CHAPTER 7: DIAGNOSIS AND TREATMENT OF PEDIATRIC TUBERCULOSIS DISEASE

INTRODUCTION

Pediatric tuberculosis (TB) differs from TB in adults in clinical presentation, diagnosis, and therapy with attention to drug dosages. Certain pediatric populations are more likely to progress to TB disease once infected; as such prompt diagnosis and treatment is essential for positive outcomes. Pediatric age groups span from infancy to adolescence and each group has distinct characteristics related to their TB diagnosis. In general, children younger than five years of age can present with rapidly disseminated disease, while adolescents (13 to 17 years of age) typically present with “classic” TB disease similar to adults.

CHARACTERISTICS OF PEDIATRIC TUBERCULOSIS DISEASE

The presentation of TB disease in children differs from adults and also varies within pediatric age groups (infants, children, and adolescents), as follows:

- Infants and children younger than five years of age are more likely to develop TB disease once infected than children five to 10 years of age
- Children with TB disease diagnosed as a result of a contact investigation are often asymptomatic
- Wheezing is an occasional manifestation of TB disease in infants due to endobronchial disease or lymph nodes compressing a bronchus

Compared to adults with TB disease:

- Infants and young children are less likely to produce a sputum specimen
- Children are more likely to have culture-negative disease
- Pediatric diagnoses often depend upon clinical and radiological response to anti-TB treatment

MEDICAL EVALUATION

TB evaluation of children differs from adults in several aspects including medical history, chest radiograph (CXR), tests for TB infection, and specimen collection. Children tend to be asymptomatic and/or present with atypical disease, and as such, a high level of suspicion for TB disease is required during the evaluation.

MEDICAL HISTORY

A medical history including a comprehensive review of the child's signs and symptoms as well as the family's prior TB history is obtained.

Signs and symptoms indicating TB disease in pediatric patients commonly include:

- Failure to thrive in infants
- Missed developmental milestones
- Behavioral changes including irritability in infants
- Headaches
- Weight loss and/or lack of weight gain

A complete medical history includes:

- Inquiries about prior TB screening results and treatment of latent TB infection (LTBI) or TB disease for the child
- Prior TB disease among household members of the child, caregivers, and visitors
- Possible TB exposures at congregate settings such as a school or daycare
- Foreign birth/details of any foreign travel

PHYSICAL EXAMINATION

A physical examination is needed for every child undergoing evaluation for TB disease. This includes evaluation of the respiratory system, as well as a directed exam for potential extrapulmonary sites of disease such as peripheral lymph nodes, central nervous system (CNS), bones and joints, liver, and spleen.

TEST FOR TUBERCULOSIS INFECTION

When evaluating a child with signs or symptoms of active TB disease, obtaining a positive test result for TB infection increases the likelihood that the child has TB disease; however, a negative result does not rule out TB disease and further diagnostic evaluation for children at high risk for TB disease is necessary. The New York City (NYC) Bureau of TB Control (BTBC) routinely uses the blood-based interferon gamma release assay (IGRA) test to screen for TB infection in individuals two years of age and older, as few indeterminate results are seen in the NYC Health Department TB clinic population. The tuberculin skin test (TST) is used to screen for TB infection in children younger than two years of age or if a blood sample cannot be obtained.

Children are commonly diagnosed with TB disease as a result of a contact investigation. In this context, and given the low prevalence of TB in NYC, a positive test result for TB infection in children is more likely a sign of recent infection, and can aid in the diagnosis of TB disease. Since it can take up to eight weeks after exposure to *M. tuberculosis* for the immune system to mount a response ("window period"), the initial (baseline) test may be falsely negative if conducted too soon after TB exposure. In general, children who are close contacts to an infectious TB patient and younger than five years of age, or children of any age with immunosuppression and an initial negative test for TB infection, are started on prophylactic treatment (preferably four months rifampin [RIF] [4R]). (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.) The initiation of prophylaxis occurs while awaiting the repeat test for TB infection eight weeks after exposure to an infectious TB patient and active TB disease has been ruled out by CXR and medical evaluation.

