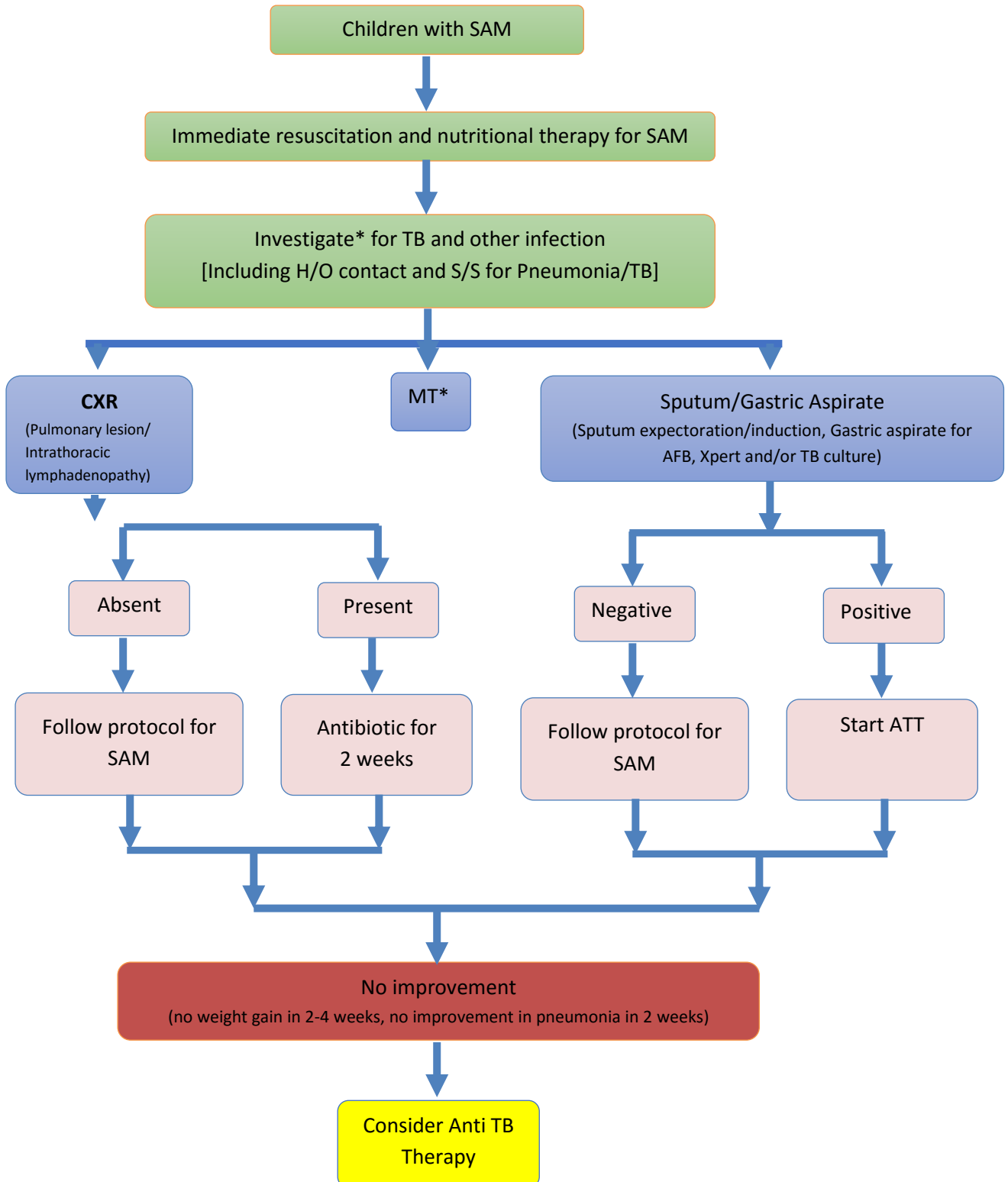
²² NDHS 2016. Population Division Ministry of Health and Population, Government of Nepal, Kathmandu, Nepal

²³ Chisti MJ, Graham SM, Duke T, Ahmed T, Ashraf H, Faruque ASG, La Vincente S, Banu S, Raqib R, Salam MA. et al. (2014) A prospective study of the prevalence of tuberculosis and bacteremia in Bangladeshi children with severe malnutrition and pneumonia including an evaluation of Xpert MTB/RIF assay. PLoS One 2014 :e93776

²⁴ Meshram H, Ali S, Shehab T. Spectrum of co-morbidities in severe acute malnutrition with unexpected dyselectrolytemia in diarrhea. International Journal of Medical Pediatrics and Oncology, January-March, 2017;3(1):6-9

²⁵ Berti A, Bregani ER, Manenti F, Pizzi C. Outcome of severely malnourished children treated according to UNICEF 2004 guideline: a one year experience in a zone hospital in rural Ethiopia. Trans R Soc Trop Med Hyg. 2008;102:939-944

The following algorithm can be helpful in screening TB in SAM child.



*Exposure to TB patient is known by contact with sputum positive TB patient (smear/Xpert/culture) or positive MT.

Note: Gene Xpert should be prioritized first for the diagnosis of TB among presumptive TB children.

MT should be done in all SAM children.

Positive MT should be correlated with other clinical conditions (eg. not gaining weight, but pneumonia improved and no contact with TB → If MT is positive, consider ATT).

MT positive SAM children improved clinically with nutritional therapy.

Symptoms and signs: Frequency by age

In general, TB is a slowly-developing chronic disease. But it may present acutely (eg. pneumonia, TBM) in young and HIV-infected children. However, pulmonary TB in children can manifest in various ways in different age groups (Table 3).

- ✓ Infants (<1 year): primarily pneumonia-like
- ✓ Children (1-9 years): usually with a chronic cough
- ✓ Adolescents (10-19 years): as in adults

Table 4: Frequency of symptoms and sign of pulmonary TB stratified by child age²⁶

| Clinical features | Infants (0-11 mo) | Children (1-9 yr) | Adolescents (10-19 yr) |
|-------------------------|----------------------|----------------------|---------------------------|
| Symptom | | | |
| Fever | Common | Uncommon | Common |
| Night sweats | Rare | Rare | Uncommon |
| Cough | Common | Common | Common |
| Productive cough | Rare | Rare | Common |
| Haemoptysis | Never | Rare | Rare |
| Dyspnoea | Common | Rare | Rare |
| Sign | | | |
| Crepitations | Common | Uncommon | Rare |
| Wheezing | Common | Uncommon | Uncommon |
| Dullness to percussion | Rare | Rare | Uncommon |
| Decreased breath sounds | Common | Rare | Uncommon |

BOX 3: Symptom criteria for PTB

- ✓ Persistent, non-remitting cough for >2 weeks not responding to conventional antibiotics (amoxicillin, co-trimoxazole or cephalosporin) and/or bronchodilators
and/or
- ✓ Persistent documented fever (>38⁰C/100.4⁰F) >2 weeks after common cases such as pneumonia, typhoid, malaria have been excluded
and/or
- ✓ Documented weight loss or not gaining weight during the past 3 months (especially if not responding to de-worming together with food and/or micronutrient supplementation) OR severe malnutrition
and/or
- ✓ Fatigue, reduced playfulness, decreased activity

²⁶ Starke JR. Tuberculosis. In: Jenson HB, Baltimore RS, editors: Pediatric infectious diseases: principles and practices. Philadelphia: WB Saunders, 2002; pp. 396–419

NB: Any one of the above symptom criteria in a child (<15 years) in close contact with a known bacteriologically confirmed TB or clinically confirmed TB should be regarded as presumptive TB case and referred to a physician for evaluation.

Extra-pulmonary TB: Signs and symptoms

EPTB is common in children than adult. In published articles from Nepal, 46.3% to 78.3% EPTB has been found to be present in children ^{12, 13, 27}.

Common EPTB in children-

1. Tubercular lymphadenopathy
2. TB pleural/pericardial effusion
3. Tubercular meningitis
4. Spinal TB (Pott’s disease)
5. Abdominal TB
6. Tubercular arthritis

Table 3: Symptoms and signs suggestive of EPTB

| Symptoms and Signs | Extra-pulmonary TB |
|--|---|
| A painless enlarged mass of matted lymph nodes (>2x2 cm), usually in the neck, not fixed to the underlying tissues, initially firm and fluctuant later, that may present with sinus, not responding to a course of antibiotics | TB lymphadenitis (commonly cervical) |
| Cough and shortness of breath | Pleural TB, Pericardial TB |
| Reduced playfulness, irritability, weight loss, headache, vomiting without diarrhea, drowsiness, lethargy, unconsciousness, convulsions; and meningitis of acute or sub-acute onset and not responding to antibiotic | TB meningitis, Tuberculoma |
| Abdominal pain, altered bowel habit, mass or ascites | Abdominal TB |
| Gibbus (acute angulation of vertebrae) | Spinal TB |
| Chronic pain and swelling of joint(s), usually single | TB arthritis |

NB: If any of the above symptoms are associated with a history of contact, possibility of TB is high.

Tubercular lymphadenopathy:

The most common extra-thoracic manifestation of TB is cervical lymphadenitis (75-90%). Sometimes it can also involve axillary (14-20%) nodes. Involvement of inguinal lymph nodes is uncommon (4-8%).^{28,29,30} TB lymphadenopathy presents as a painless visible neck mass, usually composed of matted lymph nodes, not fixed to the underlying tissues. Suppuration and spontaneous drainage of the lymph nodes may occur with the development of sinus. Lymphadenopathy with discharging sinuses in the cervical region is suggestive of tuberculous infection. Fever, weight loss, fatigue, and malaise are usually

²⁷ Shrestha S. Clinical Profile and Outcome of Childhood Tuberculosis at Dhulikhel Hospital. J Nepal Paedtr Soc 2011;31(1):11-16.

²⁸ Seth V et al. Tubercular lymphadenitis: Clinical manifestations. Indian J of Pediatr.1995;62:565-70.

²⁹ Binet H et al. Tubercular inguinal and crural lymphnodes. Dermatology.1998;196:459-60.

³⁰ Dandapat MC et al. Peripheral lymphnode tuberculosis: A review of 80 cases. Br J Surg. 1990;77:911-12.

minimal or absent. Generalized lymphadenopathy is an uncommon presentation of TB in children, unless associated with disseminated TB or AIDS.

Tuberculosis in axillary lymph node is usually unilateral. But it can also be enlarged after BCG vaccination. In such case, we should ask for recent BCG vaccination and look for a BCG scar. It usually occurs on the right axilla (BCG given over right deltoid). Enlarged lymph node in the inguinal region mimics an inguinal hernia. Differentiating clue is that the hernia will have a positive cough impulse.

Differential diagnosis of tubercular lymphadenopathy includes- acute suppurative lymphadenitis (usually tender and hot, that can be associated with scalp, ear or dental infection), scrofula (due to non-tubercular mycobacteria), reactive hyperplasia/non-specific lymphadenopathy (usually with a viral episode) and lymphoma (look for other nodes and spleen).

Tubercular Pleural and pericardial effusion

Pleural effusion from TB is the second most common EPTB occurring 4-22% among children with tuberculosis^{31,32}. Pleural effusion is infrequent in children <6 years and rare before 2 years of age. The typical history of tuberculous pleurisy reveals intermittent fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Chest pain is localized to one side of the chest associated with stony dull percussion note on the same side with diminished breath sounds. Other signs include increased respiratory rate, respiratory distress and fullness of chest. Restricted movement of the affected chest and intercostal fullness are highly suggestive of a tuberculous pleural effusion. **The child with tuberculous pleural effusion is often not sick-looking in contrast to post-pneumonic pleural effusion.** In more than half (59%) of the cases, it is accompanied by a parenchymal disease in children²⁸.

Cardiac involvement in tuberculosis is rare (0.5 to 4%) and mainly affects the pericardium. Clinical features are due to the presence of the pericardial fluid and pericardial constriction. Pericardial effusion is the most common presenting feature of the cardiac involvement of tuberculosis. Presenting symptoms are often non-specific with low-grade fever, malaise and weight loss. Though chest pain is unusual in children, tightness of chest and respiratory distress can occur. On examination muffled heart sounds, pericardial friction rub, raised jugular venous pressure (JVP) and pulsus paradoxus may be present. The disease most commonly spreads to the pericardium by direct extension from the lungs and also from the mediastinal/ hilar or subcarinal lymph nodes, the sternum or the spine.

Miliary tuberculosis

It is a disseminated form of TB and a serious complication of primary TB occurring in young children. Children <3 years of age are at highest risk.³³ Miliary TB may manifest with low-grade fever, malaise, weight loss, and fatigue. A rapid onset of fever, cough and respiratory distress may also be observed.



Miliary TB

³¹ Mishra OP et al. Evaluation of polymerase chain reaction and adenosine deaminase assay for the diagnosis of tuberculous effusions in children. Arch Dis Child. 2006; 91(12): 985–989

³² Merino JM et al. Tuberculous pleural effusion in Children. CHEST 1999; 115:26–30

³³ Gurkan F et al. Miliary tuberculosis in children: A clinical review. 1998. Scand Infect Dis Journal. 30:359-62

Physical examination findings include enlarged lymph nodes, liver and spleen. Systemic signs include fever, increased respiratory rate, cyanosis, and respiratory distress. Other signs, which are subtle and should be carefully sought in the physical examination include papular, necrotic, or purpuric lesions on the skin or choroid tubercles in the retina of the eye. A miliary or millet-seed-like pattern, seen on CXR can be helpful in the recognition of disseminated TB manifesting in the lungs.

