Canadian Tuberculosis Standards

7th Edition

Chapter 9: Pediatric Tuberculosis

Public Health Agency of Canada
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CHAPTER 9

PEDIATRIC TUBERCULOSIS

Ian Kitai, MD, BCh, FRCPC
Anne-Marie Demers, MD, FRCPC

KEY MESSAGES/POINTS

- In Canada, pediatric tuberculosis (TB) is largely a disease of Canadian-born Aboriginal and foreign-born children.
- Active TB in children is a sentinel event that should prompt a search for the source case.
- After infection in children under the age of 5 there is a high risk of progression to severe forms of TB.
- Attempts should be made to collect specimens (gastric aspirates/induced sputa) for culture before therapy.
- Sputum induction is a promising technique for diagnosis of TB disease in young children.
- Culture yield in children is low: TB often is diagnosed by the combination of a positive TST or IGRA, abnormal chest x-ray and a history of contact with a case of infectious TB, in addition to compatible clinical signs or symptoms.
- A negative TST or IGRA does not exclude active TB.
- For treatment of TB disease, daily therapy is preferred over intermittent regimens.
- Twice weekly regimens should no longer be used because each missed dose represents a larger fraction of the total number of recommended treatment doses.
- Ethambutol (EMB) is now routinely used as part of initial empiric therapy of TB disease (pending sensitivities) in infants and children, unless contraindicated or if the source case is known to be fully susceptible.
- Pyrazinamide (PZA) doses are higher than in the previous edition of the *Standards*.
- Targeted testing for latent TB infection (LTBI) is recommended according to risk of infection and progression to disease.
- Patients for whom therapy of LTBI is recommended should be informed of the risk of treatment and its side effects. Clear plans of action should be in place for monitoring toxicity.
- The principal recommended regimen for LTBI is 9 months of INH.

PRELIMINARY NOTE

We are fortunate to have World Health Organization (WHO) guidance documents which address the area of drug doses and initial choices of therapy.[74,88] The documents provide a summary of available evidence that is used throughout this chapter. Unless there are good grounds to differ, the recommendations in this chapter are aligned as much as possible with the WHO document and the American Academy of Pediatrics Red Book: 2012 Report of the Committee on Infectious Diseases (http://aapredbook.aappublications.org/).

INTRODUCTION

Childhood TB is a neglected disease; its true prevalence is significantly underestimated in global statistics.[1] There is a need for improved diagnostic tools, new drugs, easy-to-dose formulations and effective vaccines.[1] Pediatric tuberculosis in Canada is largely a disease of foreign-born children, the children of foreign-born parents and Aboriginal children.[2] The incidence of TB among those <15 years of age in Canada has declined from 6.6 per 100,000 in 1970 to <2 per 100,000 in 2009[3] (see Chapter 1, Epidemiology of Tuberculosis in Canada). Clinical management should take into account the global epidemiology of TB and the possibility of drug resistance in the foreign born.

TB in children differs from that in adults in several ways: (1) diagnosis in young children may be difficult, since signs and symptoms are often nonspecific and disease is often paucibacillary; (2) TB disease in a very young child is often a sentinel event indicating recent transmission; (3) in young children, especially infants, there is a high risk of progression from latent TB infection (LTBI) to active and sometimes severe TB disease.[4-7]

This chapter will cover the most important aspects of pediatric TB. Readers are encouraged to refer to other chapters of the *Standards* for detailed information.

PATHOGENESIS AND DEFINITIONS

Details of the pathogenesis of TB are outlined in Chapter 2, Transmission and Pathogenesis of Tuberculosis. Children inhale *Mycobacterium tuberculosis* from adults or adolescents with infectious pulmonary or laryngeal TB.[8] Rarely, children with cough and multibacillary disease may be infectious.[9,10] Inhaled bacteria are taken up by alveolar macrophages and, if not immediately destroyed, result in a primary infection that consists of a small parenchymal focus that spreads via local lymphatics to regional lymph nodes. Primary infection may be associated with complications, especially in children under 5 years of age.[11] The parenchymal lesion may enlarge and caseate, or nodes may enlarge and compress or erode through a bronchus, causing wheezing, segmental pneumonia or atelectasis.

The primary infection is usually accompanied by an occult, subclinical bacteremia that seeds distant sites, including the apices of the lungs, the lymph nodes and the central nervous system (CNS).This may rapidly lead to severe forms of disease, including miliary and CNS TB, especially in children younger than 5 years of age.[11] In general, the risk of progression to TB

disease and of severe forms of TB disease after infection is inversely related to age (Table 1).[11] However, in most cases the primary focus heals, and the bacteria continue to survive in a dormant state that is referred to as latent TB infection (LTBI). Similar to adults, children with LTBI and an immunocompromising condition are at increased risk of TB disease.

Table 1. Average age-specific risk for disease development after untreated primary infection[11]

Age at primary infection	Manifestations of disease	Risk of disease (%)
<12 months	No disease	50
	Pulmonary disease	30-40
	TB meningitis or miliary disease	10-20
12-23 months	No disease	70-80
	Pulmonary disease	10-20
	TB meningitis or miliary disease	2-5
2-4 years	No disease	95
	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
5-10 years	No disease	98
	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
>10 years	No disease	80-90
	Pulmonary disease	10-20
	TB meningitis or miliary disease	<0.5

There is no confirmatory test for LTBI. For practical purposes a child with LTBI is considered to have no symptoms related to the infection, a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA), no clinical evidence of disease and a chest x-ray that is either normal or demonstrates evidence of remote infection, such as a calcified parenchymal nodule and/or a calcified intrathoracic lymph node.[12]

Isolation of *M. tuberculosis* in culture from a clinical specimen confirms TB disease. However, because children may be too young to produce sputum or they have paucibacillary disease, recovery of the organism may be difficult, and confirmation is not always possible. The diagnosis of TB disease is often based on a clinical case definition, which usually relies on the triad of (1) a positive TST or IGRA, (2) either an abnormal chest x-ray and/or physical examination and (3) discovery of a link to a known or suspected case of infectious TB.

Many diagnostic scoring systems have been developed but are not well validated and lack specificity.[13,14] Clinical case definitions of childhood intrathoracic TB were recently proposed by an expert panel:[15] these are intended for use in clinical research to evaluate diagnostic assays and not for individual patient diagnosis or treatment decisions.

The distinction between infection and disease is not always easy and can be somewhat artificial, since infection and primary disease are parts of a continuum.[16,17]

CLINICAL PRESENTATION OF TB DISEASE

In Canada many children with TB disease are asymptomatic at presentation. They are often identified through active case finding as contacts of patients with infectious TB and are found to have abnormal chest x-rays. This is especially true of children under 5 years of age.[7]

Children may also present with symptoms or signs suggestive of disease.[7] In young infants, these may be very nonspecific: hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, lethargy or irritability.[18,19] Older children and adolescents are more likely to experience adult-type disease and often present with the classic triad of fever, night sweats and weight loss. Those with pulmonary disease are also more likely to present with respiratory symptoms (cough, sputum and sometimes hemoptysis).[7] As in adults, their physical findings are often minimal relative to their chest x-ray abnormalities.[20] The latter include lung infiltrates, typically but not always in the upper zone(s), that may be cavitated. TB disease in adolescents in Canada and other high-income countries is often extrapulmonary.[21] Presentation may be protean: TB may mimic inflammatory bowel disease or brain and bone tumours or involve almost any system in the body. Delay in diagnosis in adolescents is common and may reflect a lack of suspicion by clinicians.[22] Failure to send sputa for TB smear and culture from adolescents with a productive cough and epidemiologic risk factors for TB contributes to this delay.

Any extrapulmonary site may be involved, most commonly extrathoracic lymph nodes. Mycobacterial cervical lymphadenitis is commonly due to nontuberculous mycobacteria in the Canadian born but may be due to TB, especially in those with risk factors (see Chapter 11, Nontuberculous Mycobacteria). Miliary/disseminated disease and CNS disease, the most life-threatening forms of TB, are more likely to occur in young children and the immunecompromised.[7,19]

Epidemiologic risk factors and/or a clinical picture compatible with TB should prompt appropriate testing.