By six months of age, children should have developed a strong enough immune response to react to a TST. If an infant is tested with a TST before the age of six months and the result is negative, the test is repeated again at age six months; if positive, the child is re-evaluated for active disease and LTBI treatment is continued for the remaining duration of therapy once TB disease is ruled out. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection* and *Chapter 11: Contact Investigation*.) If the test at six months is negative and the testing is past the window period, then prophylactic therapy can be discontinued.

CHEST RADIOGRAPH

In children younger than five years of age, BTBC recommends a lateral CXR in addition to a posterior-anterior (PA) view to assess for pulmonary TB disease. Children five years of age and older receive a PA CXR only, unless additional views are clinically indicated.

›› When practical, CXR images are interpreted by a radiologist experienced in reading pediatric CXRs.

- CXR abnormalities can be present in children even if they are asymptomatic.
- The most common radiological abnormalities are persistent opacification in the lung in conjunction with enlarged hilar or subcarinal lymph nodes.
- A miliary pattern of opacification is highly suggestive of TB disease.
- Patients with persistent opacification who do not improve after a course of antibiotics should be investigated for TB disease.

SPECIMEN COLLECTION

As part of the diagnostic process for pediatric patients, the most common specimens collected include sputum, gastric aspirates, and cerebral spinal fluid (CSF) via lumbar puncture; other specimens are collected as clinically indicated. Once collected, all specimens are sent for acid-fast bacilli (AFB) smear and mycobacterial culture.

SPUTUM

Sputum induction is a safe and effective method for collecting sputum and performed in children old enough to understand and cooperate with the procedure. Sputum bacterial yields are as good as, or better than, those from gastric aspirates; however, staff training and specialized equipment are required to perform this procedure properly. (See *Appendix E: Instructions for Performing Sputum Induction*.) If possible, sputum is collected for any child with signs and symptoms consistent with TB disease or diagnosed with TB disease. At least three sputa specimens for AFB smear and mycobacterial culture are collected during the diagnostic process.

When TB is highly suspected, nucleic acid amplification (NAA) testing is requested regardless of AFB smear results. A positive NAA test result confirms the presence of TB; however, a negative NAA test result in an AFB smear-negative specimen does not rule out TB disease. (See *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*.)

GASTRIC ASPIRATION

Because young children are often unable to produce sputum **either** spontaneously or with aerosol inhalation, gastric aspirate specimens can be obtained in limited instances when it is especially important for diagnostic or treatment decisions.

- Children should fast for at least four to eight hours before gastric aspiration.
- Children with a low platelet count or bleeding tendency should not undergo gastric aspiration.
- AFB smear and mycobacterial culture are requested for testing.
- NAA testing is recommended if available. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

- The highest bacterial yields from a gastric aspiration are obtained when the patient is hospitalized.
- The specimen is taken as soon as the patient wakes in the morning, while still in bed. The first aspirate of the day will have the highest bacterial yield.
- Approximately 50 milliliters (ml) of gastric contents are aspirated via nasogastric feeding tube during three consecutive mornings.
- Obtaining a gastric aspirate specimen is more important when evaluating a child who has been exposed to an infectious individual with drug-resistant TB (DR-TB).
- Repeat gastric aspirates are not recommended once the child is on appropriate treatment.

LUMBAR PUNCTURE

For additional information on how to collect a gastric aspirate, see *Pediatric TB: A Guide to the Gastric Aspirate Procedure* at: www.currytbcenter.ucsf.edu/products/view/pediatric-tuberculosis-guide-gastric-aspirate-ga-procedure

A lumbar puncture is performed in infants and children with signs and symptoms consistent with congenital TB disease, disseminated TB disease, or TB meningitis. In these instances, the CSF is sent for cell count, protein, and glucose, as well as AFB smear and mycobacterial culture.

VISION SCREENING

Prior to initiating the use of ethambutol (EMB), a standard anti-TB drug, visual acuity and/or color vision are assessed in children old enough to be evaluated. Recent editions of the American Academy of Pediatrics (AAP) Red Book note, however, that the use of EMB in infants and young children whose visual acuity cannot be monitored requires consideration of risks and benefits, but can be used routinely to treat TB disease unless otherwise contraindicated.