Tubercular Meningitis

The most severe manifestation of TB is TB meningitis (TBM) and commonly occurs in children <4 years.⁹ Presentation can be acute or chronic. More commonly, signs and symptoms occur slowly over weeks. Rapid progression tends to occur in infants and young children, where it is frequently fatal. Presenting clinical features include fever, headache, vomiting and malaise which evolve over 1-2 weeks to signs of meningeal irritation, cranial nerve palsies, convulsions, deterioration of mental status, hemiplegia, paraplegia, coma and death. Treatment in early stage results in full recovery and poor sequelae if treated in the later stages. Treatment should be started immediately in a child with signs of TBM with history of close contact. Most important diagnostic test in TBM is CSF study. Current recommendations also include Xpert MTB/RIF as an initial study of CSF for prompt recognition and treatment.⁶

Abdominal TB:

Abdominal TB presents with non-specific and mimics symptoms of different gastrointestinal (GI) disorder. Hence the diagnosis is frequently delayed by clinicians, more so in children. Abdominal TB can involve peritoneum (40%), GIT(13%) and both peritoneum and GIT (40%)³⁴. Tuberculosis can involve any part of the GIT from the mouth to the anus, the most common site of involvement being the ileo-caecal region. The spectrum of abdominal TB disease in children is different from adults, in whom adhesive peritoneal and lymph nodal involvement is more common than GI disease. Most children have constitutional symptoms of fever, abdominal pain, constipation, alternating constipation and diarrhea, weight loss, anorexia and malaise. It can present with pain and attacks of intestinal obstruction. Abdominal distention due to ascites is the presenting feature of TB peritonitis. Other clinical features depend upon the site, nature and extent of involvement e.g. hepatosplenomegaly, doughy abdominal mass, entero-cutaneous fistula. Children are often malnourished. Pulmonary involvement can be detected in a good number of cases with abdominal TB³⁵.

Osteoarticular TB: TB spine and TB arthritis

Osteoarticular TB can involve any bone and joint, but the spine is affected commonly (50% of all osteoarticular TB)³⁶. Other common areas of involvements are hip, knee and short and long bones of the hand and foot. In growing children, the disease can destroy areas responsible for their spinal growth (growth plates in vertebra). This may cause permanent deformity of spine or neurological complications if not treated properly.

TB bacteria do not directly affect bones and joints. The primary focus of infection is generally in the lungs or lymph nodes. It starts insidiously, usually as a monoarticular involvement. Child complaints of pain in the joint which is aggravated by movement and often wakes up at night- classic “night cries”. In later stages, all movements become more restricted due to erosion of articular cartilage.

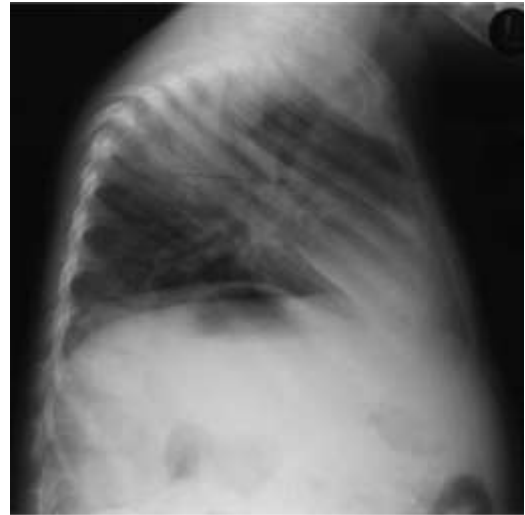
³⁴ Reto Valiente L et al. Abdominal tuberculosis in children and adolescent: A diagnostic challenge. Rev Gastroenterol Peru. 2015;35:318-322 [Abstract, article in Spanish]

³⁵ Lin YS et al. Abdominal tuberculosis in children: A diagnostic challenge. J Immunol Microbiol Infect. 2010 Jun;43(3):188-93

³⁶ Tuli SM, Srivastava TP, Verma BP et al. Tuberculosis of the spine. Acata Ortho Ped Scand 1967; 38:445-58

In *spinal TB*, common clinical features are back pain for few weeks, more at night with tenderness in the affected area. Angulation of the spine called “gibbus” deformity is a feature of Pott’s disease (severe kyphosis with destruction of the vertebral bodies). It may also present acutely as cord compression, leading to paraplegia or quadriplegia resulting in difficulty in walking and voiding of urine/stool. Cold abscess over the anterior or posterior triangle of the neck, femoral triangle or gluteal region may be seen according to involvement of region of vertebrae.

Any child with local pain and tenderness over the spine must be suspected of having spinal TB. **A rapid onset of a gibbus (‘hump back’) is almost always due to tuberculosis.**



Spinal TB

Congenital TB:

Despite TB being a common disease, congenital TB is rare. At birth, there may be no symptoms except LBW. Symptoms usually manifest at 2nd-3rd week of life. It should be suspected in neonates with nonspecific symptoms (fever, pallor, growth failure, ear discharge, respiratory distress, lethargy, irritability) born to a mother suffering from TB or, if any newborn suffering from persistent pneumonia or fever and hepatosplenomegaly and peripheral lymphadenopathy (seen in one third of cases). It usually occurs in two ways- (1) trans-placental transmission through umbilical vein causing primary complex in liver and (2) aspiration/swallowing of infected amniotic material during birth process or in utero.³⁷ The criteria for diagnosis proposed by Cantwell (1994) can be followed³⁸.

³⁷ Nemir RL, O’Hare D. Congenital Tuberculosis: review and Guidelines. Am Dis Child 1985;139:284-87.

³⁸ Cantwell MF, Shehah ZM, Costello Am, Sands L, Green WF etal. Brief report: Congenital Tuberculosis. N Eng J Med 1994; 330: 1051-54.

Danger signs requiring urgent hospital referral³⁹

Although TB is usually a chronic disease, there are certain danger signs that require urgent hospital referral.

Box 4: Danger signs requiring urgent referral

- ✓ Severe respiratory distress (TB pneumonia with/without bacterial super infection, Pleural effusion)
- ✓ Severe wheezing not responding to bronchodilators (signs of severe airway compression)
- ✓ Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis)
- ✓ Acutely ill with hepatosplenomegaly and ascites (signs of disseminated TB)
- ✓ Breathlessness and peripheral edema (signs of pericardial effusion)
- ✓ Acute angulation (bending) of the spine with/without paraplegia (sign of TB spine – “gibbus”)
- ✓ Other co-morbidities e.g. severe anemia, severe malnutrition

GROWTH ASSESSMENT

Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation programme, is a good indicator of chronic disease in children, of which TB may be the cause. SAM is a recognised risk factor of progression of TB disease in children.

Diagnostic Tests

In children except adolescent, demonstration of TB bacilli in sputum smear or culture is difficult as children (<6 years) usually cannot expectorate sputum and the disease itself is usually paucibacillary.

Mantoux test (MT)

Mantoux Test (MT) or Tuberculin Skin Test (TST) measures the delayed type hypersensitivity response to tuberculin Purified Protein Derivative (PPD) injected on the volar aspect of forearm.

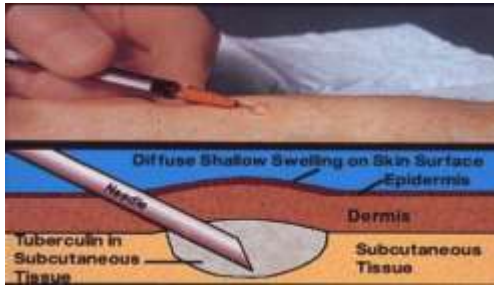
A positive MT does not indicate active disease (TB). It only indicates infection with *M. tuberculosis*. However, the MT can also be used in conjunction with other diagnostic tests. Health-care workers must be trained in performing and reading a MT.

MT is carried out by injecting 5 TU of tuberculin PPD-S into the skin (intra-dermal) on the inner aspect of the left forearm.

The MT should be regarded as positive when the induration is:

1. ≥ 10 mm diameter
2. ≥ 5 mm diameter in children with severe PEM, HIV infection and immunosuppression.

³⁹ Moore DP, Schaaf HS, Marais BJ. Childhood Tuberculosis Guidelines of the South African Society of Pediatric Infectious Disease. South Afr J Epidemiol Infect 2009;24(3):57-68



It is to be noted that interpretation of MT should be irrespective of previous BCG vaccination. It should also to be noted that, a **negative MT does not exclude TB infection or disease.**

Box 5: False negative MT may be caused by

- ❑ Severe malnutrition or other immune suppressive conditions:
 - ⊕ Measles in last 3 months
 - ⊕ Whooping cough
 - ⊕ HIV infection
 - ⊕ Drugs like steroids
- ❑ Disseminated (Miliary) TB and/or TB meningitis (TBM)
- ❑ Very recent TB exposure (<3 months)
- ❑ Administrative causes: poor cold chain, wrong intra-cutaneous injection method etc.

CHEST X-RAY (CXR)

CXR is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a health-care provider trained in reading X-ray in children. A lateral film is helpful to evaluate hilar lymphadenopathy. A CXR should always be done in all forms of TB.

Chest X-ray changes are often non-specific. CXR changes that are suggestive of TB are summarised below:

Commonest radiological pattern of TB in children

- ✓ Increased density in the hilar region due to enlarged hilar lymph nodes and/or a broad mediastinum due to enlarged mediastinal lymph nodes.
- ✓ Persistent opacity in the lung.

Less common radiological signs

- ✓ Compression of the airways due to enlarged lymph nodes. Partial occlusion may lead to **segmental or lobar hyperinflation**. Complete airway occlusion may cause **collapse of a lung segment or lobe**.
- ✓ Miliary pattern of opacification (highly suggestive in HIV-negative children)
- ✓ Pleural effusion
- ✓ Pericardial effusion

Adolescent patients with TB

- ✓ Pleural effusion
- ✓ Apical infiltrates with cavity formation being the most common form of presentation

- ✓ Cavity formation

Persistent opacification which does not improve after a course of antibiotics should be investigated for TB.

Radiological features requiring urgent hospital referral

- ✓ Miliary TB: Widespread fine millet-sized (1-2 mm) lesions indicative of disseminated TB
- ✓ Severe airway obstruction
- ✓ Severe parenchymal involvement
- ✓ Acute angulation of the spine (TB spine, gibbus)
- ✓ Pleural effusion with respiratory distress

Microbiological confirmation

Microbiological confirmation is done by smear microscopy, culture, Xpert-MTB/RIF from appropriate clinical samples to demonstrate AFB.

It is always advisable to confirm diagnosis of TB in a child using whatever specimen and laboratory facilities available. Appropriate clinical samples include sputum, gastric aspirate and certain other materials (e.g. CSF, lymph node FNAC/biopsy or any other biopsy material). Samples should be collected properly and sent to the laboratory.

Bacteriological confirmation is especially important for children who have:

- ✓ Suspected drug-resistant TB
- ✓ Severe immunosuppression including HIV infection
- ✓ Complicated or severe disease
- ✓ TBM
- ✓ Uncertain diagnosis

Smear microscopy

Common ways of obtaining samples for **smear microscopy** include the followings:

- a) Expectoration
- b) Sputum induction
- c) Gastric aspiration
- d) Fine needle aspiration cytology (FNAC)

These methods are narrated in the annexure.

Xpert MTB/RIF:

WHO approved technique, Xpert MTB/RIF is a cartridge-based, automated diagnostic test that can identify *Mycobacterium tuberculosis* (MTB) DNA and resistance to rifampicin (RIF) by nucleic acid amplification technique (NAAT). It can provide result within 2 hours. It purifies and concentrates *Mycobacterium tuberculosis bacilli* from sputum samples, isolates genomic material and subsequently amplifies the genomic DNA by PCR. This machine can also use other samples e.g. gastric aspirates/lavage, CSF, lymph node and other tissues. It may be used rather than conventional microscopy and culture as the initial test in children suspected of having TB. WHO recommends it should be used in preference to smear and culture as the initial test in suspected TBM. In suspected MDR-TB, WHO prefers it over conventional microscopy and culture as the initial test.

Culture

Culture is the gold standard for diagnosis of TB. Collection of specimens for culture should be considered where facilities are available. TB culture is of particular value in complicated cases or when there is a concern regarding drug resistance. Probability of obtaining a positive TB culture improves when more than one sample is taken. Try to obtain at least 2 samples. Isolation of organism from invasive samples (e.g. gastric aspirate, induced sputum, BAL) should also be sent for culture if facilities are available nearby.

***M. tuberculosis* culture centres in Nepal-**

1. National Tuberculosis Centre, Thimi, Bhaktapur, Phone: 977-1- 6635986
2. GENETUP, Kalimati, Phone: 977- 1- 4270483
3. Regional TB Center, Pokhara

Investigations relevant for suspected EPTB

In most of the cases, TB will be suspected from the clinical picture and confirmed by histopathology or other special investigations. The table below shows the investigations that are used to diagnose the common forms of EPTB.

Table 4: EPTB sites and diagnostic approach for common forms in children

| Site | Practical approach to diagnosis |
|---------------------------------------|---|
| Peripheral lymph nodes | Lymph node FNAC or Biopsy |
| Pleural effusion | CXR; Pleural tap to see cell count, protein, glucose, , Z-N stain and culture; Pleural biopsy and Histopathology. |
| Pericardial TB | CXR; Echocardiography and Pericardial tap; Pericardial biopsy and Histopathology |
| TB meningitis | CSF study (and CT scan if available) |
| Tuberculoma of Brain | CT scan/MRI |
| Abdominal TB | Abdominal Ultrasound; Ascitic fluid study |
| TB arthritis or Bone TB | X-ray; Joint fluid study; Synovial biopsy |
| <i>All forms require a MT and CXR</i> | |

Pleural Effusion

- If chest X-ray is suggestive of pleural effusion, pleural aspiration should always be performed for cell count, biochemical and smear examination by Z-N 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).
 - o Adenosine Deaminase (ADA) levels over 60 IU/L⁴⁰
- Pleural biopsy may be performed, where available, particularly when the fluid aspirate findings are inconclusive.

TBM

- Lumbar puncture
 - o Typically, CSF is clear to opalescent, usually does not show very high cell count (under 500 cells/mm³) with lymphocytosis. Biochemical investigations reveal increased proteins and mild reduction in glucose.
 - o CSF ADA is high (more than 10 U/L)⁴⁰
 - o CSF Xpert/RIF is done.
- Neuroimaging (CT head): basal meningeal enhancement; hydrocephalus with or without peri-ventricular ooze; tuberculoma; or infarcts may be seen in different areas, especially in basal ganglia.