DIAGNOSTIC TESTS

TUBERCULIN SKIN TEST AND INTERFERON GAMMA RELEASE ASSAYS

Please see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for details about the TST and IGRAs.

In children, the TST and/or IGRA is an important part of the clinical case definition of TB disease, especially if there is a TST conversion or a new positive TST. However, a negative TST does not exclude TB disease. Furthermore, a positive TST or IGRA does not distinguish between latent TB infection and active disease.

RADIOLOGY

Chest radiography is an important part of the diagnostic workup of pediatric TB. The quality of films is crucial. The results may be difficult to interpret, especially if there is rotation of the chest relative to the x-ray beam, or there has been inadequate inspiration or overpenetration. Ideally, films should be reviewed by a radiologist experienced in reading pediatric chest x-rays.[23,24] A classification system relates radiographic appearances of primary pulmonary TB to complications of (1) the primary focus, (2) the regional lymph nodes or (3) both.[25] Useful resources with clinical examples of pediatric TB radiology are available for further information.[15,26-29]

Frontal and lateral chest radiographs are required to detect hilar and paratracheal lymphadenopathy, the most common features expected in pediatric TB.[26] Parenchymal lesions may be anywhere in primary disease and are typically, but certainly not always, in the upper lobes in adolescents. Cavitation is rare in childhood TB but can be seen in children with either adult-type disease, from a progressive primary (Ghon's complex) focus in very young or immune-compromised children, or a caseating pneumonia secondary to lympho-bronchial disease.[25,30] Radiologic abnormalities in children may, in the short term, worsen on treatment before they improve.[4]

Computed tomography (CT) scans of the chest deliver significant radiation doses; children are more vulnerable to the effects of radiation than adults.[29,31,32] CT may be very helpful, but its use for any case must be weighed against the likely benefits of the information gained. Magnetic resonance and CT may be very helpful in the evaluation of suspected active CNS disease, bone and joint disease, and disease at other sites, such as the intra or extrathoracic lymph nodes, pericardium and peritoneum.[29]

GASTRIC ASPIRATES, INDUCED SPUTUM, AND NUCLEIC ACID AMPLIFICATION TESTS

Mycobacterial confirmation of the diagnosis of pediatric TB should always be sought; this is particularly important when (1) an isolate from a source case is not available or there is a possibility of multiple sources; (2) the source case has drug-resistant TB; (3) the child is immuno-compromised; or (4) the child has extrapulmonary TB.[24,33]

Gastric aspiration has traditionally been the diagnostic procedure of choice in young children who are unable to produce sputum.[4,5] Children are often hospitalized for the procedure, but it has also been successfully performed in outpatients.[34-36] Details about gastric aspiration, including a video, are available online[36] and in Table 2. The gastric aspirate material should be pH neutralized as soon as possible after aspiration, as gastric acid may kill *M. tuberculosis.* Unless the laboratory is available to immediately pH neutralize the sample, it should be placed in a sterile container with 100 mg of sodium carbonate[37] or a bicarbonate solution.[36] These containers may be obtained from provincial/territorial public health laboratories or made up by a hospital laboratory. The relevant laboratory should be contacted ahead of time for details regarding collection and transport of specimens. Results of acid-fast bacilli (AFB) smears of gastric aspirates usually are negative, and false-positive smear results caused by the presence of nontuberculous mycobacteria can occur.[33] Although the yield of gastric aspirate cultures in infants has been reported as up to 75%,[38] the overall diagnostic yield for culture is probably less than 50%.[33,35]

Table 2. Gastric aspirates: some tips*†

• During sleep the mucociliary mechanism of the respiratory tract sweeps mucus, which may contain TB bacteria, into the mouth. The material is swallowed and may be a source of organisms, especially if the stomach has not emptied.
• Aspirates are obtained after at least 6 hours of sleep and before the stomach has emptied.
• Patients should not drink or eat anything overnight to prevent the stomach from emptying. They should also avoid exposure to the smell or sight of food, which may encourage gastric emptying. The ideal time is just at the time of waking.
• Aspirate the stomach contents first. Then instill no more than 50 mL of sterile distilled water – the sort used for infant feeding is suitable. Aspirate back and add the aspirate to the first specimen.
• The fluid has to be adjusted to neutral pH within 4 hours of collection because acid is detrimental to mycobacteria. If that is not possible, it should be directly placed into a buffered solution (see text for details).

*With thanks to Ann Loeffler, Oregon Health Sciences University

†The complete procedure is very well explained and illustrated in:
http://www.currytbcenter.ucsf.edu/catalogue/epub/index.cfm?tableName=GAP

Sputum induction (SI) has been performed in high-burden settings as an outpatient procedure by trained personnel.[39-50] By using timed nasopharyngeal suction following administration of hypertonic saline, the technique has been safely performed in infants as young as 1 month of age. Both ultrasonic and jet nebulizers have been used. Details about the procedure[41,51,52] as well as a video[53] are available. The yield may be as good as or better than that of gastric aspirates, and the advantages over gastric aspirates include a shorter period of fasting, no killing of the organisms by gastric acid and higher acceptability to staff and parents.[54] Attention to safety issues, including management of bronchospasm and appropriate facilities and procedures to prevent nosocomial transmission, should be in place (see Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings). The diagnostic yield from bronchoscopy is no higher than that of gastric aspirates or SI, although it may be useful to detect possible tracheobronchial obstruction or explore alternative diagnoses.[55]

Other specimens can be collected if clinically indicated: bronchial washings, pleural fluid, cerebrospinal fluid, urine, other body fluids or tissue biopsy specimens. Nasopharyngeal aspiration[43,45,50,56-59] and the string test[60-62] have also been used, with variable results.[6,63] Fine-needle aspiration biopsy has been useful in children suspected of TB who present with palpable enlarged cervical nodes.[64,65] However, surgical removal has the advantages of higher yields on culture and better outcomes, as lymph nodes may continue to enlarge and drain despite therapy to which the organism is susceptible.[66] A lumbar puncture should be performed in cases of suspected congenital or neonatal tuberculosis and in infants with disseminated disease.[67,68]

Nucleic acid amplification (NAA) tests are useful in confirming the diagnosis in AFB smear-positive respiratory cases. Their ability to improve the sensitivity of gastric aspirates has been disappointing.[31,69-71] A study using a recently developed cartridge-based NAA test on induced sputum in children admitted for suspected TB detected all smear-positive cases but only a third of the smear-negative culture-positive cases: a second specimen increased the yield to 61%.[46] More data are emerging on the type, number of specimens required and the use of NAA tests for the diagnosis of pediatric TB.[50,72,73] Further details of microbiologic isolation, speciation and drug-resistance testing are provided in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

RECOMMENDED MANAGEMENT OF TB DISEASE

A diagnosis of TB infection or disease in a child should be considered a sentinel event and prompt the search for the source case, most likely an adult or adolescent in close contact with the child. Close caregivers should be evaluated to rule out TB disease. Consideration should be given to placing all close caregivers in airborne isolation until they have been evaluated (see Chapter 15).

The principles and phases (intensive and continuation) of TB treatment are discussed in Chapter 5, Treatment of Tuberculosis Disease. A team approach is very helpful in evaluating and treating children with TB disease. The team may include physicians and clinic nurse practitioners, public health nurses, a social worker and an interpreter. The team should, wherever possible, include or involve a pediatric TB specialist. Treatment is aimed at reducing morbidity and mortality, preventing acquired resistance and providing a lasting cure. Interruption of transmission is also important in adolescent patients with pulmonary disease who attend congregate settings, including schools. Before starting therapy for TB disease a baseline alanine aminotransferase, aspartate transaminase and bilirubin level should be obtained. HIV serology is recommended as standard practice for all children and adolescents being treated for TB disease: TB is an opportunistic infection, and the duration of treatment will be influenced by this result.