- If the child can both identify letters on an eye chart and discriminate colors, this can be used for monitoring potential EMB toxicity.
- If the child can discriminate colors, but cannot identify letters, color vision is used to routinely screen for potential EMB toxicity.
- If the child's vision cannot be evaluated, EMB is only used when the child:
  - Is known or likely to have DR-TB
  - Has HIV infection
  - Is immunosuppressed from another clinical condition

HUMAN IMMUNODEFICIENCY VIRUS TESTING

All patients being evaluated for TB disease, including children, should have a test for HIV. Minors under 13 years of age or persons who are deemed not to have the capacity to consent should be offered HIV testing through a parent or guardian. Children 13 to 18 years of age do not need parental authorization for HIV testing in New York State (NYS). A medical provider ordering the test must conduct an individualized assessment of every older child's or adolescent's ability to understand the nature and consequences of being tested for HIV and to make an informed decision about whether testing should occur. Any patient who tests positive for HIV is referred to an HIV specialist for appropriate follow-up and care. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

CONGENITAL AND NEONATAL TUBERCULOSIS DISEASE

Congenital TB disease is defined as disease acquired by an infant due to exposure to *Mycobacterium tuberculosis* (*M. tuberculosis*) bacilli either in utero or at delivery. Neonatal TB disease is acquired by the baby after birth. The distinction between congenital and neonatal TB is primarily epidemiologic; presentation, management, and prognosis are similar. In pregnant patients with TB disease, regardless of TB treatment status during pregnancy, the placenta should be examined microscopically for granulomas, stained for AFB, and sent for AFB culture.

Congenital/neonatal TB disease can occur in several situations:

1. **TB disease recently diagnosed in a pregnant patient prior to delivery OR TB untreated during pregnancy.** In these instances, the fetus is at risk for congenital TB and prompt evaluation of the neonate and the placenta must be coordinated and planned **prior to delivery** (i.e., submission of the placenta for AFB smear and culture, as well as gross and microscopic pathological examination).
    - When the placenta demonstrates pathological evidence of TB disease, empiric treatment of TB disease in the neonate is necessary.
    - When the placenta does not demonstrate pathological evidence of TB disease and the mother is not infectious, clinical judgment is used to guide the treatment of the neonate.
    - When the placenta does not demonstrate pathological evidence of TB disease, but the mother is infectious, a decision is made to treat the infant for presumptive TB infection. RIF is administered for four months OR until the mother is culture-negative, whichever is longer.
        - Children born to mothers with active untreated disease are more likely to develop TB disease in their first year of life if treatment for LTBI is not given to the neonate.
    - If the pregnant patient is infectious at the time of delivery, plans are made to prevent transmission to the neonate. (See *Chapter 13: Infection Control*.)

2. **The diagnosis of TB in the newborn leads to a retrospective diagnosis in the mother.** As a significant percentage of pregnant patients with pulmonary TB disease are unaware of their diagnosis and/or may be asymptomatic, the diagnosis of TB in the neonate may be the first indication of TB in the mother. These neonates are often born premature, are very ill, and are only diagnosed with TB after unsuccessful treatment for other life-threatening infectious diseases. If the mother is evaluated and found to have a normal CXR, examination for gynecological or other forms of extrapulmonary TB should be performed.

3. **When infectious TB disease is diagnosed in the mother or another individual who has close contact to the infant during the neonatal period, the neonate is at increased risk for transmission of TB after delivery.** If the mother is diagnosed with infectious TB after delivery, the placenta is typically not available for evaluation, making the distinction between congenital and neonatal TB disease in the infant difficult. Regardless of whether the mother or another individual exposed the infant to TB, a full evaluation for TB disease is indicated and clinical judgment is used to determine whether to treat the infant for active disease or presumptive LTBI. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.)

If the mother completed treatment for active TB during pregnancy and there is no evidence of active disease in the mother at the time of birth, there is minimal risk to the infant. The placenta and neonate should still be evaluated; however, there is no need for specific treatment of the neonate once TB disease has been ruled out.