TB abdomen

- The ascitic fluid is an exudate, typically showing lymphocytic predominant cellular response with high proteins (>3g/dL).
- USG abdomen: echogenic thickened mesentery with lymph nodes > 15mm in size; dilated and matted bowel loops; thickened omentum, and ascites. None of these findings, however, is specific to TB alone.

TB Pericardial effusion

- Pericardial fluid is straw-colored or sometimes blood tinged, lymphocytic exudate (proteins are increased and there is predominance of lymphocytes).
- ADA > 40 U/L

HIV Testing

Most HIV infections in children are passed from mother to child. Other associated risk factors are blood transfusions using infected blood or injections, injecting drug use and needle sharing among young people. Although sexual transmission is not a main cause of HIV/AIDS among children but may also become infected through sexual abuse or rape.

HIV testing is advised in all TB cases.

⁴⁰ Kumar A, Gupta D, Nagaraja SB, Singh V, Sethi GR, Prasad J. Updated National Guideline for Pediatric Tuberculosis in India, 2012. *Indian Pediatr* 2013;50: 301-306

Other tests

A complete blood count may be indicated in seriously ill patient but is not useful in diagnosis of TB. **ESR is a non specific test of inflammation and has no role in confirming or excluding TB in children.** Baseline liver function tests are indicated if the TB is severe or there is underlying liver disease or history of intake of hepatotoxic drugs.

Newer tests like Novel T-cell or **interferon-gamma release assays (IGRAs)** provide essentially the same information as MT and offer little additional diagnostic benefit. This should not replace routine MT test. IGRAs should not be used for the diagnosis of TB disease.

WHO does not recommend commercial serodiagnostic tests (anti-TB immunoglobulin test) for the diagnosis of TB⁴¹.

Other specialized tests e.g. CT scan and bronchoscopy are not recommended for the routine diagnosis of TB in children. These tests can be performed in higher centers under specialist's supervision.

Establishing diagnosis of TB in children

It can be a challenge to establish a confirmed TB diagnosis in children. However it is not very difficult to establish a fairly accurate presumptive diagnosis, even in the absence of sophisticated tests.

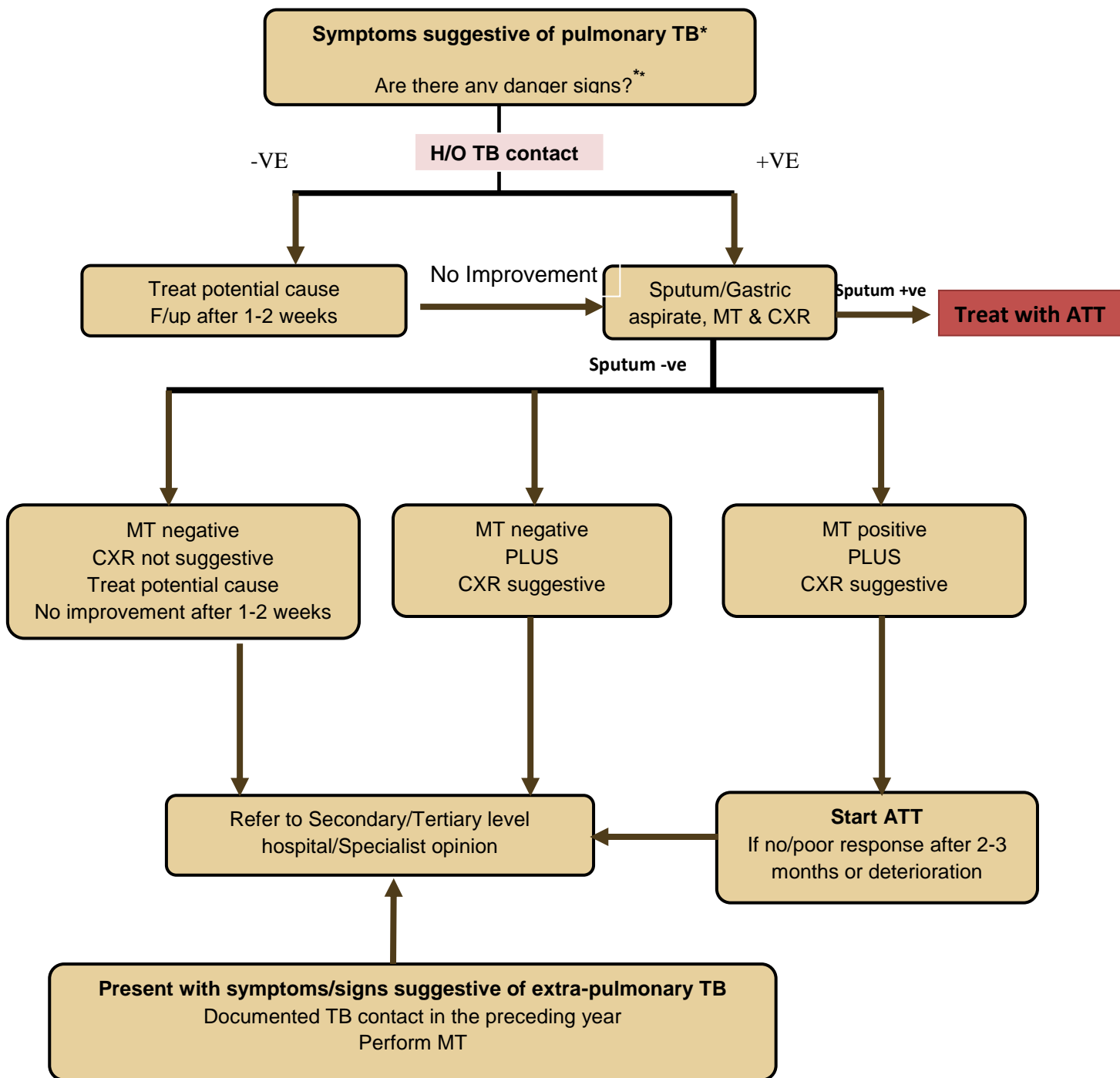
Box 6: The presence of **3 or more** following features strongly suggests a diagnosis of TB:

- ✓ Symptom criteria suggestive of TB
- ✓ History of recent close contact (within the past 12 months)
- ✓ Physical signs highly suggestive of TB
- ✓ Positive MT
- ✓ Chest X-ray suggestive of TB

NB. If a child has ≤ 2 features, expert opinion from a specialist should be sought.

⁴¹ Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5)

FIG 3: ALGORITHM FOR THE DIAGNOSIS OF TB IN CHILDREN



* See Box 3 for suggestive symptoms

** See Box 4 for the danger signs requiring urgent referral

*** Smear microscopy or Xpert MTB/RIF or MTB Culture.

Note: Xpert MTB/RIF should be prioritize than microscopy.

Chapter 4: Treatment of Tuberculosis in Children

With the availability of dispersible child-friendly fixed-dose formulations, treatment of TB in children has become much easier for physicians & care providers.

Children usually have paucibacillary pulmonary disease as cavitation is rare in the young with early TB. In contrast to adults, children develop EPTB more often. Severe and disseminated TB (e.g. TBM and miliary TB) occur more frequently in children, especially among younger age group (<3 years). All children who have been diagnosed with TB disease must receive directly observed treatment- short course (DOTS) with the appropriate regimen and must be recorded in the TB treatment register with NTP. Unless an alternative diagnosis has been confirmed, once TB treatment is started, it should be continued until completion. Treatment outcomes in children are generally good and well tolerated, even in young and immune compromised children who are at higher risk of disease progression and disseminated disease.

Objectives of anti-TB treatment

Cure a patient who has TB with optimal use of drugs by:

1. killing the causative agent, *Mycobacterium tuberculosis*;
2. preventing complications of disease progression, reducing morbidity and mortality
3. preventing relapse of TB (by eliminating the dormant bacilli)
4. reducing transmission by reducing reservoir
5. preventing the development of drug resistance
6. reducing adverse drug reactions

Anti-TB Drugs and TB bacilli

TB bacilli spread through droplets of infected persons through coughing, sneezing, talking and even during singing. As the organism not only causes morbidity to patient but also infect others easily, rapid reduction in the organism load is important to limit the disease progression, tissue damage and systemic effects with clinical improvement, transmission termination and protection against random development of drug resistance. This is achieved by bactericidal drugs that kill actively metabolizing organisms. However, there are multiple sub-populations of organisms, some extra- and others intra-cellular, with highly variable rates of metabolism requiring combination of drugs to target these specific bacillary populations. Permanent cure requires effective eradication of all organisms, including hypometabolic bacilli, at effective drug concentrations for a prolonged duration of therapy (at least 6 months).

Table 5: Anti-TB Drugs- Mode of action and activity over bacterial population

| Drug | Anti-bacterial action | Mycobacteria sub-population | Points to note |
|---------------------|---|--|--|
| INH | Bactericidal | Rapidly metabolizing extra-cellular bacilli | Most potent. Kills vast majority within first few days; good CSF levels. |
| Rifampicin | Bactericidal | Intracellular organism | Effective killer; limited penetration of blood-brain-barrier/CSF levels. |
| Ethambutol | Bacteriostatic/ bactericidal in higher concentration | Actively growing bacilli | Reduces RMP resistance in high bacillary load; limited penetration of bbb, CSF levels. |
| Pyrazinamide | Bactericidal | Extracellular bacilli within acidic centers of caseating granuloma | Effective against dormant intracellular bacteria; good CSF levels. |
| Streptomycin | Bactericidal | Extracellular bacilli | Bactericidal, particularly in tuberculous cavities |

Treatment: Regimens choice and rationale

The main variables that influence the success of chemotherapy are drug resistance, the bacillary load and its anatomical distribution. In Nepal resistance pattern in anti-TB drugs is rapidly changing⁴². In 2011/12 national survey in Nepal mono-resistance to INH was found was 2.2% and 4.2% among new and previously treated cases respectively. During that survey no mono resistance to rifampicin was found.

Table 6: Anti-TB Drug Resistance in Nepal^{37,38}

| Surveillance/Study Year | Initial MDR | Acquired MDR |
|-------------------------|-------------|--------------|
| 1999 | 3.6% | 12.0% |
| 2001/02 | 1.3% | 20.0% |
| 2006/07 | 2.9% | 11.7% |
| 2011/12 | 2.2% | 15.4% |
| 2013 | 7.1% | 19.4% |

Drug penetration into the anatomical sites involved is good and the success of the 2-month intensive phase and 4-month continuation phase is well established.

Sputum smear-positive disease implies a high bacillary load and an increased risk for random drug resistance. Once the bacillary load is sufficiently reduced, daily therapy with INH and RMP during the 4-month continuation phase is sufficient to ensure organism eradication in most of the “new” cases.

It is essential to consider the cerebrospinal fluid (CSF) penetration of drugs used in the treatment of TB meningitis. INH and PZA easily penetrate the CSF well, while RMP only achieve therapeutic levels in the presence of meningeal inflammation. **EMB penetrates the CSF in the presence of meningeal**

⁴² Surveillance on Anti Tuberculosis Drug Resistance among TB Patients in Nepal 2011/12. July 2012. National Tuberculosis Control Program, Nepal. NATA and GENETUP

inflammation. CSF penetration of streptomycin(SM) is unpredictable⁴³ which explains why EMB replaces SM in the treatment of TBM⁴⁴. Oral availability of EMB also assures better compliance and completion of treatment. Moreover the use of injections in remote and mountain region poses a logistic challenge requiring expertise and raises question of safety.

Recommended treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistant is low, as most of the organisms have already been eliminated.

The regimens are:

1. “New” cases: 2 months 4-drug therapy for intensive phase and 4 months with 2-drug therapy for continuation phase.
2. For relapse, treatment after default and failure to respond cases: 3 months intensive phase with 4 drugs and 5 months continuation therapy with 3 drugs will be sufficient to eradicate possible resistant strains.

Children more than 8 years of age are routinely treated as with adolescents and adults. Alternatively, treatment of children 25 kg and over will also follow the recommended regimen for adults.

Regular weight-based dose adjustment is important, particularly in young and/or malnourished children during the intensive phase of treatment, when weight gain may be pronounced.

Table 7: RECOMMENDED DAILY DOAGES OF FIRST-LINE ANTI-TB DRUGS FOR CHILDREN⁴⁵

| Drug | Daily dose and range (mg/kg body weight) | |
|------------------|--|------------------|
| Isoniazid (H) | 10 (7-15) | [maximum 300mg] |
| Rifampicin (R) | 15 (10-20) | [maximum 600mg] |
| Pyrazinamide (Z) | 35 (30-40) | [maximum 2000mg] |
| Ethambutol (E) | 20 (15-25) | [maximum 1200mg] |

NB: Higher dosage (mg/kg) is required for young children to achieve effective bactericidal activity, as these age group influences drug metabolism. Moreover, systematic review also shows an excellent safety profile of revised dosages and is not associated with an increased risk of toxicity (no increased risk of drug-related hepatotoxicity due to INH or PZA, or of optic neuritis due to ethambutol).

Fixed-dose-combinations (FDCs) for children:

Child-friendly formulations are ideal for use to ensure adequate therapeutic blood levels and compliance to treatment regimen. Currently available dispersible formulations contain 60 mg of Rifampicin, 30 mg of

⁴³ Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. *Pediatr Drugs* 2013;15(2): 93-117

⁴⁴ Martin Lasso B. Tubercular Meningitis:tips for diagnosis and proposals for treatment. *Rev Chilena Infectol* 2011;28(3):238-47

⁴⁵ World Health Organization. Rapid Advice: Treatment of tuberculosis in children. Geneva: WHO. 2010 [http://apps.who.int/iris/bitstream/10665/44444/1/9789241500449_eng.pdf]

INH and 150 mg of Pyrazinamide per tablet. There is a need to break these tablets based on weight bands (see Table 8). This poses uncertainty in reaching the desired levels and is also cumbersome to use. The WHO, along with the Global Alliance for TB Drug Development, has taken the initiative for a new FDC. It contains 75 mg of rifampicin, 50 mg of INH and 150 mg of pyrazinamide per tablet⁴⁶, which is child-friendly and in line with the higher WHO recommended dosage from the Rapid Advice 2010. The weight band table below is provided for ease of instruction.