The most important element of the treatment of TB is the actual ingestion of the medication by the child, since children may not tolerate the pill burden, and the existing formulations are not particularly child friendly.[4]

INDIVIDUAL DRUGS

The drugs used in the treatment of pediatric TB, their doses and side effects are summarized in Table 3. Despite recent information about TB drug pharmacokinetics in children, more research is still needed in this area.[80] In children who are younger than 12 years or who weigh less than 35 kg, isoniazid (INH) recommended doses are 10-15 mg/kg daily (maximum 300 mg).[74,81] Administration is affected by food: INH is better absorbed on an empty stomach. Fat reduces absorption.[82] Sugars, such as glucose, fructose and sucrose, inactivate INH by condensation. A sorbitol-based suspension avoids this problem but may cause diarrhea.[75] Crushed pills are ideally mixed with water, but few children will accept this, and administration with small amounts of food is often suggested.[4,83-87] If necessary, pills may be crushed in a small amount of a sugar-free, low-fat vehicle such as sugar-free pudding, baby food or yogurt.[83]

For the older child or adolescent who weighs between 35 and 60 kg, the optimal dosing of INH is an area of uncertainty. Recommendations for adults are to use 5 mg/kg of INH (see Chapter 5), whereas recommendations from the American Academy of Pediatrics are to use 10 mg/kg to a maximum of 300 mg.[33] On the other hand, forthcoming WHO recommendations state that at 25 kg, children can adopt adult dosage recommendations and use adult preparations, especially with fixed drug combinations.[88] There are no pharmacokinetic or toxicity data to clearly support either dose. For some patients, this results in a “grey zone” in which the dosing would be very different (e.g. a 40 kg adolescent would receive 300 mg of INH daily when dosed as per AAP recommendations and 200 mg when treated as per the adult guidelines).

Table 3. Drugs used for treatment of tuberculosis in children[33,74,75]

Drugs	Daily dose (range)		Thrice weekly dose† (range)		Available dosage forms	Principal side effects
	By weight (mg/kg)	Max (mg)	By weight (mg/kg)	Max (mg)		
INH	10 (10-15)‡	300	20-30	600-900	10 mg/mL suspension 100 mg tablet 300 mg tablet	– Mild liver transaminase elevation – Hepatitis – Gastritis – Peripheral neuropathy – Hypersensitivity
RMP	15 (10-20)	600	10-20	600	10 mg/mL suspension 150 mg capsule 300 mg capsule	– Orange discoloration of secretions – Vomiting – Hepatitis – Flu-like illness
PZA	35 (30-40)	2000	70 (60-80)	*	500 mg scored tablet	– Hepatotoxicity – Hyperuricemia – Arthralgia
EMB	20 (15-25)	**	40 (30-50)	***	100 mg tablet 400 mg tablet	– Optic neuritis with decreased visual acuity and decreased red-green colour discrimination – Gastrointestinal disturbance
Pyridoxine (used to prevent INH neuropathy: has no anti-TB activity)	1 mg/kg	25			25 mg tablet 50 mg tablet	– Few

†Intermittent doses should be prescribed only when directly observed therapy is available. In general daily therapy is definitely preferred over intermittent regimens.

‡Hepatotoxicity is greater when INH doses are more than 10-15 mg/kg daily. For older children and adolescents, the optimal dosing of INH is an area of uncertainty (see text).

*For PZA: 3000 mg according to the American Thoracic Society (ATS),[75] 2000 mg according to the Red Book[33]

**For EMB: 1600 mg according to the ATS,[75] 2500 mg according to the Red Book[33]

***For EMB: 2400 mg according to the ATS,[75] 2500 mg according to the Red Book[33]

Note: Information on second-line drugs for multidrug-resistant TB (MDR-TB) is available in various recent reviews[76-79] and in Chapter 8, Drug-resistant Tuberculosis.

Pyridoxine (vitamin B6) is indicated for children on meat and milk-deficient diets, breastfed infants, those with nutritional deficiencies, children with symptomatic HIV infection and adolescents who are pregnant or breastfeeding.[33]

Rifampin (RMP) is frequently compounded into suspension by pharmacists. These suspensions are usually stable for at least 1 month, and unpublished experience suggests that they are effective.

Ethambutol (EMB) is now routinely used as part of initial empiric therapy of TB disease (pending sensitivities) in infants and children unless otherwise contraindicated.[33] It can cause retrobulbar neuritis, a side effect that is dose-dependent and more likely to occur with renal impairment. It is manifest as decreased visual acuity or decreased red-green colour discrimination and may be reversible upon discontinuation of the drug. EMB should be used with caution in children who are too young for monitoring, although reviews suggest that its use is safe in children.[89,90] When possible, baseline ophthalmological assessment should be obtained in younger children before starting EMB and be repeated regularly during treatment with the agent.[75,86,91]

Acuity and colour vision should be monitored monthly in a clinic setting using isochromatic plates; this is often possible even in young children. While optic neuritis is very uncommon at an EMB dose of 15 mg/kg daily,[89,92] pharmacokinetic data suggest that drug levels may sometimes be subtherapeutic at this dose.[52,90,93] In accordance with the WHO and the AAP, 20 mg/kg daily should be used.[33,74] However, when EMB is a vital part of therapy, e.g. in drug-resistant TB, doses of 25 mg/kg daily should be used with very close monitoring of vision. Baseline serum creatinine levels should be measured to rule out occult renal impairment before initiation of therapy. EMB should be discontinued once the strain is known to be fully drug susceptible.

On the basis of pharmacokinetic data,[94] pyrazinamide (PZA) doses are higher than in the previous edition of the *Canadian Tuberculosis Standards.* The WHO has noted that there is insufficient high-quality evidence to assess whether these higher doses will lead to more hepatotoxicity.[74,81]

Information on second-line drugs for MDR-TB is available in various recent reviews[76-79] and in Chapter 8.

EMPIRIC TREATMENT

In all suspected cases, especially those for whom no source case isolate is available, specimens should be obtained for culture and drug susceptibility testing prior to starting therapy. If there is a known source case, his/her culture and susceptibility test results may be used to guide therapy provided there is no significant possibility of alternative sources (e.g. from recent foreign travel) (see Diagnosis section, above). Treatment should then begin promptly when clinical and laboratory indices support a presumptive diagnosis of active tuberculosis.[75] While culture and susceptibility results are pending or if empiric treatment is deemed necessary, therapy with INH, rifampin, EMB and PZA, unless contraindicated, should be started.[33,81] If the source case is known to be fully drug susceptible, EMB can be omitted. If there is a strong possibility of drug-resistant disease, expert consultation is strongly advised (see section on Multidrug-resistant TB below).

TREATMENT MODIFICATION AND DURATION

Once the susceptibilities of the source case or the child's isolate are available, treatment should be modified as follows:

- For fully susceptible, intrathoracic TB, INH, rifampin and PZA should be used for the first 2 months followed by 4 months of INH and rifampin. The *minimum* duration of therapy is 6 months in total. However, in patients with cavities on initial chest x-ray or positive sputum cultures after 2 months of treatment, the minimum duration of therapy should be 9 months[74,75] (see also Chapter 5).

- If hilar lymphadenopathy alone is present, treatment as for pulmonary disease should be given (unless the isolate is resistant), although regimens using only INH and rifampin have been recommended.[33,95,96] If rifampin or pyrazinamide are discontinued because of side effects, longer durations of therapy are recommended. Rifampin is a cornerstone of anti-TB therapy and should not be discontinued because of minor side effects.

Please see Chapter 5, Treatment of Tuberculosis Disease, for further details on drug side effects and management in cases of hepatotoxicity.

DAILY VS INTERMITTENT REGIMENS

There are few studies of TB treatment in children. Recent systematic reviews have found poorer cure rates with intermittent regimens and prompted the WHO to recommend daily therapy over intermittent regimens for treating pediatric TB disease, especially where HIV infection is common.[74,97,98] Comparing treatment studies is a challenge, considering the important differences in the epidemiology of childhood TB in industrialized countries when compared with that of low- or middle-income countries[99] and since pediatric TB disease cannot be viewed as a single entity.[11] Although intermittent regimens have been successfully used in Canada and the United States, daily regimens are recommended during treatment wherever possible.

Daily regimens are strongly suggested during the intensive phase. On the basis of expert opinion the Canadian Thoracic Society suggests that when daily treatment in the initial phase is very difficult, some patients with minimal mediastinal/hilar lymphadenopathy TB or peripheral TB lymphadenitis may be treated with thrice weekly therapy (directly observed therapy [DOT]) after the first 2 weeks if they are HIV-uninfected, have a low bacillary load (i.e. have noncavitary, smear-negative disease) and have demonstrated excellent adherence to their DOT in the first 2 weeks.