EVALUATING NEONATES FOR TUBERCULOSIS DISEASE

All neonates being evaluated for TB disease have:

- Medical evaluation
- TST (usually negative in newborn infants with congenitally or perinatally-acquired infection)
  - If not performed initially due to presumed lack of immune response, a test for TB infection should be performed at six months of age or older.
- CXR
- Three gastric aspirates on three consecutive days
- Lumbar puncture if there is a high clinical suspicion for active TB disease
- Examination of the placenta if available for pathology and AFB smear and culture

In infants suspected of having congenital TB disease, treatment is started with isoniazid (INH), RIF, pyrazinamide (PZA), and an injectable agent if hospitalized. Amikacin (AK) is recommended, but streptomycin (SM) can be used. Ethionamide (ETA) is considered as an alternative.

- Corticosteroids are added if the neonate has meningitis.

TREATMENT OF PEDIATRIC TUBERCULOSIS DISEASE

The treatment of TB disease in children differs from adults in several aspects. Children younger than five years of age are more likely to be culture-negative and to have been recently exposed to a person with infectious TB disease. In these instances, the drug-susceptibility test (DST) results from the source patient who likely infected the child are used to develop an appropriate treatment regimen. Despite differences in the treatment of TB in adults and children, directly observed therapy (DOT) is the standard of care in pediatric TB as it is in adult TB and is the best way to ensure successful therapy. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)

STANDARD REGIMEN

Children who are treated empirically or who are suspected to have drug-susceptible TB are treated with a four-drug regimen of INH, RIF, PZA, and EMB. Once DST results are available, the regimen is modified accordingly. (See *Table 7.1: Selected Drug Regimens for Pediatric Tuberculosis* and *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.)

Anti-TB medications are administered daily within a specific milligram (mg)/kilogram (kg) dose range. Additionally, children metabolize most drugs more rapidly than adults and therefore may require higher mg/kg dosing. Recent publications recommend daily dosing of RIF at 15 to 20 mg/kg/day. The recommended daily dose of EMB is higher in children than in adults at 20 mg/kg.

Daily dosing of RIF for TB disease is recommended at 15 to 20 mg/kg/day.

EMB may be omitted or discontinued from the regimen if the child:

- Cannot participate in visual acuity/color vision assessments
- Is culture-negative and the isolate of child's source case is drug-susceptible

PZA and EMB are discontinued if:

- The DST of the child's isolate shows sensitivity to INH and RIF.
  - EMB is discontinued once susceptibilities to first-line medications confirm susceptible TB.
  - PZA can be discontinued after the two-month intensive phase.
- The child is culture-negative and the results from the source case show sensitivity to INH and RIF. EMB is discontinued immediately and PZA after completion of the intensive phase.
- The child has no reportable DST results and drug resistance is not suspected. EMB and PZA are discontinued after completion of the intensive phase.

TABLE 7.1: Selected drug regimens for pediatric tuberculosis*

INTENSIVE PHASE		CONTINUATION PHASE[1,2,3]		NOTES
Drugs	Interval and Duration	Drugs	Interval and Duration	
INH **RIF** **PZA** **EMB**[5]	7 days/week for 8 weeks (56 doses)	**INH** **RIF**	**PREFERRED:** 7 days/week for 18 weeks (126 doses) 3 days/week for 18 weeks with DOT[4] (54 doses)	• Drug-susceptible TB disease or TB presumed to be drug-susceptible
INH **RIF** **PZA** **ETA/AK**	7 days/week for 8 weeks (56 doses)	**INH** **RIF**	7 days/week for 28-40 weeks (196-280 doses) --- or --- 3 days/week for 28-40 weeks (84-120 doses)	• TB meningitis when drug resistance is not suspected • Injectable agent commonly added for hospitalized patients is AK • ETA is well-tolerated in children and has increased penetration into the CNS
INH **RIF** **PZA** **EMB**[5]	7 days/week for 8 weeks (56 doses) (PZA and EMB used until susceptibility results available)	**INH** **RIF**	7 days/week for 28 weeks (196 doses) --- or --- 3 days/week for 36 weeks[4] (108 doses)	• *M. bovis*; universally resistant to PZA • When the laboratory identifies *M. bovis*, PZA and EMB are discontinued • The total length of treatment for *M. bovis* is 9 months

Adapted from: Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195.