Table 8: Formulations available:

| FDC tablet | Current FDC | Upcoming FDC* |
|------------|----------------|----------------|
| 3 | R60, H30, Z150 | R75, H50, Z150 |
| 2 | R60, H30 | R75, H50 |

*In 3 flavors- mango, strawberry, raspberry

Table 9: Weight band table with the currently available FDC

| Body weight Kg | Intensive Phase (2 months) Number of Tablets RHZ* 60,30,150 plus Ethambutol | Continuation phase (4 months) Number of Tablet RH 60,30 |
|-------------------|--|---|
| 2-2.9 | ½ | ½ |
| 3-5.9 | 1 | 1 |
| 6-8.9 | 1½ | 1½ |
| 9-11.9 | 2 | 2 |
| 12-14.9 | 2½ | 2½ |
| 15-19.9 | 3 | 3 |
| 20-24.9 | 4 | 4 |
| 25-29.9 | 5 | 5 |
| 30-35.9 | 6 | 6 |

*R – Rifampicin, H – Isoniazid; Z – Pyrazinamide

Table 10: Example of Weight band table for using “new”/upcoming FDCs

| Weight Bands (Kg) | Number of Tablets | | |
|----------------------|-----------------------------|--------|--------------------|
| | Intensive Phase | | Continuation Phase |
| | RHZ (mg) plus Ethambutol | E (mg) | RH (mg) |

⁴⁶ Scott, CC. TB Alliance: Update on new pediatric FDCs. 5th Conference of The Union Asia-Pacific Region. Sydney, Australia. August 31, 2015.

| | RHZ 75/50/150 | 100 per tablet | 75/50 per tablet |
|--------------|---|-----------------------|-------------------------|
| 4-7 | 1 | 1 | 1 |
| 8-11 | 2 | 2 | 2 |
| 12-15 | 3 | 3 | 3 |
| 16-24 | 4 | 4 | 4 |
| 25+ | Go to adult dosages and preparations | | |

Note: To transition from current FDC to upcoming new FDC NTC will circulate formal letter of initiation. So, request all reader to wait for NTC letter before initiating new FDC for childhood TB.

Table 11: Treatment Regimens for Children in Each TB Diagnostic Category

| Patient | TB cases | Regimen | |
|---|---|---------------------|--------------------|
| | | Intensive phase | Continuation phase |
| “New” cases | <ul style="list-style-type: none"> New Pulmonary TB cases (PBC+PCD) New EP –TB cases (BC+CD) | 2(HRZE) | 4(HR) |
| | Treatment of severe forms of complicated EP TB cases: <ul style="list-style-type: none"> CNS TB TB Pericarditis Miliary TB Musculo-skeletal TB Other severe forms of EP TB | 2(HRZE) | 10(HRE) |
| Retreatment cases (For all who requires retreatment for TB DST needs to be performed) | <ul style="list-style-type: none"> If DST cannot be performed | 2(HRZES) + 1 (HRZE) | 5 (HRE) |
| | In case of resistance follow DR diagnostics and treatment protocol | | |
| Drugs resistant cases | Follow DR management as adult | | |
| *Use of Streptomycin: <ul style="list-style-type: none"> Streptomycin can still be used when: <ul style="list-style-type: none"> Other drugs have to be replaced because of toxicity of FLD NB: Where treatment failure is in doubt, DR-TB should be considered and worked upon. | | | |

*For children with osteoarticular tuberculosis, treatment may be extended up above 12 months based on clinical judgment.

Pyridoxine

Supplemental pyridoxine (5–10 mg/day) is recommended in HIV-positive or malnourished children being treated for TB.⁴⁷ Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on ART.

Corticosteroid

Corticosteroids may be used for the management of some complicated forms of TB.

BOX 7: Indications for oral steroids in children with TB

- ⊕ TB meningitis
- ⊕ TB pericarditis (reduces the risk of restrictive pericarditis)

In cases of advanced TB meningitis, corticosteroids have been shown to improve survival and decrease morbidity, and thus are recommended in all cases of TB meningitis. As rifampicin is a powerful inducer of prednisolone metabolism hence higher dose of prednisolone is required.⁴⁸ Sudden withdrawal can cause serious side effects such as adrenal crisis. The following dosage schedule is recommended:

Prednisolone- 2-4 mg /kg/day (max. 60mg) for 4 weeks, then tapered over 1-2 weeks

Directly Observed Treatment-Short Course (DOTS)

DOT is a very important component of internationally recommended policy package for TB control-DOTS strategy. DOTS means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures that a patient takes right anti-TB drugs, in the right doses, at the right interval and for the right period of time. Nepal has initiated DOTS in 1994-96 and “DOTS All Over” has been achieved in 2001. Current DOTS success of NTP is 91%.

Treatment of TB should always be directly observed and drugs are used as a fixed-dose combinations (FDC). Ethambutol needs to be added additionally with the FDC when indicated. Drug dosages, depending on the body weight of the child, are given daily (7 days per week). **The dose should be adjusted as the weight changes during the course of treatment.** Children should therefore be weighed at least after 1, 2, 3 (or at a lesser interval when necessary) and 6 months of therapy. Their weight should be documented on the TB treatment card. If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment) they should be referred for urgent assessment by a competent physician.

Parents and caregivers should be counseled about TB and the importance of treatment adherence to ensure a good outcome.

Referral

The following children should be referred for expert opinion:

- ✓ All children with severe forms of TB (TB meningitis, cavitory PTB, miliary TB, TB peritonitis, spinal or osteoarticular TB)

⁴⁷ *Guidance for national tuberculosis programmes on the management of tuberculosis in children.* Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).

⁴⁸ Kyriazopoulou V, Parparousi O, Vagenakis AG. Rifampicin-induced adrenal crisis in Addisonian patients receiving corticosteroid replacement therapy. *J Clin Endocrinol Metab.* 1984 Dec;59(6):1204-6

- ✓ Children with presumptive MDR-TB, XDR-TB (or in contact with MDR-TB, XDR-TB case and not responding to first-line therapy)
- ✓ If there is poor response to therapy (no weight gain, persistent symptoms after 2 months of treatment)

Follow up of children during treatment

Children should be followed up on a monthly basis for the first 3 months. Children responding to treatment should experience improvement or resolution of symptoms and gain weight within 2-3 months. It is important to accurately document the child's weight on the growth chart at each of the follow-up visits and to adjust the drug dosages accordingly. Children with sputum smear-positive TB should be followed as adult patients with repeat sputum examinations done after 2, 5 and at 6 months of treatment.

The chest X-ray is a poor indicator of treatment response and lymph nodes may initially enlarge as a result of an improvement in the child's immune response. Routine follow-up chest X-rays are not required in children. Follow-up X-rays are only recommended in children with persistent symptoms or poor response to treatment, or if new symptoms develop on treatment.

Causes of deterioration during TB treatment

Children may sometimes deteriorate or experience a worsening of symptoms despite adequate therapy. The most important questions to answer are:

- ✓ Is the drug dosage correct?
- ✓ Is the child taking the drugs as prescribed (good adherence)?
- ✓ Is the child HIV-infected?
- ✓ Is the child severely malnourished?
- ✓ Is there a reason to suspect drug-resistant TB (the index case has drug resistant TB or is a re-treatment case or is also not responding to therapy)?
- ✓ Is there another reason for the child's illness other than TB?

Severely malnourished children, children following nutritional rehabilitation or HIV-infected children on highly active antiretroviral therapy may sometimes develop a temporary worsening of symptoms due to the recovery of their immune responses. This is referred to as immune reconstitution inflammatory syndrome (IRIS). Any child with severe persistent symptoms should be referred for assessment.

Drug related adverse events

Table 12: Toxicities related to dose and regimens of TB drugs

| Anti-TB Drugs | Mode & mechanism of action | Main toxicities | Single daily dose mg/kg (range); [maximum dose, mg] |
|-----------------------|----------------------------|---------------------------------------|---|
| 1st line Drugs | | | |
| Isoniazid | Bactericidal | Hepatitis* Peripheral neuropathy** | 10 (7-15) [300] |
| Rifampicin | Bactericidal | Hepatitis* Orange discoloration of | 15 (10-20) [600] |

| | | | |
|--------------|----------------|--|----------------------|
| | | secretions Drug interactions | |
| Pyrazinamide | Sterilizing | Hepatitis* Arthralgia | 35 (30-40) [2000] |
| Ethambutol | Bacteriostatic | Visual disturbance (acuity, color vision) | 20 (15-25) [1200] |

2nd line Drugs

| | | | |
|---|----------------|--|---|
| Aminoglycosides Kanamycin Amikacin Streptomycin | Bactericidal | Ototoxic & nephrotoxic | 15-30 [1000] 12-18 [1000] |
| Fluoroquinolones Ofloxacin Levofloxacin Moxifloxacin | Bactericidal | Arthralgia (rare) Insomnia, confusion | 15-20 [800] 7.5-10 [750] 7.5-10 [400] |
| Ethionamide | Bactericidal | Vomiting Hypothyroidism Hepatitis* | 15-20 [1000] |
| Polypeptides Capreomycin | Bacteriostatic | Ototoxic & nephrotoxic | 15-30 [1000] |
| Cycloserine derivative Terizidone | Bacteriostatic | Psychosis, depression, convulsions | 10-20 [1000] |
| Para-aminosalicylic acid (PAS) | Bacteriostatic | Diarrhea & vomiting Hypothyroidism | 150-200 [12gm] Divided in 2-3 doses/day |

Note:

Hypersensitivity reactions and drug rashes may occur with any drug.

WHO endorsed new recommendations for dosing of first-line TB drugs in children.

Streptomycin is rarely used, since there is no indication for using the retreatment regimen in children.

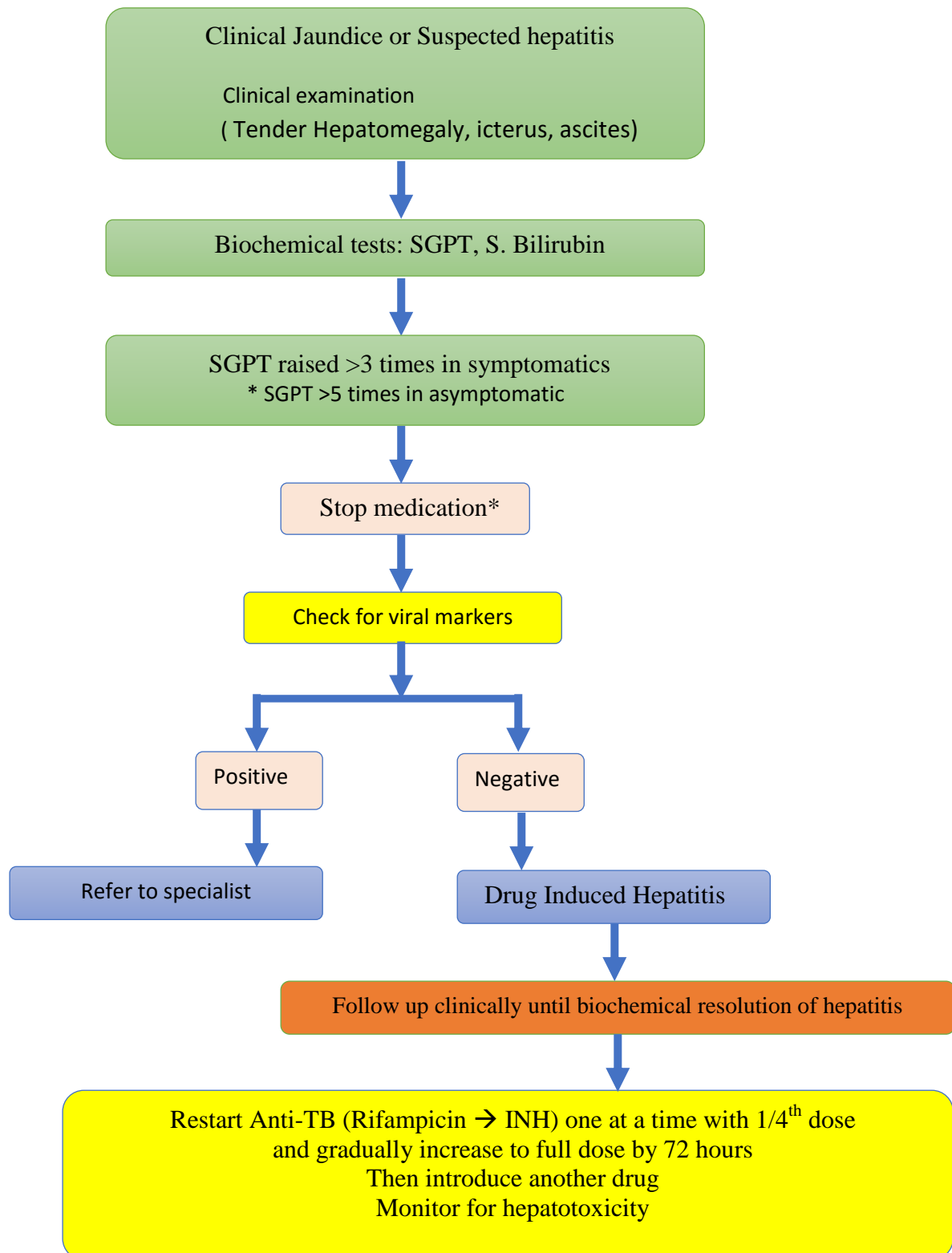
Ciprofloxacin has the weakest activity and is no longer indicated for TB treatment.

Adverse events caused by TB drugs are much uncommon in children than in adults.⁴⁹

Adverse events occur in the following order PZA>INH>RMP. It is not required to monitor liver enzyme routinely, as asymptomatic mild elevation of serum liver enzymes (<5 times normal values) is common and is not an indication to stop TB treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to further investigation (urgent referral).

⁴⁹ Alexis R. Frydenberg and Stephen M. Graham. Toxicity of first-line drugs for treatment of tuberculosis in children: review. Trop Med Int Health 2009; Vol14(11):1329-1337

Fig 4: Management of Drug Induced Hepatitis



*In TBM, Disseminated TB and military TB: After withdrawal of the suspected offending drugs, continue medication with streptomycin, ethambutol and fluoroquinolones till restarting first line drugs after resolution of drug induced hepatitis.