Intermittent three times weekly regimens (i.e. therapy only given on three days of the week, typically with higher doses) should only be considered in the continuation phase for select HIV-uninfected children with pulmonary TB or peripheral TB lymphadenitis. These intermittent regimens should only be used under strict thrice weekly DOT. Twice weekly regimens should no longer be used because each missed dose represents a larger fraction of the total number of recommended treatment doses.[81] However, in exceptional circumstances, patients with minimal disease who are known to be reliable with DOT may be considered for twice weekly therapy in the continuation phase[33] (see also Chapter 5).

DIRECTLY OBSERVED THERAPY AND ADHERENCE

A decision to initiate treatment of TB disease or latent TB should also imply a decision to monitor, minimize the risks of toxicity, follow closely and ensure that therapy is completed. If clinicians cannot achieve this they should immediately refer the patient to centres or teams that can. All patients should receive counselling about side effects and medication administration, and detection of side effects before the next scheduled appointment; access by parents and patients to clinicians and the health service should be facilitated, particularly if there are language and social barriers. If DOT is used, this involves much more than simple observation of pills taken. Integrating a liaison public health nurse into the treatment team facilitates DOT and monitoring, as well as assuring follow-up for patients. In concordance with AAP guidelines, DOT (not by the parents/guardians alone) for the full duration of therapy is strongly recommended for children and adolescents.[33]

Although therapy is given on all days of the week, daily therapy can be given as five observed doses. If resources for DOT are very limited, under all circumstances DOT should always continue for the following cases: (1) Disease due to suspected or proven drug-resistant strains, (2) HIV coinfection, (3) previous treatment failure of active disease, (4) retreatment disease, (5) suspected nonadherence or previous nonadherence, (6) reasonable doubts about the ability of the parents/guardians to supervise treatment for children, (7) substance abuse in an adolescent and (8) psychopathology.[100,101] For those not receiving daily DOT, regular supervision of therapy may help detect side effects and administration errors (see also Chapter 5).

ADJUNCTIVE THERAPY

Corticosteroids are used as adjunctive therapy when the tuberculous inflammatory response is threatening to cause a life-endangering complication.

Corticosteroids are indicated for children with TB meningitis. In prospective, randomized trials they decreased mortality rates, and they may affect neurologic complications, neurologic sequelae and cognitive dysfunction.[102] Dexamethasone (0.3-0.4 mg/kg daily for the first week and weaning over 6 weeks) or prednisone (60 mg/day for 3 weeks tapered over the next 3 weeks) has been used in children older than 14 years of age.[102,103] For children, the AAP[33] and other experts[104] suggest as adequate 2 mg/kg per day of prednisone (maximum, 60 mg/day) or its equivalent for 4 to 6 weeks followed by tapering. Higher prednisone doses (4 mg/kg with a taper over 4-6 weeks) have been evaluated and considered if increasing intracranial pressure continues.[102] Corticosteroids have also improved survival and reduced the need for pericardiectomy in patients with TB pericarditis (see also Chapter 5).

The use of corticosteroids in pleural TB is not supported by current evidence. On the basis of expert opinion, corticosteroids may have a role in endobronchial disease to relieve obstruction and atelectasis.[33,52] They may also be considered for children with severe miliary disease and in the presence of paradoxical reactions, especially when they involve airway compromise.[33] Corticosteroids should only be used in conjunction with effective antituberculosis therapy and should be tapered slowly over weeks to avoid a rebound reaction. Generally in non-meningitic conditions 2 mg/kg daily of prednisone (maximum 60 mg/day) or its equivalent is used, tapered over 6 to 8 weeks.[33,52]

While several reports suggest that a high proportion of children with TB disease and infection may have low vitamin D levels,[105] vitamin D supplementation does not affect treatment outcomes.[106,107]. Existing recommendations regarding vitamin D supplementation for the population should be followed, and monitoring of serum levels in at-risk populations should be considered.[108,109]

SIDE EFFECTS AND MONITORING DURING TREATMENT

Patients and their parents should be informed of the side effects indicating hepatotoxicity and other drug toxicities and should be asked to recall these at each clinic visit. They should be provided with a clear plan of action, preferably written, including contact telephone numbers, should symptoms arise.

Patients should undergo clinical evaluation at least monthly.[33,75,83] At each visit they should be asked about individual side effects and symptoms of TB disease, and undergo a full clinical examination. Monitoring of weight, especially in infants and young children, is especially important to the adjustment of drug doses, since children may rapidly “grow out of” the recommended dose range. On the basis of probable increases in weight some clinicians recommend prescribing 12 mg/kg of INH for infants younger than 12 months rather than 10 mg/kg. Please see Chapter 5 for the management of common adverse reactions.

For adolescents or older children with adult-type disease, follow-up sputum examinations should be performed in the same way as for adults.[6] Repeat cultures from other clinical specimens are not necessary if the patient is improving clinically but should be strongly considered in MDR cases.[110]

Chest radiography 2 months into treatment is recommended to rule out extension of disease.[33] However, persistent radiographic signs are not an indication to change treatment if there is clinical improvement.[30] At the end of a satisfactory course of treatment there may be residual lymphadenopathy or scarring that can persist for 2-3 years.[6,83] Normal radiography is not necessary to discontinue therapy.[33]

Patients should be followed for at least 1 year after treatment completion to achieve clinical health and stability or continued resolution of radiographic findings.[4] Deteriorations (development or worsening of existing lesions and lymphadenopathy) during therapy may occur even with appropriate therapy for drug-susceptible disease in both HIV-infected and uninfected patients. Many of these reactions are paradoxical, due to immune reconstitution, but are difficult to differentiate from acquired drug resistance or clinical failure.[111] Low weight and high disease burden may be associated with more reactions. Clinically significant occlusion of bronchi by enlarging intrathoracic lymph node masses may occur by this mechanism and often responds well to corticosteroid therapy. Drug resistance should be ruled out or accounted for in the treatment regimen if corticosteroids are used.[111]

TREATMENT OF EXTRAPULMONARY TB

It is recommended that extrapulmonary TB in children be treated with the same regimens as pulmonary disease, with the exception of CNS TB, disseminated/miliary TB, and bone and joint TB, for which the recommended duration of treatment is 9 to 12 months. Please see Chapter 7, Nonrespiratory Tuberculosis, for further details.

TREATMENT OF MDR-TB

Please see Chapter 8, Drug-resistant Tuberculosis. Children and adolescents at risk of drug-resistant TB include (1) those with a history of treatment of TB disease, (2) contacts of a patient with drug-resistant contagious TB disease, (3) those born in or who have resided in countries with high prevalence of drug-resistant TB and (4) infected patients whose source case has positive smear for acid-fast bacilli or cultures after 2 months of appropriate therapy or is not responding to a standard treatment regimen.[33] Details of microbiologic isolation, speciation and drug-resistance testing are provided in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

If drug-resistant TB is isolated, an expert opinion should be obtained from a physician experienced in the management of drug-resistant TB. Recent resources summarize drug doses and side effects for the treatment of drug-resistant disease in children.[76-79]

TB AND HIV

Children with LTBI and HIV infection may have an accelerated progression from infection to disease.[112,113] The TST is often negative in HIV-coinfected children. A search for an infectious adolescent or adult is an important step towards diagnosis.

Usually the clinical features of TB in HIV-infected children are similar to those in children without HIV infection, although the disease usually is more severe and can be difficult to differentiate from illnesses caused by other opportunistic infections.[86,114]

The optimal treatment of pulmonary TB in children and adolescents with HIV infection is unknown. Advice from a TB expert should be sought. Please see Chapter 10, Tuberculosis and Human Immunodeficiency Virus for further details.