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, ed. Red Book: 2018-2021 Report of the Committee on Infectious Diseases, 31st Edition. Elk Grove Village, IL: American Academy of Pediatrics; 2018: 829-853.

*Provided dosages in the table are estimates based on an approximate number of weeks of treatment; actual doses need to be calculated based on patient's actual treatment

1. Biweekly treatment regimens during the continuation phase are not recommended due to high rates of relapse
2. For missed doses, extend treatment to make up the doses, unless there has been prolonged treatment interruption
3. Patients with a positive *M. tuberculosis* culture at 2 months of treatment regardless of CXR, extensive disease, or PZA not given for the 2 month intensive phase should receive a 7-month continuation phase (31 weeks; either 217 doses daily or 93 doses 3 times per week)
4. Not recommended for patients with HIV infection
5. Exclude EMB when the child is not able to participate in monitoring for potential visual toxicities

Abbreviations Used: AK=amikacin; CXR=chest radiograph; DOT=directly observed therapy; EMB=ethambutol; ETA=ethionamide; HIV=human immunodeficiency virus; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; TB=tuberculosis

SPECIAL CONSIDERATIONS FOR DRUG ADMINISTRATION TO YOUNG CHILDREN

- INH or PZA tablets can be divided, crushed, or added to food or liquids such as fruit, juice, pudding, or gelatin.
- RIF may be emptied from the capsule and added to food or liquids just before ingestion.
- Liquid formulations are considered when available; however, sorbitol-free formulations for INH are preferable to reduce the likelihood of gastrointestinal (GI) side effects that may complicate treatment adherence.
- RIF and other first-line agents (except for INH) can be compounded by the BTBC Pharmacy for patients receiving clinical care at a NYC Health Department TB clinic.

LENGTH OF TREATMENT

The six-month treatment duration for culture-positive drug-susceptible TB disease in children is the same as with adults and consists of a two-month intensive phase followed by a four-month continuation phase. In culture-negative pediatric TB, children are treated for six months (instead of the four-month regimen used for adults).

In certain situations, treatment length can be extended based on clinical characteristics and/or site of disease. Treatment length can also be extended based on clinical indication.

In the following situations, treatment is usually given for nine months total; however, it can be extended to 12 months based on clinical judgment:

- Patients who have positive sputum cultures after two months of therapy, regardless of CXR results
- Patients whose treatment regimen did not include PZA in the intensive phase or who are resistant to PZA (i.e., *M. bovis*)
- Patients with extensive disease or who have findings of a cavitary CXR, if poor clinical response to treatment is observed
- Patients with disseminated TB in more than one site of disease
- Patients with HIV infection who are not on antiretroviral therapy (ART) during TB treatment
- Patients who have central nervous system (CNS) TB disease; treatment of CNS TB disease is usually nine to 12 months total

For all other extrapulmonary sites of disease, see *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease* in *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults.*

For children with hilar adenopathy or extrapulmonary TB disease, treatment should be given for a total of six months with the same regimen as for pulmonary TB.

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

The treatment of DR-TB in children follows the basic strategy used for adults and is customized according to isolate DST, molecular and conventional. Some experts are now recommending an all-oral regimen in children; however, outcome data is still pending. Expert consultation is necessary to optimize treatment regimens and outcomes. For treatment of DR-TB, see *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults* and *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

SPECIAL CONSIDERATIONS FOR CENTRAL NERVOUS SYSTEM TUBERCULOSIS DISEASE

Children with CNS TB disease can rapidly develop devastating neurological complications and may benefit from hospitalization until their clinical status has stabilized. These patients are at high risk of long-term disability and require specialized care.