However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to further investigation (urgent referral). Perform serum liver enzyme levels and stop all potentially hepatotoxic drugs. Children should be evaluated for other causes of hepatitis (e.g. Hepatitis A,B,C,E). No attempt should be made to reintroduce these drugs until the liver functions have normalized. When the liver function becomes normal, previous anti-TB drugs should be restarted one by one with full dose in an interval of 48 to 72 hours and started with less hepatotoxic drugs such as rifampicin then isoniazid, but not pyrazinamide. An expert should be involved in the further management of these cases.

**INH may cause peripheral neuropathy (symptomatic pyridoxine deficiency) particularly in severely malnourished, HIV-infected children on HAART, chronic liver disease and renal failure. Supplemental pyridoxine is recommended in older children and multi-vitamin syrup in infants.

Retreatment

Failure of treatment in children is not expected but its cause has to be sought for better care. The most likely cause for treatment failure or relapse within 6 months of treatment completion is non-adherence to treatment instructions. In children when anti-TB treatment fails or a relapse occurs, every effort should be made to find the most likely cause for the failure or relapse. There are multiple (psychosocial, economic and practical) reasons why people are non-adherent.

Mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases before starting treatment, depending on what is known about the risk of MDR-TB in this group of patients. If an adult source case with drug-resistant TB is identified, the child should be treated according to the drug susceptibility pattern of the source case's strain, in case isolate from the child is not available.

Management of drug-resistant cases is discussed further in the following section.

Chapter 5: Drug Resistant TB (DR-TB) in Children

Introduction

According to the fifth National Drug Resistance Survey (2011-2012), MDR-TB in Nepal is estimated at 2.2% and 15.4% among new and previously treated TB cases respectively³⁷. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic. Children with paucibacillary TB are unlikely to acquire drug resistance and contribute little to the creation and/or transmission of drug-resistant strains. Children with DR-TB provide an accurate estimation of transmitted (primary) drug resistance within communities. MDR-TB in children is mainly newly transmitted drug resistance. Contact tracing and follow-up of children exposed to MDR/XDR-TB should receive high priority.

Types of Drug Resistant TB in children

1. Mono Resistance

TB in a patient whose infecting isolates of *M. tuberculosis* are resistant in vitro to one of the first line anti-TB drugs except rifampicin. Rifampicin mono resistance is categorized separately.

Table 13: Pattern of resistance to 1st line Anti-TB drug In Nepal (2011)³⁷

| Drug Resistance pattern | New (%) | | Previously treated (%) | | Total (%) | |
|--------------------------------|----------|--|------------------------|--|-----------|--|
| | DRS 2011 | | DRS 2011 | | DRS 2011 | |
| Mono-resistance to INH | 2.2 | | 6.1 | | 2.9 | |
| Any resistance to RIF | 2.2 | | 15.4 | | 4.7 | |
| Any resistance to Ethambutol | 1.6 | | 6.2 | | 2.5 | |
| Any resistance to Streptomycin | 6.1 | | 14.1 | | 7.6 | |

2. Poly Resistance

TB in a patient whose infecting isolates of *M. tuberculosis* are resistant in vitro to more than one of the first line anti-TB drugs, other than to both isoniazid and rifampicin.

3. Multi Drug resistance (MDR)

TB in a patient, whose infecting isolates are resistant in vitro to both isoniazid and rifampicin with or without resistance to other first-line drugs.

4. Pre-XDR⁵⁰

TB bacilli are resistant to isoniazid and rifampicin and with either a fluoroquinolone or second line injectable agent but not both (amikacin, capreomycin or kanamycin).

5. Extensive Drug Resistance (XDR) TB⁵¹

TB in a patient, whose infecting isolates are resistant in vitro to both rifampicin and isoniazid along with resistance to any quinolone and one of the the second-line injectable anti-TB drugs.

⁵⁰ Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, KIM T-H et al. Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis. *AJRCCM* 2010;182(1):113-119

⁵¹ World Health Organization. Extensively drug resistant tuberculosis (XDR-TB): Recommendations for prevention and control. *Wkly Epidemiol Rec* 2006;81:430-432
[http://www.searo.who.int/bangladesh/publications/drs_2011_1.pdf]

6. Rifampicin Resistance (RR)

Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs except isoniazid.

Is drug resistant TB infectious?

Drug-resistant TB is as infectious as drug-susceptible TB. Children usually become infected from adult or adolescent MDR-TB contact. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic.

How to recognize a presumptive drug-resistant patient?

Drug-resistant TB is a laboratory diagnosis, but should be presumed if any of the following features are present in a child:

- **Features in a child suggestive of having drug resistant TB-**
 - ❑ Contact with a known case of MDR-TB
 - ❑ Child not responding to adhered standard TB treatment
 - ❑ Child with TB recurrence after completing TB treatment

- **Features in the index case suggestive of drug-resistant TB-**
 - ❑ Index case remaining smear-positive after 3 months of treatment
 - ❑ History of previous TB treatment interruption or recurrence after completion of TB treatment

Case-Finding Strategies^{52,53}

The following groups should be targeted as risk groups for culture and DST:

High Risk:

- ❑ Failure: remains SS+ve at 5 months or SS-ve becomes SS+ve at 2 months
- ❑ Close contact of a MDR-TB patient with symptoms

Medium Risk:

- ❑ Non-converters (remain SS+ve at month 2-3)
- ❑ All relapses
- ❑ treatment after lost to follow-up
- ❑ Any smear negative or EPTB patient doing clinically poorly on TB Therapy

Low Risk:

- ❑ All TB/HIV patient at the start of therapy

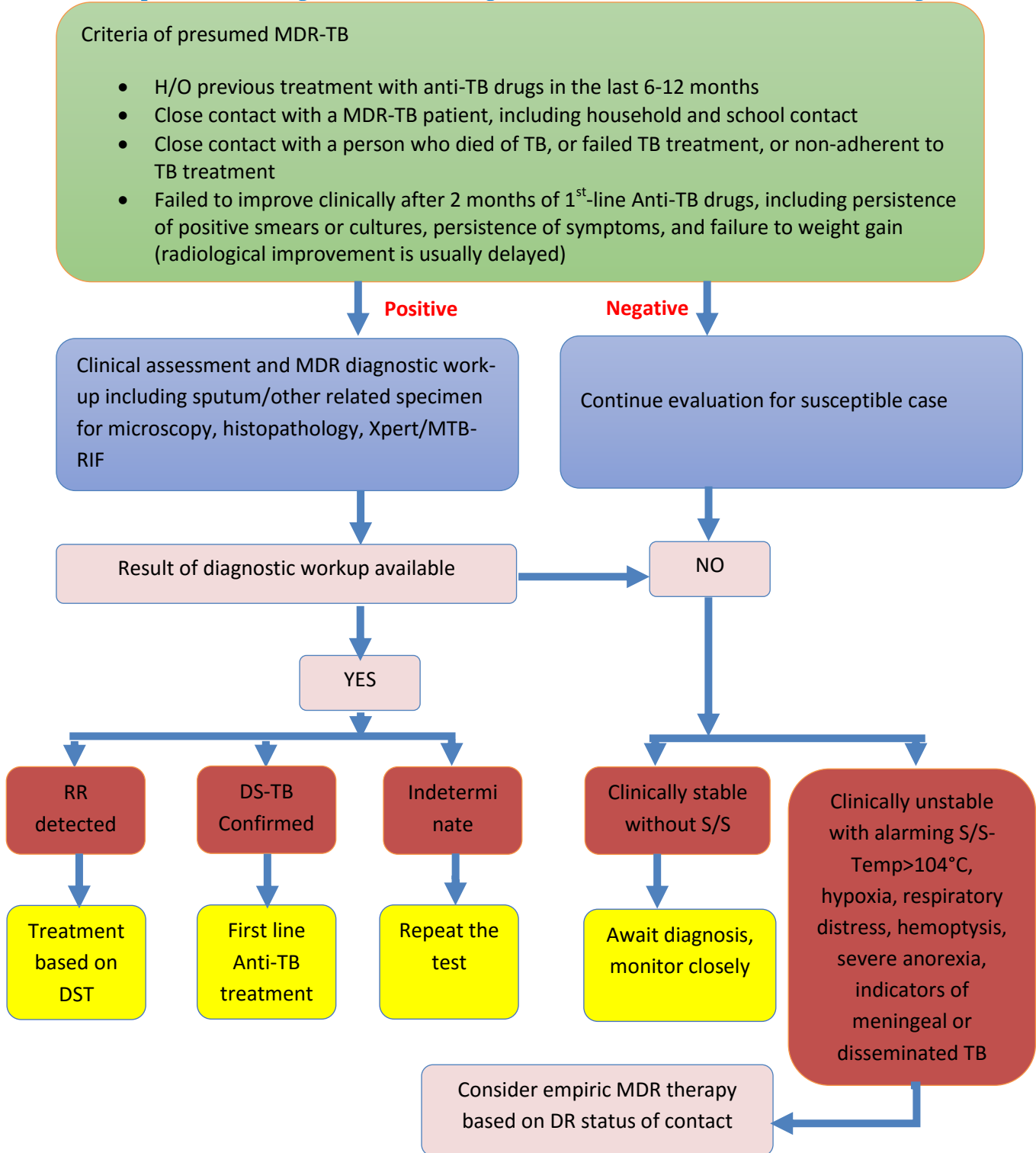
Diagnosis of MDR-TB in children

In younger children, bacteriological confirmation may not be possible for unavailability of sample, yet diagnosis of MDR-TB can be made on clinical and radiological data in most cases. A child over 8 years can expectorate sputum for bacteriology and DST. In younger children who are unable to provide specimen, a high index of suspicion is needed to initiate empiric therapy. An algorithm of presumed child MDR-TB is given below.

⁵² Draft National MDR TB Guideline of Nepal 2017

⁵³ National Guidelines and Operational Manual for Programmatic Management of Drug Resistant TB, National Tuberculosis Control Programme, DGHS, Bangladesh, WHO-Bangladesh, 2nd Edition, April 2013

Figure 4: Algorithm for Presumed MDR-TB in a Child⁵⁴
 (Adapted from Management of Multidrug Resistance Tuberculosis in Children: Field guide)



⁵⁴ Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2012

Principles of Management of MDR-TB in Children⁵⁵

- ❑ Manage in a specialized MDR-TB treatment facility
- ❑ DOTS is essential.
- ❑ Be aware of drug groups / cross-resistance.
- ❑ NEVER add one drug to a failing regimen.
- ❑ Use standard national recommended DR drug regimen. Counsel the patient/parents at every visit for support, importance of adherence and adverse events.
- ❑ Do Drug Susceptibility Testing (DST) for 2nd-line drugs when indicated.
- ❑ Follow-up is essential- done clinically and by cultures (monthly in the intensive phase and then quarterly in the continuation phase). Radiological follow-up may be done 6-monthly and when indicated.

Standard MDR-TB Regimen in Children

Children with confirmed MDR-TB can be managed as per

1. **Conventional MDR-TB regimen** for 20 months.
2. **Shorter MDR-Regimens:** Bangladesh Regimen; Given for 9-12 months.

1. Conventional MDR-TB regimen:⁵⁶

8(Km-Z-Lfx-Eto-Cs) / 12(Z-Lfx-Eto-Cs)

- Intensive phase regimen includes: 8 (Z-Km-Lfx-Eto- Cs)
- Regimen in continuation phase includes: 12 (Z-Lfx-Eto-Cs)

The numbers in front of the drug abbreviations represent the average number of months the drugs are given. In the intensive phase five drugs are used; four of them are second-line anti-TB drugs of which one is an injectable (Km). Although pyrazinamide is a first-line drug, it is also added, because the probability of susceptibility is still high.

If kanamycin is not available, amikacin can be substituted. Prothionamide can be substituted for ethionamide.

2. Shorter MDR-Treatment Regimen for Children

To reduce the duration of treatment, 9-month shorter regimen has given favorable outcome in 87% of adult MDR-TB in comparison to WHO standard regimen.⁵⁷ This regimen also has lesser side effects than the conventional MDR regimen.

Shorter treatment regimen consists of-

4-6 Km-Mfx-Pto-Cfz-Z-H^{high-dose}-E / 5 Mfx-Cfz-Z-E

⁵⁵ Caminero JA, ed. Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis. Paris, France: International Union Against Tuberculosis and Lung Disease, 2013

⁵⁶ General Manual. National Tuberculosis Control Program, Nepal. 3rd Edition, 2012

⁵⁷ Aung KJM, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18:1180–7. <http://dx.doi.org/10.5588/ijtld.14.0100>

Recently treatment of children with shorter regimen has been successful in children in a study conducted in South Africa over 48 children aged <18 years. WHO has updated conditional approval of 9-12 months shorter regimen for children⁵⁸.

Treatment Success

Treatment outcomes in child with MDR TB is encouraging. In Nepal, treatment success rate (TSR) of all MDR patients was 71%, however the TSR of XDR is low at 33%. A recent meta-analysis in multidrug resistant tuberculosis in HIV infected child is found to have better outcome than adult (83.4% vs. 49.9%)⁵⁹. Side effects reported to occur among 39.1%, most common were nausea and vomiting while most serious side effects were hearing loss, hypothyroidism and psychiatric effects.

Table 14: Pediatric Dosing of Second-Line Anti-TB Drugs

| Drug | Daily dose (mg/kg) | Frequency | Maximum daily dose |
|--|--|--|------------------------|
| Pyrazinamide 400mg, 500mg | 35 (30-40) | Once daily | 2000mg |
| Kanamycin (Km) (1 g vial) | 15–30 | Once daily | 1 g |
| Amikacin (Amk) (1 g vial) | 15-22.5 | Once daily | 1 g |
| Streptomycin (1gm) | 20-40 | Once daily | 1g |
| Capreomycin (Cm) (1 g vial) | 15–30 | Once daily | 1 g |
| Ofloxacin (Ofx) (200 mg) | 15–20 | Once daily | 1000 mg |
| Levofloxacin (Lfx) (250 mg, 500 mg) | 15-20 < 5 years 10 > 5 years | Once daily | 1000 mg |
| Moxifloxacin (Mfx) (400 mg) | 7.5–10 | Once daily | 400 mg |
| Ethionamide (Eto) (250 mg) | 15–20 | Once daily | 1 g |
| Protionamide(Pto) | 15-20 | Once daily | 1 g |
| Cycloserine (Cs) (250 mg) | 10–20 | Once or twice daily | 1 g |
| Para-amino salicylic acid (PAS) (4 g sachets) | 300 | Twice or thrice daily | 12 g |
| Clofazimine(Cfz) (50 and 100 mg) | 2-3 | Twice daily | 200 mg |
| Amoxicillin/Clavulanate (Amx/Clv) (500/125) – dosing is base on Amoxicillin component. | 30 < 3 months 45 > 3 months and <40 kg | Thrice daily | 2000 mg of Amoxicillin |
| Linezolid(Lzd) | 10 mg/kg | three times daily in children up to 11 years of age and 10 mg/kg | 600 mg |

⁵⁸ www.who.int/entity/tb/areas.../children/MalgosiaGrzemska_MDRTBguidelines.pdf?ua...

⁵⁹ Issakidis P, Casas E.C, das M, Tseretopoulou X, Ntzani E.e and Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. Int J Tuber lung Dis 2015;19(8):969-978

| | | | |
|----------------|--|-------------------------------|--|
| | | twice daily in older children | |
| Delaminid(Dlm) | | 100 mg twice daily | |

NB: For children all drugs, including the fluoroquinolones, are dosed at the higher end of the recommended ranges.

Table 15: Summary of DR- TB regimens: current and proposed

| Patients subgroup | Treatment regimen | |
|---|--|--|
| | Current | Proposed |
| RR/MDR TB susceptible to Inj and FQs | 8 Km-Lfx-Eto-Cs-Z 12 Lfx-Eto-Cs-Z | 8 Km- Lfx/Mfx -Eto-Cs-Z 12 Lfx/Mfx -Eto-Cs-Z |
| RR/MDR TB with resistance to FQ | 8 Cm-Mfx-Eto-Cs-Cfz-Z- Amx/clv, PAS/ 12 Mfx-Eto-Cs-Cfz- Amx/clv-PAS | -Consider replacing FQs with new TB drugs (BDQ or DLM) to strengthen regimen. 8 Km-Cs-Eto-Lzd-Cfz-Z - Bdq/Dlm (6 months) 12 Eto-Cs-Lzd -Cfz- Z |
| RR/MDR TB with resistance to Inj | | 8 Lfx- Eto-Cs- Lzd -Cfz- Z Bdq/Dlm (6 months) 12 Lfx- Eto/Cs- Lzd - Cfz- Z |
| XDR TB | 12 Cm-Mfx-Eto-PAS-Lzd- Amx/clv-Z-Cfz 12 Mfx-Eto-PAS-Amx/clv- Z-Lzd | 12 Eto-Cs- Lzd - Cfz- Z–Bdq/Dlm (6 months) 12 Eto-Cs- Lzd - Cfz- Z -Consider adding Cm where possible -Consider adding add on agents (PAS, Imp) if low confidence in effectiveness of any group C drugs |

Note: For both shorter MDR regimen and proposed other DR regimen shall be started after NTC officially circulates letter of initiation.

Chapter 6: TB-HIV Co-Infection

HIV is the most potent risk factor for TB. HIV infection increases the risk of TB disease by 30-fold compared with HIV-seronegative in high HIV prevalence countries⁶⁰. This increased risk of TB is for two reasons. First they are likely to be exposed to TB as their HIV-infected parents are more likely to have TB. Secondly, the risk of developing TB disease following TB exposure/infection is greatly increased in HIV-infected children due to decreased immunity. Among HIV-infected children, TB-coinfection is found to be 19.5%, with 59% being pulmonary TB in high HIV-burden country⁶¹. In 2014 TB prevalence surveyed in HIV patients was 8.5%.⁴ HIV-infected children may develop multiple episodes of TB and a previous TB episode does not exclude future TB.

To further complicate diagnosis of TB, HIV-infected children often have other lung disease related to HIV infection, including *Pneumocystis jiroveci* pneumonia (PJP)-previously known as PCP, lymphocytic interstitial pneumonitis (LIP) and viral or bacterial pneumonia. In addition, there may be multiple and concurrent opportunistic infections.

Whom to Investigate for HIV Infection?

All TB infected child needs to be screened for HIV and all CLHIV needs to be screened for TB at regular basis.

Diagnosing TB in HIV-Infected Children

In HIV-infected children the diagnosis of TB disease is more complex because:

- ❑ The symptoms and signs of TB and those of other HIV-related lung diseases could be indistinguishable. Symptoms such as chronic cough, weight loss, lymphadenopathy and persistent fever are common to both HIV related lung diseases and TB.
- ❑ The MT test is frequently negative even though the child may be infected with TB or has TB disease.
- ❑ The radiological features are usually similar to those found in HIV-negative children. But the picture could also be atypical. Radiological changes of HIV-related lung diseases are often confused with TB, e.g. LIP may look very similar to miliary TB.
- ❑ The differential diagnosis of pulmonary disease is much broader and includes: bacterial or viral pneumonia, fungal infections, *Pneumocystis jiroveci* pneumonia, pulmonary lymphoma and Kaposi's sarcoma.

There is a risk that TB may be over-diagnosed, resulting in unnecessary TB treatment. TB may also be missed, resulting in increased morbidity and mortality. LIP is the most difficult condition to distinguish from TB, due to radiological similarities, although it is usually associated with typical clinical signs such as clubbing and/or parotid enlargement. However, TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection. Despite these difficulties, TB can be diagnosed with a fair degree of accuracy in the majority of HIV-infected children. Severe weight loss has been found to have a fairly good sensitivity (88.9%) and specificity (88.6%) with positive predictive value of 23% for TB in HIV-co-infected children²⁵. **The diagnostic approach for TB among HIV-infected children is essentially the same as for HIV-uninfected children.** Since the symptoms of TB can be confused with

⁶⁰ World Health Organization. Global tuberculosis control 2009: epidemiology, strategy, financing. Geneva: WHO; 2009.

⁶¹ Okechukwu AA, Okechukwu OI. Clinical correlate of tuberculosis in HIV co-infected children at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. Nigerian Journal of Clinical Practice. 2011;14(2):206-2011

the symptoms of HIV disease and the chest X-ray is more difficult to interpret, every effort should be made to establish a bacteriological diagnosis.

Treatment of TB in HIV-Infected Children

Treatment of TB in CLHIV is same as standard treatment for non HIV child. Possible causes for treatment failure such as non-adherence to therapy, poor drug absorption, drug resistance, and alternative diagnoses should be investigated in children who are not improving on TB treatment.

General HIV Care for Co-Infected Children

Once a child with TB has been diagnosed with HIV-infection, it is the responsibility of TB staff to communicate and refer the child to HIV staff/program to ensure that the child and family receive appropriate HIV-related care.

Co-Trimoxazole Prophylaxis and IPT

Daily co-trimoxazole prophylaxis prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalization. All HIV-infected children should be treated with co-trimoxazole. All patients living with HIV should also receive IPT for at least 6 months.

Table 16: Co-Trimoxazole Prophylaxis Dosing Schedule for Children

| Body weight (Kg) | Once daily dose Oral suspension (200+40=240mg); Tablet (400+80=480mg) mL oral suspension or Tablet |
|------------------|---|
| <5 | 2.5 mL |
| 5-14.9 | 5 mL or 1/2 tablet |
| 15-29.9 | 10 mL or 1 tablet |
| ≥30 | 2 tablets |

Antiretroviral Therapy (ART)

Appropriate arrangements for access to ART should be made. All children with TB disease and HIV infection requires ART. In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. The decision on when to initiate ART after starting TB treatment should consider the child's immune status and clinical severity of disease, the child's age, pill burden, potential drug interactions, overlapping toxicities and possible IRIS. This should be weighed up against the risk of further HIV disease progression and immune suppression with associated increase in mortality and morbidity in the absence of ART. **Recommendations are to try and initiate ART within 2-8 weeks after starting TB treatment.** Early initiation is of particular importance in the severely immune compromised child.

Rifampicin causes liver enzyme induction, resulting in reduced serum drug levels of protease inhibitors, especially lopinavir. Therefore, the doses need to be adjusted during concurrent TB and HIV treatment. Liver enzyme induction persists for 1-2 weeks after rifampicin is stopped. Given the complexity of co-administration of TB treatment and ART, it is important to refer to the latest national HIV guidelines for current recommendations regarding the co-treatment of TB and HIV in children.

Chapter 7: Prevention of TB in Children

WHO has adopted a global strategy framework (The End TB Strategy) to achieve its vision of a world free of tuberculosis and the end the global tuberculosis epidemic as post-2015 strategy with some targets. Besides other targets, WHO envisioned to reduce TB incidence by 50% (of 2015) by 2025 and 90% (of 2015) by 2035⁶². To achieve this, early diagnosis and preventive treatment of people at risk is important.

Preventive measures can be taken through-

1. Rational and proper case management of adult TB cases
2. Intensified Case Finding (ICF)
3. Contact tracing and investigation
4. Preventive measures-
 - 4.1. INH preventive therapy (IPT)
 - 4.2. BCG vaccination
5. TB infection control

Intensified Case Finding (ICF)

Finding and treating adults with TB is an important step to prevent disease transmission to child. But is not enough in preventing disease. All close contacts and family members including children should be screened and provided appropriate diagnosis and treatment. Children are 50% less likely to develop TB when this strategy is adopted⁶³.

⁶² http://www.who.int/tb/post2015_TBstrategy.pdf

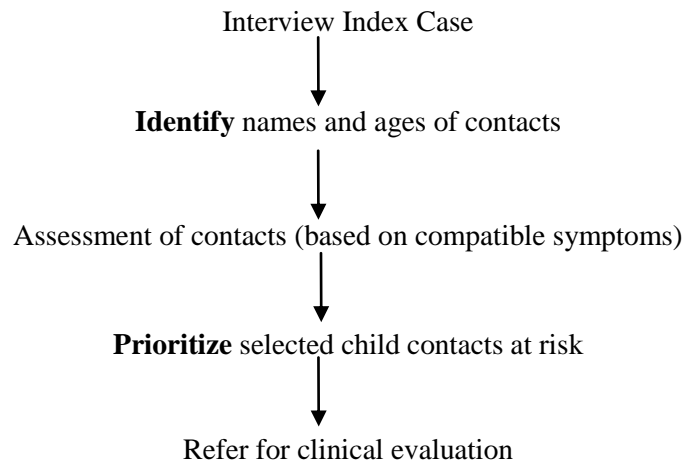
⁶³ CREATE Newsletter January 2012 [Internet]. 2012 January [cited 2015 August 17]. Available from <http://tbhiv-create.org/sites/default/files/secure/january>

Contact Tracing and Investigation

This is a systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. It consists of two components:

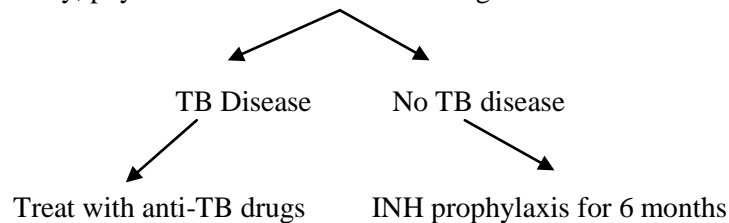
a. Identification and prioritization-

Systematic approach for identifying contacts who have or are at risk of developing TB disease.



b. Clinical evaluation-

History, physical examination and investigation of selected cases



Clinical evaluation should also be done in children or other close contacts with-

1. Symptoms suggestive of TB disease
2. Age < 5 years
3. Immunocompromised conditions (e.g. those living with HIV, on anti-cancer medication)
4. Index case is considered MDR-TB or Pre-XDR-TB or XDR-TB

Through contact screening, a TB case could be identified early and treated, thereby reducing not only the risk of developing serious disease but also preventing transmission. Young children (< 5 years) are immune-immature and if they are in close/household contact with a sputum-positive case, the chance of getting the disease is very high (5-50%)¹². Besides, a child with HIV is 30 times more likely to get TB than with immunocompetent children⁶⁴. A meta-analysis of 95 studies in middle and low income countries found contact tracing can identify 3.1% of DS-TB cases and 3.4% MDR-TB cases⁶⁵. A study in Nepal found 1.6% TB prevalence among household contact aged >5 years⁶⁶. Child TB case notification has

⁶⁴ Hesseling AC, Cotton MF, Jennings T, Whitelaw A, Johnson LF, Eley B et al. High incidence of TB among HIV-infected children: evidence from an South African based study highlights the need for improved tuberculosis control strategies. *Clin Infect Dis* 2009;48(1):108-14

⁶⁵ Fox GJ et al. Contact investigation for TB: Systematic review and meta-analysis. *Eur Respir J*. 2013;41:14-56

⁶⁶ Giyawali N et al. Prevalence of tuberculosis in household contacts of sputum smears positive cases and associated demographic risk factors. *Nepal Med Coll J* 2012; 14(4): 303-307

been significantly increased with active case finding strategy in intervention districts in Nepal in comparison to control districts⁶⁷.

INH Preventive Therapy (IPT)

IPT is providing INH (for 6 months) to children less than 5 years of age, who do not have TB disease to prevent risk of developing TB disease in the near future. These children are household contacts or close contacts with a TB index case, and highly likely to be infected with the *Mycobacterium tuberculosis*. IPT should also be provided to all immunocompromised children with a history of contact, regardless of age. IPT is safe and effective. Side effects in children are rare and minor. Efficacy is over 65% when taken correctly⁶⁸. It reduces TB incidence by 37% among HIV-infected persons when taken along with ART.

Who Should Receive Preventive Therapy?

Due to limited resources, preventive therapy is only given to the most vulnerable children (those at highest risk to develop TB disease in the near future) following documented TB exposure and/or infection, after active disease has been ruled out.

The following should receive IPT:

- ❑ Very young (immune immature) children (<5 years of age)
- ❑ Immunocompromised children (e.g. severely malnourished or HIV-infected, or on steroids/ immunosuppressive drugs), irrespective of their age
- ❑ Baby born to infected mother

Previous TB preventive therapy or treatment does not protect the child against subsequent TB exposure/infection. Therefore highly vulnerable children (as defined above) should receive preventive therapy after each episode of documented TB exposure, unless the child is currently receiving TB prophylaxis or treatment. **Always exclude TB disease before starting preventive therapy with INH.**

- ❑ **Asymptomatic children** (playful and thriving, no cough or wheeze, no fever, no unusual fatigue or lethargy, no visible neck mass or gibbus) do not require additional tests to exclude TB disease, before providing preventive therapy^{12,51}. Children <5 years of age or immunocompromised children of any age in close contact with an adult or adolescent with pulmonary TB, should receive a course of INH prophylaxis to prevent the development of TB⁶⁹. Adherence to IPT is a major issue, which varies from 15-28% in South Africa to 57-74% in Australia and 26% in Indonesia.⁷⁰ If a child aged >5 years and have a positive MT, s/he should also receive IPT even in the absence of contact history.
- ❑ **Symptomatic children** should be evaluated to exclude TB disease. Chest X-ray is preferable, however, symptom-based approach is sufficient to exclude TB disease in settings where MT and/or chest X-ray are not readily available⁷¹.

⁶⁷ Joshi B. Impact of intensified case-finding strategies on childhood TB case registration in Nepal. Public Health Action. 2015; 5:93-98

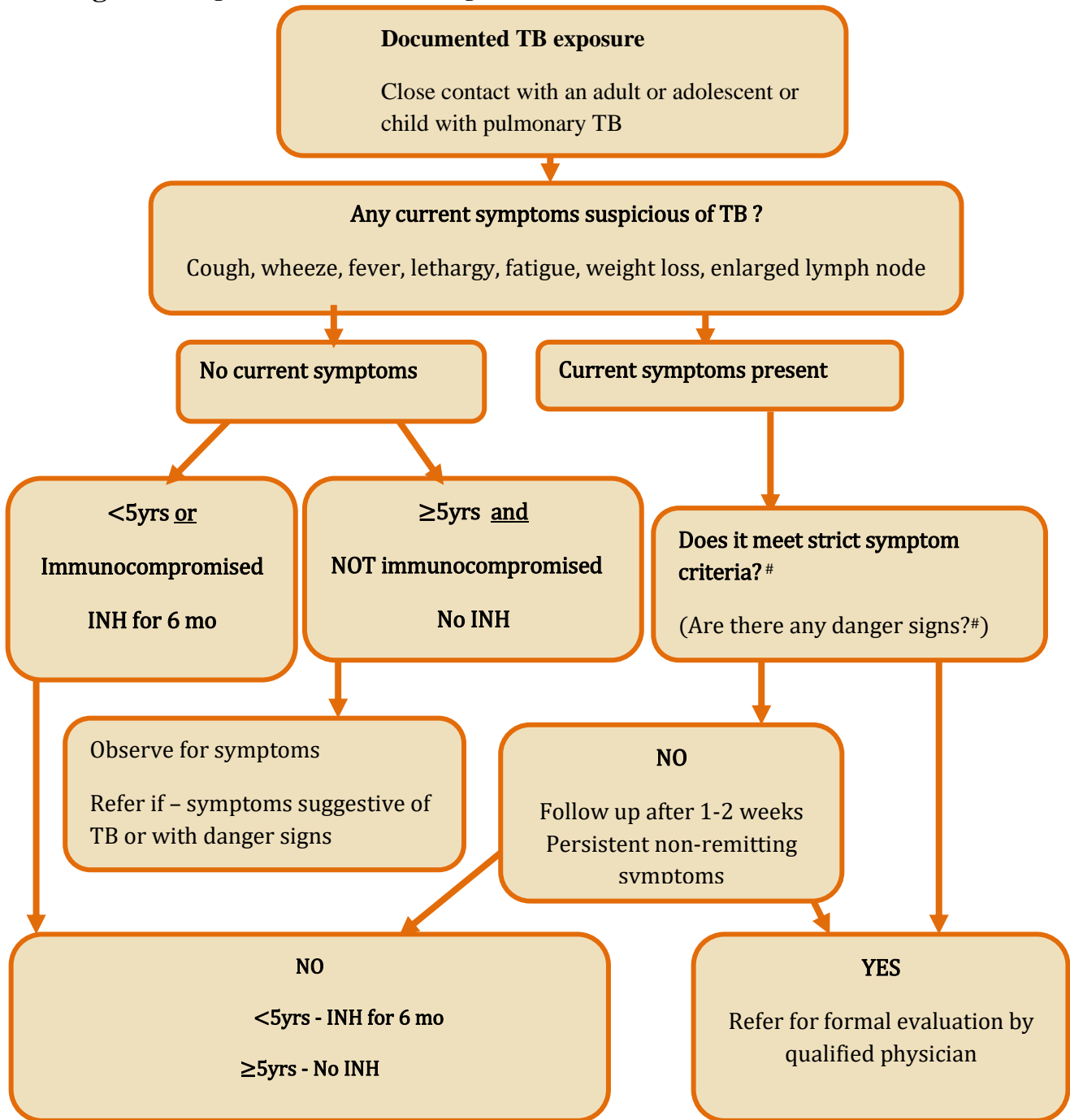
⁶⁸ Spyridis P, Sinaniotis C, Papadea I, Oreopoulos L, Hadjiyiannis S, Papadatos C. Isoniazid liver injury during chemoprophylaxis in children. Isoniazid liver injury during Chemoprophylaxis in Children. Arc Dis Child 1979,54(1);65-67.

⁶⁹ Churchyard GJ, Chaisson RE, Maartens G, Getahun H. Tuberculosis preventive therapy: an underutilised strategy to reduce individual risk of TB and contribute to TB control. S Afr Med J. 2014 Apr 16;104(5):339-43

⁷⁰ Rutherford ME, Ruslami R, Maharani W, Yulita I, Lovell S, Van Crevel R, Alisjahbana B, Hill PC. Adherence to isoniazid preventive therapy in Indonesian children: a quantitative and qualitative study. BMC Research Notes 2012, 5:7

⁷¹ Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. Pediatrics 2008;121:e1646–e1652

Figure 6: Algorithm for the Screening of Children in Close/Household Contact



#Refer if – symptoms suggestive of TB of danger signs

How is Preventive Therapy Given?

Preventive therapy comprises of isoniazid mono-therapy for 6 months. This is usually not given as DOTS, but poor adherence is a serious concern. Hence parents/caregivers must be adequately counseled to explain why the medicine is given and to encourage good adherence. Parents/caregivers should also be counseled to recognize the symptoms of TB disease, such as a persistent non-remitting cough or fever, unusual fatigue or lethargy and/or weight loss, which should prompt them to bring the children back to the clinic for further evaluation. Follow-up should be carried every months after initiation of IPT. Cases should be recorded in IPT register.

Chance of Developing INH Resistance with IPT

There is little or no risk of isoniazid resistance in children receiving IPT, even if the diagnosis of active TB is missed. A meta-analysis since 1951 of studies on IPT did not show any increased risk of developing INH resistance.⁷²

TABLE 16: Guidance for Dosing of INH Preventive Therapy

| Dose recommendations for INH preventive therapy in children | |
|---|--------------------|
| Body weight (kg) | INH 100mg /tablet* |
| 2-4.9 | 1/2 |
| 5-9.9 | 1 |
| 10-19.9 | 1 1/2 |
| 20-29.9 | 2 1/2 |
| >30 | 3 |

*10 mg/kg/day, single dose

BCG(Bacillus Calmette-Guerin) Vaccination

BCG is prepared from a strain of the attenuated (virulence-reduced) live bovine tuberculosis bacillus, Mycobacterium bovis, that has lost its ability to cause disease in humans. BCG is not fully protective against TB disease in children but it provides some protection against severe forms of TB (73% in TBM and 77% in miliary TB⁷²). Many children continue to get TB despite routine BCG vaccination and the youngest remain the most vulnerable. Nevertheless BCG vaccination is recommended to avoid life threatening TB diseases.



Adverse Events Following BCG Immunization

These are adenitis, local BCG abscess, lymphadenopathy, wart-like nodules, large ulcers, osteomyelitis, local bacterial infections and lupoid reactions.

⁷² Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006 April 8; 367 (9517): 1173-80

The commonest complication is **BCG adenitis**.⁷³

BCG adenitis is of following two forms-

1. Non-suppurative- is a benign condition.
2. Suppurative- afebrile axillary (rarely cervical and supra-clavicular) lymphadenopathy with no identifiable cause of adenitis. It develops abruptly within 2-5 months of vaccination ipsilateral to the site of vaccination, size 1-5 cm with absent or minimal tenderness.⁷⁴



Non suppurative BCG adenitis on Day 1

Day 14 without medication

Management:

1. Non-suppurative BCG adenitis is best left alone.
2. Suppurative and fluctuating adenitis: Needle aspiration or total excision is necessary to reduce scar from spontaneous rupture.
3. If there is a high risk of disseminated disease e.g. in HIV positive children, then treatment is with multiple drugs. Please note that *BCG is resistant to PZA* and may be intermediately resistant to INH, depending on strain used.

How should a baby born to a mother or other close contact with TB be managed?

A baby born to a mother diagnosed with TB in the last two months of pregnancy (or who has no documented sputum smear-conversion) needs to be carefully managed.

If the baby is symptomatic (difficulty breathing, feeding problems, poor weight gain, abdominal distension, enlarged liver or spleen, or jaundice):

- ❑ Refer to hospital for evaluation to exclude TB
- ❑ If TB is diagnosed, the baby should receive full course of TB treatment.

Ensure correct dosages in consultation with a pediatrician.

If the baby is asymptomatic:

- ❑ Withhold BCG at birth
- ❑ Give IPT for 6 months
- ❑ Give BCG after completion of 6 months of INH
- ❑ Follow up for symptoms. If symptomatic, the baby needs to be referred to a hospital for evaluation to exclude TB.

Mother should be encouraged to breastfeed. Anti-TB drugs are secreted in breast milk, but the concentrations are very low and do not affect the baby. The drug levels in breast milk are too low to protect the baby and therefore the baby must receive INH preventive therapy as indicated.

As the TB drugs are likely to kill the live BCG vaccine, BCG should not be given at birth in patients receiving IPT or TB treatment. BCG should be given after completion of 6 months IPT or TB treatment. BCG is contra-indicated if the infant is known to be HIV-infected.

TB Infection Control

Prevention of TB transmission and infection in the household and health facilities are important components of control and management because children spend prolonged time with adults in overcrowded and under-ventilated waiting room (where adults are coughing).The following simple procedures are effective in TB infection control at home and clinics:

1. Early diagnosis and treatment of adult TB cases in the household.
2. At the clinic, promptly identify potential and known infectious cases of TB. Separate and treat them with minimal delay by conducting triage and screening. Place posters in all patient and staff areas containing TB (Infection and Environment Control) IEC messages.
3. Provide health education about TB transmission without stigmatizing TB patient.
4. Encourage proper cough hygiene both at home and at health facilities-
 - ❑ Cover nose and mouth with back of the hand(s), arm (sleeve), tissue, cloth or face mask when coughing or sneezing.
 - ❑ Turn head away from others when coughing or sneezing.
 - ❑ Use in the nearest waste bin to dispose of the tissue, cloth etc. after use.
 - ❑ Spit in a cloth or container with lid.
 - ❑ Perform hand hygiene (e.g. hand washing with soap and water, antiseptic hand wash) after having contact with respiratory secretions.
4. Ensure natural ventilation and sunlight:
 - ❑ Keep doors and windows open on opposite sides of the TB clinic and other clinics for effective ventilation- air circulation and changing.
 - ❑ Segregate children from adult TB patients if possible. Where children and adults stay together, keep windows open with ventilation fans.
 - ❑ Advise TB patients to do the same at home.
 - ❑ Apply the same in the clinics.
6. HCWs/ care givers should be screened out if symptomatic.
7. Personal protection of health care workers, by use of respirator device (e.g. N-95 mask or FFP2 mask) when appropriate (eg. sputum induction, bronchoscopy, BAL etc.)
8. Prompt recognition and treatment of TB patients at community settings will act as the most effective measure of decreasing nosocomial transmission of TB.

Annex

Annex 1: Procedure for obtaining clinical samples for Bacteriological examination

This annex reviews the basic procedures for the more common methods of obtaining clinical samples from children for smear microscopy: expectoration, sputum induction and gastric aspiration.

A. Expectoration

Background

1. The sputum smear remains a valuable test to perform in any child who is able to produce a sputum specimen. Sputum should always be obtained in older children who are pulmonary TB suspects. All sputum specimens produced by children should be sent for AFB (acid fast bacilli) test and, where available, mycobacterial culture. Children who can produce a sputum specimen may be infectious. So, as with adults, they should be asked to do this outside and not in enclosed spaces (such as toilets) unless there is a room especially equipped for this purpose. Three sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), an early morning specimen and a second on-the-spot specimen (at follow up visit)

Procedure

2. Give the child confidence by explaining him or her (and any family members) the reason for sputum collection.
3. Instruct the child to rinse his or her mouth with water before producing the specimen. This will help to remove food and any contaminating bacteria in the mouth.
4. Instruct the child to take two deep breaths, holding the breath for a few seconds after each inhalation and then exhaling slowly. Ask him or her to breathe in a third time and then forcefully blow the air out. Ask him or her to breathe in again and then cough. This should produce sputum from deep in the lungs. Ask the child to hold the sputum container close to the lips and to spit into it gently after a productive cough.
5. If the amount of sputum is insufficient, encourage the patient to cough again until a satisfactory specimen (2-5 ml) is obtained. Remember that many patients cannot produce sputum from deep in the respiratory track in only a few minutes. Give the child sufficient time to produce an expectoration which he or she feels is produced by a deep cough.
6. If there is no expectoration, consider the container used and dispose it in the appropriate manner.



B. Sputum Induction

Note that, unlike gastric aspiration, sputum induction is an aerosol-generating procedure. Wherever possible, this procedure should be performed in an isolation room that has adequate infection control precautions (negative pressure, ultraviolet light (turned on when room is not in use) and extractor fan).

Sputum induction is regarded as a low-risk procedure. Very few adverse events have been reported, and they include coughing spells, mild wheezing and nosebleeds. Recent studies have shown that this procedure can safely be performed even in young infants though the staff will need to have specialized training and equipment to perform this procedure.

General approach

Examine children before the procedure to ensure they are well enough to undergo the procedure. Children with the following characteristics should not undergo sputum induction.

- ❑ Inadequate fasting: if a child has been fasting for <3 hours, postpone the procedure until the appropriate time.
- ❑ Severe respiratory distress (including rapid breathing, wheezing, hypoxia).
- ❑ History of significant asthma (diagnosed and treated by a clinician)
- ❑ Reduced level of consciousness.
- ❑ Intubated.
- ❑ Bleeding: low platelet count, bleeding tendency, severe nosebleeds (symptomatic or platelet count <50,000/mm³)

Procedure

1. Administer a bronchodilator (e.g. salbutamol) to reduce the risk of wheezing.
2. Administer nebulized hypertonic saline (3% NaCl) for 15 minutes or until 5 ml of solution has been fully administered.
3. Give chest physiotherapy if necessary. This is useful to mobilize secretions.
4. For older children who are now able to expectorate, follow procedures as described in section A above to collect expectorated sputum.
5. For children who are unable to expectorate, do gastric aspirate/lavage.

Any equipment that is reused needs to be disinfected and sterilized before use for a subsequent patient.

C. Gastric aspiration/lavage

Background

Children with TB may swallow mucus which contains *M. tuberculosis*. Gastric aspiration is a technique used to collect gastric contents to try to confirm the diagnosis of TB by microscopy and mycobacterial culture.

Microscopy can sometimes give false-positive results (especially in HIV-infected children who are at risk of having non tuberculous mycobacteria). Culture enables the determination of the susceptibility of the organism to anti-TB drugs.

It is most useful for young hospitalized children. The diagnostic yield (positive culture) of a set of three gastric aspirates is only about (25-30%) but the specificity is very high (90-99%) with active TB. However, a negative smear or culture never excludes TB in a child. Gastric aspirates are collected from young children suspected of having pulmonary TB. During sleep, the lung's muco-ciliary system beats mucus up into the throat. The mucus is swallowed and remains in the stomach until the stomach empties. Therefore, the highest-yield specimens are obtained from early morning sample.

Gastric aspiration on each of three consecutive mornings should be performed for each patient. This is the number that seems to maximize yield of smear-positivity. Of note, the first gastric aspirate has the highest

yield. Performing the test properly usually requires two people (one doing the test and an assistant). Children not fasting for at least 4 hours (3 hours for infants) prior to the procedure and children with a low platelet count or bleeding tendency should not undergo the procedure.

The following equipments are needed:

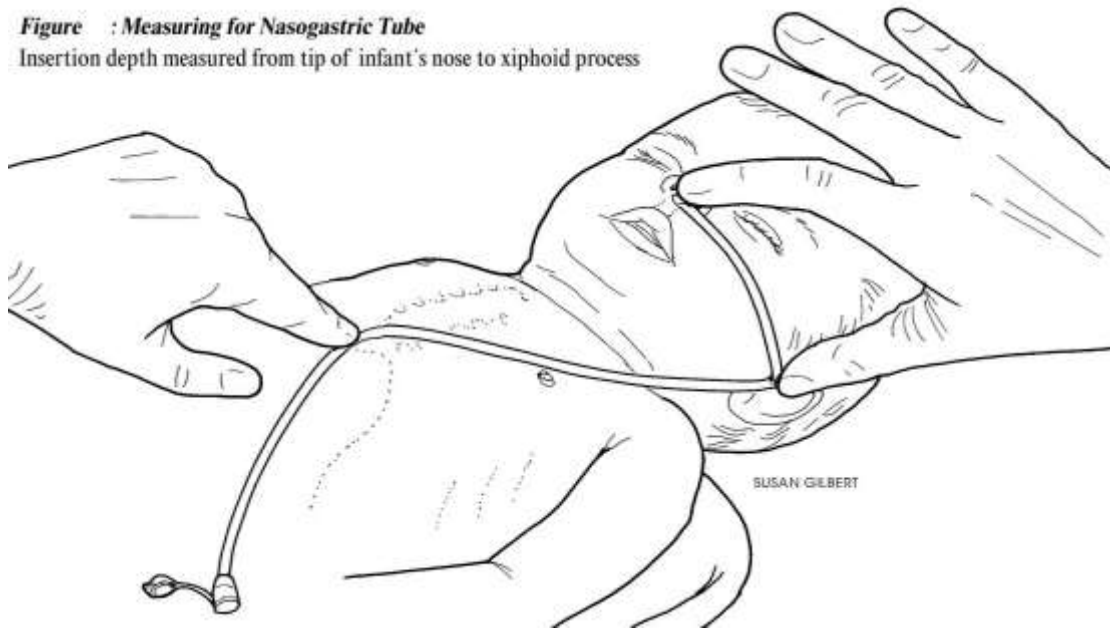
- ❑ Gloves
- ❑ Nasogastric tube (usually 10 French or larger)
- ❑ 5, 10, 20 or 30 ml syringe, with appropriate connector for the nasogastric tube
- ❑ Specimen container
- ❑ Pen (to label specimens)
- ❑ Laboratory requisition form
- ❑ Sterile water or normal saline (0.9% NaCl)
- ❑ Alcohol/chlorhexidine.

Procedure

The procedure can be carried out as an inpatient first thing in the morning when the child wakes up, at the child's bedside or in a procedure room on the ward (if one is available), or as an outpatient (provided that the facility is properly equipped). The child should have fasted for at least 4 hours (infants for 3 hours) before the procedure.

1. Find an assistant to help.
2. Prepare all equipment before starting the procedure.
3. Position the child on his or her back or side. The assistant should help to hold the child.
4. Measure the distance between the nose and stomach (from nose to tragus and to xiphoid process) to estimate distance that will be required to insert the tube into the stomach.
5. Attach a syringe to the nasogastric tube.
6. Gently insert the nasogastric tube through the nose and advance it into the stomach.
7. To check that the position of the tube is correct, push some air (e.g. 3–5 ml) from the syringe into the stomach and listen with a stethoscope over the stomach.
8. Once the position of the tube is ensured, withdraw (aspirate) gastric contents (2–5 ml) using the syringe attached to the nasogastric tube.
9. If no fluid is aspirated, insert 5–10 ml sterile water or normal saline and attempt to aspirate again. If still unsuccessful, attempt this again (even if the nasogastric tube is in an incorrect position and water or normal saline is inserted into the airways, the risk of adverse events is still very small). Do not repeat more than three times.
10. Withdraw the gastric contents (**ideally at least 5–10 ml**)
11. Transfer gastric fluid from the syringe into a sterile container (sputum collection cup).[#]

Figure : *Measuring for Nasogastric Tube*
Insertion depth measured from tip of infant's nose to xiphoid process



An equal volume of sodium bicarbonate solution can be added to the specimen (in order to neutralize the acidic gastric contents, so as to prevent destruction of tubercle bacilli).

After the procedure

1. Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
2. Fill out the laboratory requisition form.
3. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
4. If it is likely to take more than 4 hours for the specimen to be transported, place it in the refrigerator (2–8 °C) and store until transported. Specimen can be stored upto 7 days.⁷³
5. Give the child his or her usual food.

Safety

Gastric aspiration is generally not an aerosol-generating procedure. As young children are also at low risk of transmitting infection, gastric aspiration can be considered a low risk procedure for TB transmission and can safely be performed at the child's bedside or in a routine procedure room.

D. Fine Needle Aspiration Cytology (FNAC)

In children with palpable peripheral lymph node masses, FNAC is the diagnostic modality of choice. It also assists to rule out malignancy as a possible alternative diagnosis.

⁷³ Specimen Transportation manual. National Reference Laboratory. NTP-Pakistan.

ANNEX 2: Basics of the Chest Radiograph Interpretation in Children⁷⁴

Chest radiography is the cornerstone of the diagnosis of intrathoracic tuberculosis. The great danger is that the chest radiograph is seen in isolation, without taking into account the clinical history, examination and MT. A balanced view is needed to ensure that there is not over or under diagnosis.

The following basic conditions must be met:

1. Full-size chest radiographs must be taken. If possible, a lateral chest radiograph should also be taken, as this increases the diagnostic yield in childhood TB.
2. All previous chest radiographs should be available for accurate interpretation.
3. A good viewing box makes the examination easier.
4. The chest radiograph should be examined in a systematic manner.

Basic approach to the chest radiograph (Figs. 1, 2):

1. First check the identity of the patient and the date of the chest radiograph.
Name, age, date, gender and mark of right/left.
2. Now look at three aspects concerning the quality of the chest radiograph:
 - a. **Rotation**
Check rotation by looking at the clavicle head ends or by ensuring that the rib ends are equidistant from the chest edge. The position of the patient is also important as lordotic views are difficult to evaluate.
 - b. **Penetration**
Correct penetration is ensured when the intervertebral spaces can just be distinguished through the heart shadow
 - c. **Inspiration**
Adequate inspiration is when the 8th-9th posterior rib, or the 6th anterior rib is visible.
3. The next step is to look at the **three** structures that are **white**:
 - a. **Soft tissue**
Examine the soft tissue of the chest for swelling or lumps.
 - b. **Bony structures**
Examine the bony tissue for fractures, signs of rickets or areas of infiltration.
 - c. **Cardiac shadow**
Examine the cardiac shadow for position, size and shape.
4. The next step is to look at the **three** structures that are **black**:
 - a. **The trachea and the bronchi**
Follow the trachea and bronchi carefully, look for displacement or narrowing.
 - b. **The right and left lung**
 - c. **Stomach bell**
Look to ensure that the gas shadow in the stomach does not extend into the chest (hernia).
 1. When looking at the **lung** always follow these **three** steps:
 - a. Compare the sizes of the two lungs.
 - b. Compare the vascularity of the two lungs.
 - c. Compare the two hilar shadows for:
 - a. Position
 - b. Size
 - c. Shape

⁷⁴ Gie R. Diagnostic atlas of intrathoracic tuberculosis in children: A guide for low income countries. International Union Against

2. Check **three** aspects of the diaphragm and pleura:
 - a. The position of the left and right diaphragms
 - b. The two costophrenic angles
 - c. The pleura on both sides

Quality Features of CXR

Rotation is absent when the clavicle ends are equidistant from the midline. This is often difficult to see in small children. A useful technique is to measure the ribs ends projecting over the lung fields and compare the two sides, which should be similar (Fig. 1).

Inspiration is adequate if 8th-9th posterior ribs or 6th anterior ribs are visible. In young children, counting the posterior ribs is more accurate as their ribs are more horizontal, making counting anterior ribs inaccurate.

Penetration is adequate if the intervertebral spaces are just visible through the heart shadow. Ensure that the radiographs are not lordotic as this can make interpretation difficult.

One of the normal structures that often causes considerable difficulty in deciding if the mediastinum is wider than usual and therefore containing enlarged lymph glands is the thymic shadow. The thymus is normally not visible in children older than four years. The classic sign of the thymic shadow is the sail sign (Fig. 3).

It is important to ensure that the chest radiograph is of acceptable quality. A poor quality chest radiograph can lead to an incorrect diagnosis.



Normal chest radiograph: Note the good inspiration, lack of rotation, and good penetration. The rib ends are marked to aid in evaluating absence of rotation.



Normal lateral chest radiograph: It is a common mistake to interpret pulmonary artery as enlarged lymph glands.



This is a poor-quality chest radiograph. The radiograph is of insufficient penetration, of poor inspiration, and is rotated, leading to the possible misinterpretation of hilar lymph glands.

Annex 3: Team involved to develop Childhood TB Guideline and Manual

7.1 Members of Childhood TB mission to develop Childhood TB Strategy, Roadmap, Guideline and Manual

| Position | Name |
|--|---------------------------|
| Director NTC, Nepal | Dr. Sharat Chandra Verma |
| Senior TB Consultant, KNCV | Dr. Christine Whalen |
| GF TB Technical Advisor, KNCV | Tushar Kanti Ray |
| Senior TB Consultant, KNCV | Dr. Kathy Fiekert |
| Technical Specialist - TB, SCI/ GF | Dr. Suvesh Kumar Shrestha |
| HRD Consultant, KNCV | Marleen Heus |
| Paediatrician/ Consultant, SCI (International) | Dr. Shakil Ahmad |
| Paediatrician/ Consultant, SCI (National) | Dr. Asim Shrestha |

7.2 List of Participants on Workshop of Benchmarking Tool for Childhood TB Policies, Practices and Planning

| SN | Name of Participants | Organization | Position |
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| 2 | Dr. Mohan Kr. Parsai | NTC | Senior Chest consultant |
| 3 | Anil Thapa | NTC | Chief PME section |
| 4 | Dr. Naveen Shah | NTC | Consultant Chest Physician |
| 5 | Kamala Wagle | NTC | PHN officer |
| 6 | Dr. Binod L. Bajracharya | NEPAS | President |
| 7 | Dr. Ram Hari Chapagain | NEPAS | General Secretary |
| 8 | Dr. Renu Parsai | KCH | Pediatrician |
| 9 | Dr. Binod M. Shrestha | KCH | Consultant Pediatrician |
| 10 | Dr. Ajit Rayamaghi | KCH | Pediatrician |
| 11 | Tara Chetry | Save the Children | CoP |
| 12 | Dr. Suvesh Kumar Shrestha | Save the Children | Technical Specialist-TB |
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| 18 | Marleen Heus | KNCV | Consultant |
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| 22 | Dr. B. Srivastava | SBH | NAIHS |
| 23 | Dr. Shakil Ahmed | SHSMC, Bangladesh | Assoc. Professor of Pediatrician |
| 24 | Chahana Singh Rana | UNICEF | PO |
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7.3 List of participants to finalize Childhood TB Guideline and Manual

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