RECOMMENDED MANAGEMENT OF LTBI

In general, LTBI should be treated with INH (see Table 3 for doses) for 9 months unless the child has been linked to an INH-resistant source case. Routine liver function testing is not indicated for asymptomatic children who do not have underlying liver disease, do not have disseminated disease and are not taking other hepatotoxic drugs. However, although rare, severe hepatotoxicity requiring transplantation or leading to death has occurred during INH treatment of LTBI in children.[115] Therefore, it is strongly recommended that patients receiving INH therapy be advised by the prescribing physician and other relevant health care providers to stop taking the INH *immediately* if they have symptoms such as anorexia, nausea, vomiting, abdominal discomfort, unexplained fatigue, dark coloured urine, scleral icterus or jaundice, and to contact them as soon as possible for further evaluation. They should be provided with a clear written plan of action, including contact telephone numbers, should symptoms arise. If symptoms occur, evaluation should include a physical examination and investigation of liver transaminase values and bilirubin levels. Patients may appear clinically well despite impending significant liver toxicity.[116]

Children should be evaluated monthly, and parents should be questioned about what side effects to watch for, any side effects that have occurred, any symptoms of active TB, adherence to therapy and results of skin testing of family members and other contacts (see also Chapter 6, Treatment of Latent Tuberculosis Infection). Loeffler has offered many helpful suggestions to improve adherence and completion rates (Table 4).[4] Most health departments do not have the resources for directly observed preventive therapy (DOPT). DOPT should be strongly considered for children infected with drug-resistant strains and where adherence is in doubt. DOPT can also be combined with DOT visits for household contacts of adults with TB disease.

Table 4. Recommendations to improve adherence and completion rates for TB therapy[4]

- Use tablets crushed into semisoft vehicles, such as sugar-free pudding, to avoid stomach upset from the liquid preparation.
- Warn the family that the first couple of weeks of therapy will be challenging.
- See the patients monthly and supply only 1 month of medication at a time.
- Provide written educational material regarding reasons for therapy and symptoms of TB and toxicity.
- Develop a small, dedicated and enthusiastic team of staff of providers, nurses and interpreters.
- Develop systems to encourage adherence, such as having the child put a sticker on the calendar for each dose taken.
- Provide convenient clinic hours and short waiting times.
- Develop a system of following up patients who have missed appointments.
- Praise the family and child for good adherence and clinic attendance.

If the source case is INH resistant or there is epidemiologic reason to suspect that the child is infected with an INH-resistant strain, then RMP is recommended for 4 months (see Table 3 for doses).[117] US guidelines recommend the use of RMP daily for 6 months,[118] but this is based on limited experience in adolescents and young adults aged 15 to 23 years.[119] Children taking anticonvulsants and either INH or RMP should be monitored closely because both of these drugs can affect the metabolism and serum levels of anticonvulsants.[75]

Children judged to be infected with a multidrug-resistant strain of *M. tuberculosis* should be referred to a TB specialist (refer also to Chapter 8, Drug-resistant Tuberculosis).

Rifapentine (RPT) is currently unavailable in Canada, except perhaps pursuant to a practitioner's application for the treatment of a patient under the Special Access Program (SAP) (see: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php). If RPT is obtained through the SAP, clinicians should be aware that there have been some concerns about hypersensitivity reactions. A once-a-week RPT regimen for LTBI has recently been approved in the United States for patients >12 years of age.[120] Please see Chapter 6 for more details on this and other alternative regimens.

A common question is whether INH, or an alternative regimen, should be given for treatment of LTBI in people who have no known contact with a drug-resistant case but have immigrated to Canada from countries with high rates of drug-resistant TB. It is important to remember that 9 months of INH has the best documented efficacy, and of foreign-born individuals less than 20%, in total, of those whose infection is reactivated in Canada have resistant strains. For these two reasons, 9 months of INH is recommended in these people (please see Chapter 6).

MANAGEMENT OF CONTACTS

The most efficient way to prevent pediatric TB is the prompt evaluation and treatment of children exposed to an infectious adult source case. Missed opportunities to prevent cases of pediatric TB include delayed diagnosis of infectious TB, delayed reporting of a source, failure to identify an exposed child during the contact investigation, failure to achieve adherence of the source case, failure to document sterilization of cultures, failure to start preventive therapy or LTBI treatment in the child and failure to ensure that the child takes the treatment.[117] With each pediatric active TB case, the case management team should determine which of these factors may have played a role in the child becoming infected with TB and take corrective action to prevent future cases.

All exposed children should have a symptom inquiry and TST. Those less than 5 years of age, all close childhood contacts and all symptomatic children should also have a physical examination and chest radiography. Children less than 5 years of age with a negative TST and no evidence of active TB by examination or radiology should be given "window" of preventive therapy to prevent the development of TB. This is because it may take up to 8 weeks after infection for the TST to convert to positive, during which time the infection may progress to disease. For children presumed to have been exposed to a drug-susceptible isolate, INH is recommended. The INH may be discontinued if, after a period of 8 weeks after the last contact, the repeat TST is negative, and the child remains asymptomatic and is immunocompetent and more than 6 months of age (for infants <6 months of age, see section on Perinatal Issues: Recommended Management of the Newborn Infant Exposed to TB).

In the exposed child, if the initial TST is positive (≥5 mm) and there is no clinical or radiographic evidence of disease, then a full course of treatment for LTBI is recommended. When a child

with new, active TB is the index case, reverse contact tracing must be undertaken, i.e. a vigorous search should be carried out for the source case. Although most source cases are found among adolescent or adult household contacts of the child, other source cases may be found among adolescent or adult non-household contacts, such as babysitters and other caregivers either in or outside the household. Molecular characterization of *M. tuberculosis* isolates by genotyping can lead to identification of previously unrecognized source cases.[121] If the child is hospitalized it is advisable to screen adolescent or adult visitors for evidence of active TB.[122]

The optimal treatment of children in contact with patients with MDR-TB is uncertain.[33,123] Consultation with a TB specialist is recommended (see Chapter 8 for more details).

TARGETED TESTING FOR LATENT TB INFECTION

Universal screening of school children and infants is not indicated. Resources should be devoted to the task of testing children at high risk of LTBI or progression of LTBI to TB disease.[118] These include (1) contacts of a known case of TB, (2) children with suspected active disease, (3) children with known risk factors for progression of infection to disease (see Chapter 4, Diagnosis of Latent Tuberculosis Infection), (4) children who have travelled or resided for 3 months or longer in an area with a high incidence of TB, especially if the visit involved contact with the local population (see Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations) and (5) children who arrived in Canada from countries with a high TB incidence. In the United States, risk assessment questionnaires have been developed to identify children with risk factors for TB and LTBI who should undergo a TST.[12,118] In Canada, a school-based TB screening program and associated investigation targeting recently immigrated children have been evaluated and found to be effective.[124]

PERINATAL ISSUES: RECOMMENDED MANAGEMENT OF THE NEWBORN INFANT EXPOSED TO TB

Management should proceed according to the following principles:

- Untreated TB presents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. INH, RMP and EMB are considered safe in pregnancy, and PZA is likely safe as well (see Chapter 5).
- Administration of first-line TB drugs is not an indication for termination of pregnancy. If second-line drugs are needed, advice from a TB expert should be sought immediately, as several of these agents are known teratogens.[125]
- HIV-negative women receiving first-line agents, including INH and rifampin, may continue to breastfeed. While some of the drugs enter the breast milk, they are deemed safe. The concentrations of drugs in breast milk are insufficient to protect the newborn. Supplementary pyridoxine should be given to the nursing mother receiving INH and to her child.[67]

Infants born to mothers with suspected/confirmed active TB or LTBI need to be managed according to the categorization of the maternal infection. See Table 5 on the next page.

Evaluation of an infant for congenital TB should include a clinical examination, TST, chest radiography, appropriate cultures, including a lumbar puncture, and abdominal ultrasound. A head ultrasound should also be considered. The TST result is usually negative initially, although it may become positive after 1 to 3 months of treatment. There are very few data on the utility of IGRAs in infants. Cases of infants with negative skin tests and positive IGRA whose mothers had TB have been reported.[67]

Table 5. Recommended management of the newborn infant exposed to TB[33,67]

Situation 1	Evaluation of mother	Evaluation of infant
Mother or household contact with clinical or radiographic evidence of infectious TB at or close to the time of delivery	• Evaluate for TB disease (See Chapter 3). • HIV testing. • Examine placenta for histology smears and cultures.	• Evaluate for congenital TB (see text).
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Separate mother (or household contact) and child until mother (or household contact) and infant are receiving appropriate care, tolerating medication and mother (or household contact) is noninfectious and clinically improving. • If the mother (or household contact) has possible MDR-TB or has poor adherence to treatment and DOT is not possible, the infant should be separated from the mother (or household contact).	• If congenital TB is diagnosed, start appropriate treatment (see text). • If congenital TB is excluded, INH at a dose of 10-15 mg/kg (see text for duration of INH) is advised.	Women with TB disease who have been treated appropriately for at least 2 weeks and who are not considered infectious can breastfeed.
Situation 2	**Evaluation of mother**	**Evaluation of infant**
Mother treated for TB during pregnancy	• Mother should have follow-up smear examinations to confirm she is no longer infectious. • HIV testing. • Examine placenta for history, smears and cultures.	• Evaluate for congenital TB (see text).
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Provided treatment has been adequate to produce clinical improvement and the mother is no longer infectious, separation is not recommended. • If in doubt, proceed as in Situation 1.	• If congenital TB is diagnosed, start appropriate treatment (see text). • If congenital TB is excluded and mother is confirmed to be not infectious and no other household contacts have TB disease, INH is not necessary. • If in any doubt, proceed as in Situation 1.	Women with TB disease who have been treated appropriately for at least 2 weeks and who are not considered infectious can breastfeed.
Situation 3	**Evaluation of mother**	**Evaluation of infant**
Mother with abnormal chest x-ray but no evidence of active disease	• If the chest x-ray abnormality is considered to be secondary to old, healed TB and the mother has not been previously treated, she should be evaluated, including testing of induced sputum. • HIV testing. • The mother should be treated for LTBI if not previously treated.	• The infant should be evaluated clinically and radiographically at birth. • Consider evaluation for congenital TB (see text). • Consider a repeat TST at 3 and 6 months of age.
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• If the mother is no longer infectious, separation is not recommended. • If in doubt, proceed as in Situation 1.	• If there is uncertainty about the status of the mother, the child should be provided with preventive treatment (see Situation 1).	The mother can breastfeed.
Situation 4	**Evaluation of mother**	**Evaluation of infant**
Mother with LTBI and no abnormality on chest x-ray		• No special investigation for the newborn is recommended.
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Separation of mother and infant is not recommended.	• No treatment is recommended.	The mother can breastfeed.

The duration of INH treatment in newborns exposed to TB remains an area of uncertainty. Because of a question of the unreliability of the TST in very young infants – for which data are poor – some authorities recommend continuing an appropriate prophylactic regimen until the infant is 6 months of age,[4,52,126-128] when the TST can be repeated, while others recommend at least 4 months.[33,67,129;130]

Practically, according to expert opinion, if the exposure is higher risk (e.g. household or smear-positive source case) then 6 months of preventive therapy should be used, but if the source case is less infectious and there is no evidence of conversion in exposed older contacts then preventive therapy could be discontinued at 4 months if the TST is negative. The TST could be repeated at 6 months of age.

If the repeat TST is positive, the infant should be reassessed for TB disease. If TB disease is excluded, preventive therapy should be continued for a total of 9 months.

For other aspects not covered in this chapter, please refer to Chapter 11, Nontuberculous Mycobacteria, Chapter 12, Contact Follow-Up and Outbreak Management in Tuberculosis Control, Chapter 15, Prevention and Control of Tuberculosis Transmission in Healthcare and Other Settings and Chapter 16, Bacille Calmette-Guérin (BCG) Vaccination in Canada.

CONCLUSIONS

TB continues to be an important disease in Canadian children. Canadian health care workers should use available tests (currently the TST) to screen children at high risk of infection, both to protect these children now and to avoid their becoming the next generation of adults with infectious TB.

A team approach is recommended for the treatment of pediatric TB and should take into account the possibility of drug resistance. Ultimately, elimination of pediatric TB in Canada depends on controlling the disease globally. We should all find ways to assist with that international struggle. In doing so, we will also serve the interests of present and future Canadian children.[118]

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REFERENCES

1. Sandgren A, Cuevas LE, Dara M, et al. Childhood tuberculosis: progress requires advocacy strategy now. *Eur Respir J* 2012;40(2):294-97.
2. Phypers M. Pediatric tuberculosis in Canada. *Can Commun Dis Rep* 2003;29(16):139-42.
3. Public Health Agency of Canada. Tuberculosis in Canada 2009 pre-release. Ottawa: Public Health Agency of Canada, 2010.
4. Loeffler AM. Pediatric tuberculosis. *Semin Respir Infect* 2003;18(4):272-91.
5. Mandalakas AM, Starke JR. Current concepts of childhood tuberculosis. *Semin Pediatr Infect Dis* 2005;16(2):93-104.
6. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis* 2010;50(Suppl 3):S184-S194.
7. Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med* 2012;367(4):348-61.
8. Starke J. Tuberculosis in infants and children. In: Schlossberg D, ed. *Tuberculosis and Nontuberculous Mycobacterial Infections* (6th edition). Washington DC: ASM Press, 2011;456-75.
9. Matlow A, Robb M, Goldman C. Infection control and paediatric tuberculosis: a practical guide for the practicing paediatrician. *Paediatr Child Health* 2003;8(10):624-6.
10. Cruz AT, Starke JR. A current review of infection control for childhood tuberculosis. *Tuberculosis (Edinb)* 2011;91(Suppl 1):S11-S15.
11. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;8(4):392-402.
12. Pediatric Tuberculosis Collaborative Group. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics* 2004;114(4):1175-201.
13. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis* 2002;6(12):1038-45.
14. Graham SM. The use of diagnostic systems for tuberculosis in children. *Indian J Pediatr* 2011;78(3):334-39.
15. Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis* 2012;205(Suppl 2):S199-S208.
16. Hatherill M, Verver S, Mahomed H. Consensus statement on diagnostic end points for infant tuberculosis vaccine trials. *Clin Infect Dis* 2012;54(4):493-501.
17. Mandalakas AM, Detjen AK, Hesseling AC, Benedetti A, Menzies D. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2011;15(8):1018-32.
18. Whittaker E, Kampmann B. Perinatal tuberculosis: new challenges in the diagnosis and treatment of tuberculosis in infants and the newborn. *Early Hum Dev* 2008;84(12):795-99.

19. Schaaf HS, Collins A, Bekker A, Davies PD. Tuberculosis at extremes of age. *Respirology* 2010;15(5):747-63.

20. Nemir RL, Krasinski K. Tuberculosis in children and adolescents in the 1980s. *Pediatr Infect Dis J* 1988;7(6):375-9.

21. Phongsamart W, Kitai I, Gardam M, Wang J, Khan K. A population-based study of tuberculosis in children and adolescents in Ontario. *Pediatr Infect Dis J* 2009;28(5):416-9.

22. Kam A, Ford-Jones L, Malloy P, Khan K, Kitai I. Active tuberculosis among adolescents in Toronto, Canada: clinical features and delays in diagnosis. *Pediatr Infect Dis J* 2007;26(4):355-6.

23. Swingler GH, du Toit G, Andronikou S, van der Merwe L, Zar HJ. Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis. *Arch Dis Child* 2005;90(11):1153-56.

24. Yip D, Bhargava R, Yao Y, Sutherland K, Manfreda J, Long R. Pediatric tuberculosis in Alberta: epidemiology and case characteristics (1990-2004). *Can J Public Health* 2007;98(4):276-80.

25. Marais BJ, Gie RP, Schaaf HS, et al. A proposed radiological classification of childhood intra-thoracic tuberculosis. *Pediatr Radiol* 2004;34(11):886-94.

26. Gie R. Diagnostic atlas of intrathoracic tuberculosis in children: a guide for low income countries. Available from: http://www.theunion.org/index.php?id=103&cid=110&fid=57&task=download&option=com_flexicontent&Itemid=43&lang=en

27. Andronikou S, Vanhoenacker FM, De Backer AI. Advances in imaging chest tuberculosis: blurring of differences between children and adults. *Clin Chest Med* 2009;30(4):717-44, viii.

28. Daley CL, Gotway MB, Jasmer RM. Radiographic manifestations of tuberculosis: a primer for clinicians, 2nd ed. 2011. Available from: http://www.currytbcenter.ucsf.edu/radiographic/docs/Radiographic_Complete_2ndEd.pdf

29. Smith KC, John SD. Pediatric TB radiology for clinicians. 2012. Available from: URL: http://www.heartlandntbc.org/products/pediatric_tb_radiology.pdf

30. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Respir Crit Care Med* 2006;173(10):1078-90.

31. Neu N, Saiman L, San Gabriel P, et al. Diagnosis of pediatric tuberculosis in the modern era. *Pediatr Infect Dis J* 1999;18(2):122-6.

32. Brenner DJ, Hall EJ. Computed tomography – an increasing source of radiation exposure. *N Engl J Med* 2007;357(22):2277-84.

33. American Academy of Pediatrics. *Tuberculosis. Red Book: 2012 Report of the Committee on Infectious Diseases* (29th ed). Elk Grove Village, IL: American Academy of Pediatrics, 2012.

34. Lobato MN, Loeffler AM, Furst K, Cole B, Hopewell PC. Detection of *Mycobacterium tuberculosis* in gastric aspirates collected from children: hospitalization is not necessary. *Pediatrics* 1998;102(4):E40.

35. Stockdale AJ, Duke T, Graham S, Kelly J. Evidence behind the WHO guidelines: hospital care for children: What is the diagnostic accuracy of gastric aspiration for the diagnosis of tuberculosis in children? *J Trop Pediatr* 2010;56(5):291-98.

36. Francis J. Curry National Tuberculosis Center and California Department of Public Health. Pediatric tuberculosis: a guide to the gastric aspirate (GA) procedure. Available from: http://www.currytbcenter.ucsf.edu/catalogue/epub/index.cfm?tableName=GAP

37. Pfyffer GE, Palicova F. Mycobacterium: general characteristics, laboratory detection, and staining procedures. In: Murray PR, Baron EJ, American Society for Microbiology, eds. *Manual of Clinical Microbiology* (10th edition). Washington, DC: ASM Press, 2011;472-502.

38. Vallejo JG, Ong LT, Starke JR. Clinical features, diagnosis, and treatment of tuberculosis in infants. *Pediatrics* 1994;94(1):1-7.

39. Shata AM, Coulter JB, Parry CM, Ching'ani G, Broadhead RL, Hart CA. Sputum induction for the diagnosis of tuberculosis. *Arch Dis Child* 1996;74(6):535-7.

40. Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D, Hussey G. Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Arch Dis Child* 2000;82(4):305-8.

41. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 2005;365(9454):130-34.

42. Iriso R, Mudido PM, Karamagi C, Whalen C. The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. *Int J Tuberc Lung Dis* 2005;9(7):716-26.

43. Owens S, Abdel-Rahman IE, Balyejusa S, et al. Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Arch Dis Child* 2007;92(8):693-96.

44. Hatherill M, Hawkridge T, Zar HJ, et al. Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Arch Dis Child* 2009;94(3):195-201.

45. Al-Aghbari N, Al-Sonboli N, Yassin MA, et al. Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 2009;4(4):e5140.

46. Nicol MP, Workman L, Isaacs W, et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. *Lancet Infect Dis* 2011;11(11):819-24.

47. Moore HA, Apolles P, de Villiers PJ, Zar HJ. Sputum induction for microbiological diagnosis of childhood pulmonary tuberculosis in a community setting. *Int J Tuberc Lung Dis* 2011;15(9):1185-90, i.

48. Qureshi UA, Gupta AK, Mahajan B, et al. Microbiological diagnosis of pulmonary tuberculosis in children: comparative study of induced sputum and gastric lavage. *Indian J Pediatr* 2011;78(11):1429-30.

49. Maciel EL, Peres RL, do Prado TN, et al. Saline nebulization before gastric lavage in the diagnosis of pulmonary tuberculosis in children and adolescents. *J Trop Pediatr* 2010;56(6):458-59.

50. Zar HJ, Workman L, Isaacs W, et al. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clin Infect Dis* 2012;55(8):1088-95.

51. Grant LR, Hammitt LL, Murdoch DR, O'Brien KL, Scott JA. Procedures for collection of induced sputum specimens from children. *Clin Infect Dis* 2012;54(Suppl 2):S140-S145.

52. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization, 2006. Report No. WHO/HTM/TB/2006.371.

53. MSF South Africa. Paediatric sputum induction procedure. Available from: URL: http://www.youtube.com/watch?v=sbGITrNP8j8

54. Schaaf HS, Hesseling AC. Induced sputum microbiology in confirming pulmonary tuberculosis in children. *Int J Tuberc Lung Dis* 2011;15(9):1139.

55. Arlaud K, Gorincour G, Bouvenot J, Dutau H, Dubus JC. Could CT scan avoid unnecessary flexible bronchoscopy in children with active pulmonary tuberculosis? A retrospective study. *Arch Dis Child* 2010;95(2):125-29.

56. Franchi LM, Cama RI, Gilman RH, Montenegro-James S, Sheen P. Detection of *Mycobacterium tuberculosis* in nasopharyngeal aspirate samples in children. *Lancet* 1998;352(9141):1681-82.

57. Montenegro SH, Gilman RH, Sheen P, et al. Improved detection of *Mycobacterium tuberculosis* in Peruvian children by use of a heminested IS6110 polymerase chain reaction assay. *Clin Infect Dis* 2003;36(1):16-23.

58. Oberhelman RA, Soto-Castellares G, Caviedes L, et al. Improved recovery of *Mycobacterium tuberculosis* from children using the microscopic observation drug susceptibility method. *Pediatrics* 2006;118(1):e100-e106.

59. Oberhelman RA, Soto-Castellares G, Gilman RH, et al. Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infect Dis* 2010;10(9):612-20.

60. Vargas D, Garcia L, Gilman RH, et al. Diagnosis of sputum-scarce HIV-associated pulmonary tuberculosis in Lima, Peru. *Lancet* 2005;365(9454):150-52.

61. Chow F, Espiritu N, Gilman RH, et al. La cuerda dulce – a tolerability and acceptability study of a novel approach to specimen collection for diagnosis of paediatric pulmonary tuberculosis. *BMC Infect Dis* 2006;6:67.

62. Bae WH, Salas A, Brady MF, et al. Reducing the string test intra-gastric downtime for detection of *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2008;12(12):1436-40.

63. Nicol MP, Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. *Paediatr Respir Rev* 2011;12(1):16-21.

64. Wright CA, Hesseling AC, Bamford C, Burgess SM, Warren R, Marais BJ. Fine-needle aspiration biopsy: a first-line diagnostic procedure in paediatric tuberculosis suspects with peripheral lymphadenopathy? *Int J Tuberc Lung Dis* 2009;13(11):1373-79.

65. Wright CA, Warren RM, Marais BJ. Fine needle aspiration biopsy: an undervalued diagnostic modality in paediatric mycobacterial disease. *Int J Tuberc Lung Dis* 2009;13(12):1467-75.

66. Fontanilla JM, Barnes A, von Reyn CF. Current diagnosis and management of peripheral tuberculous lymphadenitis. *Clin Infect Dis* 2011;53(6):555-62.

67. Starke JR, Cruz AT. Tuberculosis. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, eds. *Infectious Diseases of the Fetus and Newborn Infant* (7th edition). Philadelphia: W.B.Saunders Company, 2011;577-600.

68. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: pathogenesis and clinical aspects. *Clin Microbiol Rev* 2008;21(2):243-61.

69. Delacourt C, Poveda JD, Chureau C, et al. Use of polymerase chain reaction for improved diagnosis of tuberculosis in children. *J Pediatr* 1995;126(5 Pt 1):703-9.

70. Fauville-Dufaux M, Waelbroeck A, De Mol P, et al. Contribution of the polymerase chain reaction to the diagnosis of tuberculous infections in children. *Eur J Pediatr* 1996;155(2):106-11.

71. Gomez-Pastrana D. Tuberculosis in children – Is PCR the diagnostic solution? *Clin Microbiol Infect* 2002;8(9):541-44.

72. Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. *Clin Infect Dis* 2012;54(10):1388-96.

73. Bates M, O'Grady J, Maeurer M, et al. Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. *Lancet Infect Dis* 2013;13(1):36-42.

74. World Health Organization. Rapid advice: treatment of tuberculosis in children. Geneva: World Health Organization, 2010. Report No. WHO/HTM/TB/2010.13.

75. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167 4):603-62.

76. Curry International Centre. Drug-resistant tuberculosis: a survival guide for clinicians, 2nd ed. 2008. Available from: http://www.currytbcenter.ucsf.edu/drtb/

77. Al-Dabbagh M, Lapphra K, McGloin R, et al. Drug-resistant tuberculosis: pediatric guidelines. *Pediatr Infect Dis J* 2011;30(6):501-5.

78. Seddon JA, Hesseling AC, Marais BJ, et al. Paediatric use of second-line anti-tuberculosis agents: a review. *Tuberculosis (Edinb)* 2012;92(1):9-17.

79. Seddon JA, Furin JJ, Gale M, et al. Caring for children with drug-resistant tuberculosis. *Am J Respir Crit Care Med* 2012;186(10):953-64.

80. Ramachandran G, Kumar AK, Swaminathan S. Pharmacokinetics of anti-tuberculosis drugs in children. *Indian J Pediatr* 2011;78(4):435-42.

81. Graham SM. Treatment of paediatric TB: revised WHO guidelines. *Paediatr Respir Rev* 2011;12(1):22-6.

82. Peloquin CA, Durbin D, Childs J, Sterling TR, Weiner M. Stability of antituberculosis drugs mixed in food. *Clin Infect Dis* 2007;45(4):521.

83. Starke JR, Jacobs RF. *Mycobacterium tuberculosis.* In: Long S, ed.*Principles and Practice of Pediatric Infectious Diseases* (3rd edition, revised reprint). Philadelphia: Elsevier Inc., 2009;770-88.

84. Francis J. Curry National Tuberculosis Center. Medication delivery tips. Available from: http://www.currytbcenter.ucsf.edu/pediatric_tb/docs/MedicationDeliveryTips.doc

85. New Jersey Medical School Global Tuberculosis Institute. Management of latent tuberculosis infection in children and adolescents: a guide for the primary care provider. Available from: http://www.umdnj.edu/globaltb/products/mgmtltbi.htm

86. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep* 2009;58(RR-11):1-166.

87. Medicines for Children. Available from: http://www.medicinesforchildren.org.uk/search-for-a-leaflet/isoniazid-for-the-treatment-of-tuberculosis/

88. World Health Organization. Guidance for national tuberculosis prgrammes on the management of tuberculosis in children, Second edition. Geneva: WHO, (2013 edition in preparation).

89. Trebucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tuberc Lung Dis* 1997;1(1):12-15.

90. Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis* 2006;10(12):1318-30.

91. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis* 20031;3(10):624-32.

92. Graham SM, Daley HM, Banerjee A, Salaniponi FM, Harries AD. Ethambutol in tuberculosis: time to reconsider? *Arch Dis Child* 1998;79(3):274-78.

93. Zhu M, Burman WJ, Starke JR, et al. Pharmacokinetics of ethambutol in children and adults with tuberculosis. *Int J Tuberc Lung Dis* 2004;8(11):1360-67.

94. McIlleron H, Willemse M, Schaaf HS, Smith PJ, Donald PR. Pyrazinamide plasma concentrations in young children with tuberculosis. *Pediatr Infect Dis J* 2011;30(3):262-65.

95. Reis FJ, Bedran MB, Moura JA, Assis I, Rodrigues ME. Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. *Am Rev Respir Dis* 1990;142(5):996-99.

96. Jacobs RF, Abernathy RS. The treatment of tuberculosis in children. *Pediatr Infect Dis* 1985;4(5):513-7.

97. Ridge A, Whyte P, Grzemska M, Donald P, Hill S. Beyond randomized trials – TB treatment in children. *Evid -Based Child Health* 2010;5(4):1566-77.

98. Menon PR, Lodha R, Sivanandan S, Kabra SK. Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials. *Indian Pediatr* 2010;47(1):67-73.

99. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. *Int J Tuberc Lung Dis* 2004;8(5):636-47.

100. Te Water Naude JM, Donald PR, Hussey GD, et al. Twice weekly vs. daily chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J* 2000;19(5):405-10.

101. Varudkar BL. Short course chemotherapy for tuberculosis in children. *Indian J Pediatr* 1985;52(419):593-97.

102. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009;59(3):167-87.

103. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;(1):CD002244.

104. Donald PR, Schoeman JF. Tuberculous meningitis. *N Engl J Med* 2004;351(17):1719-20.

105. Gray K, Wood N, Gunasekera H, et al. Vitamin D and tuberculosis status in refugee children. *Pediatr Infect Dis J* 2012;31(5):521-3.

106. Wejse C, Gomes VF, Rabna P, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009;179(9):843-50.

107. Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev* 2011;(11):CD006086.

108. Elias AF, Dunn J, Huntington MK. Tuberculosis and profound hypovitaminosis D in an infant. *Pediatr Infect Dis J* 2011;30(11):1008-10.

109. Battersby AJ, Kampmann B, Burl S. Vitamin D in early childhood and the effect on immunity to *Mycobacterium tuberculosis*. *Clin Dev Immunol* 2012;2012:430972.

110. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev* 2011;12(1):31-8.

111. Thampi N, Stephens D, Rea E, Kitai I. Unexplained deterioration during antituberculous therapy in children and adolescents: clinical presentation and risk factors. *Pediatr Infect Dis J* 2012;31(2):129-33.

112. Verhagen LM, Warris A, van Soolingen D, de Groot R, Hermans PW. Human immunodeficiency virus and tuberculosis coinfection in children: challenges in diagnosis and treatment. *Pediatr Infect Dis J* 2010;29(10):e63-e70.

113. Marais BJ, Rabie H, Cotton MF. TB and HIV in children – advances in prevention and management. *Paediatr Respir Rev* 2011;12(1):39-45.

114. Marais BJ, Graham SM, Cotton MF, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. *J Infect Dis* 2007;196 Suppl 1:S76-S85.

115. Centers for Disease Control and Prevention. Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection – United States, 2004-2008. *Morb Mortal Wkly Rep* 2010;59(8):224-29.

116. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174(8):935-52.

117. Lobato MN, Mohle-Boetani JC, Royce SE. Missed opportunities for preventing tuberculosis among children younger than five years of age. *Pediatrics* 2000;106(6):E75.

118. Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2005;54(RR-12):1-81.

119. Villarino ME, Ridzon R, Weismuller PC, et al. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. *Am J Respir Crit Care Med* 1997;155(5):1735-38.

120. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *Morb Mortal Wkly Rep* 2011;60(48):1650-53.

121. Wootton SH, Gonzalez BE, Pawlak R, et al. Epidemiology of pediatric tuberculosis using traditional and molecular techniques: Houston, Texas. *Pediatrics* 2005;116(5):1141-47.

122. Munoz FM, Ong LT, Seavy D, Medina D, Correa A, Starke JR. Tuberculosis among adult visitors of children with suspected tuberculosis and employees at a children's hospital. *Infect Control Hosp Epidemiol* 2002;23(10):568-72.

123. Seddon JA, Godfrey-Faussett P, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*. *Lancet Infect Dis* 2012;12(6):469-79.

124. Brassard P, Steensma C, Cadieux L, Lands LC. Evaluation of a school-based tuberculosis-screening program and associate investigation targeting recently immigrated children in a low-burden country. *Pediatrics* 2006;117(2):e148-e156.

125. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis* 2012;55(11):1532-49.

126. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiological investigation, and management of exposures. *Clin Infect Dis* 1998;27(3):474-77.

127. Centers for Disease Control and Prevention (CDC) Division of Tuberculosis Elimination (DTBE). Core curriculum on tuberculosis: what the clinician should know. Available from: http://www.cdc.gov/tb/education/corecurr/index.htm

128. Bekker A, Du Preez K, Schaaf HS, Cotton MF, Hesseling AC. High tuberculosis exposure among neonates in a high tuberculosis and human immunodeficiency virus burden setting. *Int J Tuberc*

129. Laartz BW, Narvarte HJ, Holt D, Larkin JA, Pomputius WF, III. Congenital tuberculosis and management of exposures in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2002;23(10):573-79.

130. Crockett M, King SM, Kitai I, et al. Nosocomial transmission of congenital tuberculosis in a neonatal intensive care unit. *Clin Infect Dis* 2004;39(11):1719-23.