Children diagnosed with CNS TB disease have a modified treatment regimen from those with pulmonary TB disease due to poor penetration of most TB medications into the CNS. The AAP recommends starting empiric treatment with either an injectable agent (aminoglycoside or capreomycin [CM]) or ETA as the fourth drug along with INH, RIF, and PZA even before laboratory confirmation of disease, if clinically indicated. INH, RIF, and PZA penetrate the blood-brain barrier efficiently; ETA and the injectable agent penetrate the barrier only when meninges are inflamed. Because the penetration of some drugs is poor (i.e., RIF), treatment regimens for CNS TB and miliary TB will most likely benefit from the higher end of recommended dose ranges. (See *Appendix I: The Use of Anti-Tuberculosis Drugs and Pregnancy, Breastfeeding, Tuberculosis Meningitis, and Renal and Hepatic Failure*.) In NYC, the injectable agent most commonly used while the patient is hospitalized is AK. The AAP recommends ETA as the fourth drug rather than EMB, as it is better tolerated in children and has increased penetration into the CNS. While a daily dose of 15 to 20 mg/kg of RIF is usually recommended, some experts recommend using a dose of 20 to 30 mg/kg/day for infants and toddlers.

Corticosteroids are routinely recommended when treating any patient with CNS TB, especially when treating a patient with a symptomatic tuberculoma, or any patient with CNS TB disease who has a decreased level of consciousness. Corticosteroids improve survival in individuals with severe disease and may reduce neurologic morbidity as well. If corticosteroids are used in a patient with a tuberculoma, dosages and tapering are similar as those for meningeal TB. Expert consolation with a neurologist is obtained as necessary. Corticosteroids are only given if the patient is on appropriate anti-TB therapy. Expert opinion on the optimal dosage for steroids varies; however, most experts recommend two mg/kg per day of prednisone (maximum 60 mg/day) or its equivalent for four to six weeks followed by tapering.

ADVERSE EVENTS IN CHILDREN

Adverse events caused by anti-TB drugs are less common in children than in adults and overall clinical monitoring is similar in adults and pediatric TB patients. The most serious adverse event is the development of hepatotoxicity, which can be caused by most TB medications; however, it is more commonly seen with INH, PZA, and RIF. Serum liver enzyme levels do not need to be monitored routinely unless the child has underlying hepatic disease or symptoms of hepatic disease.

The occurrence of liver tenderness, hepatomegaly, or jaundice results in investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. The patient is evaluated for other causes of hepatitis and anti-TB medications are reintroduced in a step-wise fashion. If continuation of TB treatment is necessary, a liver-sparing regimen can be considered in the interim (i.e., EMB, an injectable agent, and a fluoroquinolone [FQN]). (See *Chapter 8: Clinical Monitoring and Follow-Up for Tuberculosis Treatment*.)

SUMMARY

The diagnosis of TB disease in children requires the provider to have a high index of suspicion, and in young children is in part informed by the diagnosis of infectious TB disease in a family member or caretaker. A TB diagnosis is more likely to be established clinically after empiric treatment has been initiated since children are more likely to have AFB smear- and culture-negative results. Children may need increased mg/kg dosages of some TB medications and tolerate medications better than adults. Outcomes in children are excellent when treatment is initiated promptly.

KEY SOURCES

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, ed. *Red Book: 2018-2021 Report of the Committee on Infectious Diseases, 31st Edition*. Elk Grove Village, IL: American Academy of Pediatrics; 2018: 829-853.

Davis A, Meintjes G, Wilkinson RJ. Treatment of tuberculous meningitis and its complications in adults. *Curr Treat Options Neurol*. 2018 Feb 28;20(3):5.

Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med*. 2018 Aug 2;379(5):454-463.

Iseman MD. *A Clinician's Guide to Tuberculosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017 Jan 15;64(2):111-115.

Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e147-e195.

Schaaf HS, Garcia-Prats AJ, Hesseling AC, Seddon JA. Managing multidrug-resistant tuberculosis in children: review of recent developments. *Curr Opin Infect Dis*. 2014 Jun;27(3):211-9.

World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. Geneva: World Health Organization; 2014. http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf