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Tuberculosis in Children

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NATURE OF THE PROBLEM

TB is an infectious disease caused by *Mycobacterium tuberculosis* complex (Mtb).[1] Each year, 7.5 million children are infected with TB and 1.1 million children develop tuberculosis disease worldwide, representing 12% of the global TB burden.[2] At the same time, children have a disproportionately higher mortality, with 230,000 deaths annually.[2] The high mortality rate is a reflection of the challenges in diagnosing and treating TB in children, especially the most vulnerable including young children under 5 years old and children with HIV co-infection.[3–6] The incidence of TB disease further increases when they enter adolescence and begin to develop adult-type disease.[5, 7]

In the United States (US), TB cases have shifted towards foreign-born adults,[8, 9] but 4% of the national TB disease prevalence is still in children less than 15 years old and 10% are adolescents and young adults 15–24 year old.[8] Disparities exist with disproportionately higher rates among non-white ethnic groups and in the US-affiliated islands.[10] Treatment of TB infection in children and adolescents is critical to prevent progression to TB disease and to prevent them from becoming the future reservoir for TB transmission.[11]

In this review, we will outline the current approach to diagnosis and treatment of TB infection and disease in children, focusing on the main issues that arise during clinical care and concluding with emerging diagnostic and therapeutic options.

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TB INFECTION

DIAGNOSIS

Latent TB infection (LTBI) represents a state in which the child has evidence of an immune response to Mtb, but does not have signs and symptoms of TB disease. In this stage, the mycobacteria are thought to be controlled but not eliminated by the immune system.[12] As a consequence, children with LTBI are not infectious.[1] LTBI evaluation requires a combination of risk factor assessment and immunological evidence of infection, while ensuring there is no clinical or radiographic evidence of TB disease.

The American Academy of Pediatrics (AAP) recommends screening for TB risk factors at the first well-child visit, every 6 months for the first year of life, and then annually.[13] Schools may require TB screening as a requirement for entry and juvenile detention centers may perform initial screening as a congregate setting. Multiple screening tools are available, and the suggested questions are outlined in Table 1. The risk factors for infection or progression to TB disease fall into three categories: 1) Birth or significant time spent in a TB endemic setting; 2) Known or suspected TB exposure, or a high risk of TB exposure, and 3) Immunosuppression. Immunosuppression can be due to HIV infection, cancer, organ transplantation, biologic response modifiers (including anti-TNF alpha inhibitors), and prolonged steroid use. Children with HIV are at an increased risk of TB disease, and should be tested annually if previously negative.[13] Additional risk factors, such as renal failure requiring hemodialysis, homelessness, or ingestion of unpasteurized milk products, should be included as relevant to the local demographics of TB disease in the community.

TB INFECTION TESTING

Testing for TB infection in low incidence settings such as the US should be performed only for those with risk factors since testing the general population will have a low positive predictive value and increases the likelihood of false positivity.[14] Testing options for TB infection include the tuberculin skin test (TST), also referred to as purified protein derivative (PPD), and interferon-gamma release assays (IGRAs). For children that have been recently exposed to TB, negative testing is repeated 8–10 weeks after the last exposure to Mtb to allow for the development of an adaptive immune response.[15] As LTBI testing reflects an immune response after exposure to TB, there is low utility in serial or future testing after a positive result.

Tuberculin Skin Testing—TST involves intradermal injection of a tuberculin protein mixture, with measurement of the induration caused by a delayed hypersensitivity reaction after 2–3 days.[1] The cut-off for induration is 5 mm for children with a TB contact, symptoms concerning for TB, or are immunocompromised (including HIV), and 10 mm for children under 5 years old or who have lived in a TB endemic setting.[13] A 15 mm cut-off is for children 5 years and older without risk factors. The advantages of TST are that it can be performed in the community without a laboratory and is affordable, making it attractive for large-scale screening activities. However, tuberculin needs to be refrigerated, testing requires two visits, technical placement can be difficult, and inter-reader reliability can be variable.[16]

The overall performance of TST is moderate in children, with sensitivity ranging from 67–85%,[16–19] and specificity ranging from 70–92%.[16, 19] TST can cross-react with other non-TB mycobacteria (NTM), including *Mycobacterium Avium* Complex or MAC, and the Bacillus Calmette–Guérin (BCG) vaccine, leading to false positive results.[15] BCG vaccine is often given at birth, and the cross-reaction will wane over time,[20] but are more likely to persist if the individual received the vaccine or a booster when older (local guidelines are available at http://www.bcgatlas.org/). False negative results can occur in children who are less than 6 months old, immunosuppressed, have severe TB disease, recent TB infection, other concomitant bacterial infections, and if recently given a live virus vaccine including measles.[18] In addition, technical challenges in storing, administering and reading TSTs can lead to false negative results.

Interferon-gamma release assays (IGRAs)—IGRAs are blood-based assays that measure T-cell release of interferon-gamma after exposure to TB-specific antigens ESAT-6 and CFP-10.[1] The two most common assays are QuantiFERON Gold Plus (QFT, Qiagen, Germantown, MD, USA) and T-SPOT.TB test (Oxford-Immunotec, Abingdon, United Kingdom), with cut-offs determined by the amount of interferon-gamma detected relative to the background from a negative control. If the positive and/or negative controls fail, the assays will result as indeterminate or invalid. T-SPOT.TB also has a borderline category that is between a negative and positive result.

Compared to TST, IGRAs have similar sensitivity (57–85%),[17–19] but improved specificity (85–100%).[17–19] The higher specificity is because IGRAs do not cross-react with the BCG vaccine and are less likely to interact with other NTMs. In addition, only a single visit is needed unlike the TST.[15] Consequently, IGRAs are preferred over TST for LTBI testing in the US,[1, 15] and is required for all immigrants 2 years and older as part of the civil surgeon medical evaluation.[21] While TST has been preferred for children under 2 years old, growing evidence suggests that IGRAs perform similarly to TST in young children and discordant results have not resulted in missed TB cases,[22] although both have reduced sensitivity in younger children.[13, 19] The AAP still recommends that a TST be used for children under 2 years old, but they do allow IGRA testing.[13]

Several limitations of IGRAs can impact their implementation. IGRAs use blood samples that can be invasive and difficult to obtain in children, and requires laboratory infrastructure.[16, 23, 24] IGRAs are more expensive than the TST, although a family may have reduced costs by not requiring an additional visit.[19] Indeterminate, invalid or borderline results can complicate interpretation and negates the benefits of a single visit if repeat testing is needed. Also, false negatives can still occur with IGRAs in individuals who are immunosuppressed, young children, early TB infection, or advanced TB disease.[18]

Interpretation of TST or IGRA results—Interpretation of either a TST or IGRA should take into account the risk factors that initiated LTBI testing. A positive result from either a TST or IGRA in a child with TB risk factors should be considered a true positive unless there is a clear alternative diagnosis. We generally do not obtain both a TST and IGRA, unless we are concerned about a false negative and want to repeat testing. In children less than 2 years old with BCG vaccination, a positive TST should account for the child's

TB risk factors, but if concerned for a false positive an IGRA can be performed. If TST and IGRA results are discordant, we would consider the likelihood of a false positive by TST, whether any technical factors may have led to a false negative by one of them, or the possibility of alternative diagnoses including NTM infection if TST positive and IGRA negative. However, we would again consider the risk factors of the child for TB progression and complications, and would have a low threshold for classifying them as positive if no clear alternative explanation exists. Indeterminate, invalid or borderline IGRA results should be repeated, either with the same or different IGRA, or with a TST.

Excluding TB disease—Neither TST or IGRA can differentiate TB infection from disease, and it is critical to rule out symptomatic disease before initiating LTBI treatment.[13] Symptom screening should include fever, cough, weight loss or failure to thrive, with a complete clinical exam including growth assessment and evaluation of extrapulmonary manifestations including lymphadenopathy. Two-view antero-posterior and lateral chest x-rays (CXR) are recommended in the US, especially as children can have subtle or absent symptoms. If abnormal, we would consider further evaluation of TB disease including sputum-based testing before initiating LTBI treatment.

TREATMENT OF LATENT TB INFECTION

Isoniazid monotherapy has been the mainstay of LTBI treatment presumed to be susceptible to isoniazid and rifampin for decades. Meta-analyses of isoniazid prophylaxis in adults and children showed isoniazid preventive therapy reduces the risk of TB disease by 60% over the subsequent two years.[25, 26] Some studies have shown effectiveness of > 90% when restricting the analysis to those who were adherent.[27] However, the effectiveness of isoniazid for TB prevention has been limited by low adherence and completion rates due to prolonged treatment durations (6–9 months) and by the risk of hepatotoxicity. Rifamycin-based treatment regimens are now the preferred regimens for LTBI treatment due to higher treatment completion rates and decreased hepatotoxicity.[28, 29] These regimens include 3 months of once-weekly isoniazid plus rifapentine (3HP), 4 months of daily rifampin (4R), and 3 months of daily isoniazid plus rifampin (3HR). Drug-drug interactions with rifamycins, particularly with HIV antiretroviral therapy, may limit their use in some populations.

Isoniazid and rifapentine weekly for three months (3HP)—3HP is a preferred regimen among children aged 2 years and older. This regimen is non-inferior to 9 months of daily isoniazid in adults, children aged 2 to 17 years and adults with HIV.[30–32] Though not well studied in children with HIV, this regimen is expected to be as efficacious in this population. Although initial studies were done with directly observed therapy, programmatic data have shown high completion rates with self-administered therapy and directly observed therapy is no longer mandatory.[28, 33, 34] Children tolerate 3HP well with lower rates of adverse events compared with adults, this include hepatoxicity which has not yet been shown in children. Side effects of 3HP include isolated rash and mild, self-resolving influenza-like symptoms including fever, fatigue, headache, dizziness, nausea, myalgia, and rarely hypotension and syncope, which typically occur several hours after ingestion of the third or fourth dose.

Rifapentine is a potent inducer of the cytochrome P-450 enzyme and the P-glycoprotein transport systems and drug-drug interactions are anticipated. 3HP can be administered in children taking an efavirenz-based antiretroviral therapy regimen, but not to children on integrase inhibitors, protease inhibitors, and some non-nucleoside reverse transcriptase inhibitors (NNRTIs) including nevirapine. Planned studies will assess the drug-drug interaction with dolutegravir in children.

Dosing for the 3HP regimen in children is shown in Table 2. Currently, rifapentine is only formulated as a 150 mg film-coated tablet. The pharmacokinetics of the crushed tablet have been studied and current dosing recommendations account for an estimated 30% reduction in oral bioavailability associated with crushing the tablet.[35] Crushed tablets are bitter tasting, but tolerable and should be mixed with high-fat foods like ice cream or pudding to enhance absorption. While some parents prefer daily regimens to enhance adherence, others may prefer intermittent regimens to decrease the total number of doses required. Drawbacks of the 3HP regimen include the lack of dosing for children aged less than 2 years, the lack of a child-friendly formulation, the relatively high cost of the regimen, and drug-drug interactions.

Rifampin daily for four months (4R)—Four months of daily rifampin is a preferred regimen for adults and children of all ages. Compared with 9 months of isoniazid (9H), 4R has non-inferior efficacy, an improved safety profile, and higher rates of treatment completion with self-administered therapy.[34, 36, 37] Drug-induced hepatitis remains the most common severe adverse event, but is less common than with 9H. There are limited data for efficacy of the 4R regimen in people living with HIV, but no reason to believe it would be less efficacious.

Side effects of rifampin include minor gastrointestinal symptoms (common) and dermatologic reactions (rare).[36] Hepatotoxicity is reported, but rare in children occurring in 0–2% of children.[36] Rifampin notably results in temporary orange discoloration of bodily fluids such as saliva, urine, sweat, and tears.

Dosing for rifampin is shown in Table 2. Rifampin is formulated as capsules (150mg and 300mg), which can be opened and sprinkled in food and as an extemporaneous solution (10 mg/mL) made at compounding pharmacies.

Rifampin is a potent inducer of the cytochrome P-450 enzyme and the P-glycoprotein transport systems, resulting in multiple clinically significant drug interactions. Concomitant use of certain classes of drugs should be avoided where possible including oral contraceptives, azole antifungal agents, and calcium channel blockers. Other drug classes require close monitoring and/or dosage adjustments including HMG-CoA reductase inhibitors, warfarin, glucocorticoids, methadone, and tacrolimus. Rifampin has significant drug interactions with antiretroviral agents including integrase inhibitors, protease inhibitors and some NNRTIs including nevirapine. Importantly, this limits the use of rifampin not only among children with HIV, but also HIV exposed, uninfected children who remain on nevirapine prophylaxis.[38] Twice daily dolutegravir was safe and sufficient to overcome the enzyme-inducing effect of rifampin for children.[39]

Isoniazid and rifampin daily for three months (3HR)—A regimen of three months of daily isoniazid and rifampin is recommended for adults and children of all ages including those children with HIV, although use in this population may be limited by drug interactions. Overall, for HIV-negative adults and children, this regimen has been shown to have similar efficacy, hepatotoxicity, and adverse events requiring discontinuation of therapy as those receiving at least 6 months of isoniazid. Other side effects apart from hepatotoxicity include gastrointestinal intolerance and rash.

Dosing for the 3HR regimen is shown in Table 2. In the US, these drugs are formulated separately and result in a high pill burden, limiting the utility of this daily regimen. Globally, the dispersible fixed dose combination (75/50mg) makes this regimen attractive while we await a child-friendly formulation of rifapentine. Although this regimen may be used in children with HIV, drug interactions have been shown between rifampin and multiple antiretroviral agents as described above, limiting its use in some children.

6 or 9 months of isoniazid (6H or 9H)—Although rifamycin-based therapies are now preferred, 6H and 9H are alternative regimens to treat LTBI in children with or without HIV who are unable to take a preferred regimen due to drug-drug interactions or intolerability.[28] Isoniazid has been well-studied in many populations including adults and children with and without HIV. Drug-induced hepatitis remains the most common severe adverse event, occurring in about 1% of children. Early symptoms include poor appetite, nausea and abdominal pain. When symptoms are identified early and the drug is stopped, hepatotoxicity is reversible.

Dosing for 6H and 9H are shown in Table 2. Isoniazid comes in 100mg scored tablets that are easily crushed and mixed with formula, breast milk, or food. Isoniazid solution causes significant GI disturbance and is not tolerated in over 50% of children. There are few drug-interactions with isoniazid, making it an attractive regimen for children with HIV and children taking medicines known to interact with rifamycins.

Treatment of Latent TB after Exposure to Drug-resistant TB—There are no established regimens for LTBI after exposure to isoniazid and rifampin-resistant TB. Observational data suggest monotherapy with a fluoroquinolone may be sufficient for treatment,[40] but some experts recommend dual therapy. Consultation with pediatric disease experts is recommended.

LTBI treatment and Development of Drug-Resistance—Concerns over the development of drug resistance have hindered implementation of LTBI treatment. Resistance can largely be avoided by adequately ruling out TB disease prior to the initiation of LTBI treatment to avoid monotherapy and the risk of resistance.[41] Early TB disease may be missed with clinical evaluation. Because early disease and most pediatric disease is paucibacillary, the risk of developing resistance with one or two-drug LTBI treatment, even in the presence of TB disease, is considered rare.

Nitrosamines—In August 2020, the FDA reported that nitrosamines had been identified in both rifapentine and rifampicin, including 1-cyclopentyl-4-nitrosopiperazine (CPNP) and

1-methyl-4-nitrosopiperazine (MNP). While no data show an associated between CPNP or MNP and cancer, this is assumed based on long term animal studies with similar compounds. The risk of cancer with any of these short-course LTBI treatment regimens is unknown. When weighing the alternatives of withholding LTBI treatment or using INH monotherapy, the risk of developing TB disease, hepatoxicity or liver failure far outweighed the potential future cancer risk. The FDA has temporarily raised the acceptable nitrosamine threshold in rifamycins while pharmaceutical companies work to lower nitrosamine levels in all rifamycins.

TB DISEASE

DIAGNOSIS

Currently, no single test can reliably and accurately diagnose TB disease in children. Instead, we depend on the child's TB risk factors combined with clinical, radiographic and microbiological evidence to support a diagnosis,[42, 43] recognizing the limitations of each approach. Given the challenges in TB diagnosis, and that 96% of pediatric TB deaths are in children who were not started on treatment,[3] it is critical to have a low threshold to initiate empiric treatment if there is sufficient, albeit incomplete, evidence to suggest TB.

Clinical evaluation—Clinical signs and symptoms for TB disease in children include fever, prolonged cough (>1–2 weeks), weight loss and failure to thrive. While pulmonary TB is the most common type, children are more likely than adults to have extrapulmonary manifestations, including lymph node, abdominal, bone, joint and central nervous system (CNS) disease. Thus, a complete clinical exam is essential, including evaluation of growth. In spinal TB, collapse of the vertebral bodies may create a kyphosis known as a Gibbus deformity. CNS disease can manifest with altered mental status, cranial nerve palsies, headache, vomiting, or seizures.[44]

Radiographic findings—Children should receive a two-view (antero-posterior and lateral) CXR. Chest radiographic findings reflect the pathophysiology of pediatric pulmonary TB, which is often primary TB disease as opposed to reactivation disease seen in adolescents and adults.[18, 45] Primary pulmonary TB disease manifests with mediastinal lymphadenopathy which may or may not have a granulomatous parenchymal inflammation (Ghon focus), referred together as the Ghon complex.[18, 46]

Each component (lymph node and parenchymal inflammation) can then progress to create further complications. The lymphadenopathy can cause airway obstruction that can lead to lung collapse, a post-obstructive expansile pneumonia, or create a ball-valve effect to hyperinflate the lungs. Lung consolidation, cavitation and bronchiectasis can result either from evolution of the parenchymal involvement or from extension of a lymph node into the lung tissue or bronchioles. This can further extend to the pleura, and cause a pleural effusion or empyema. In disseminated disease, a diffuse small nodular "miliary" pattern reflects the hematogenous spread. Adolescents can have adult-type TB, which can present with cavitation, upper lobe consolidations and fibrosis or scarring, and are more likely to have a pleural effusion than younger children.[47]

The wide range and non-specific radiographic manifestations in children make it difficult to diagnose TB solely by CXR.[48–50] Chest ultrasound has been evaluated to assess mediastinal lymphadenopathy,[48] but can be operator-dependent. There is a limited role for chest computed tomography (CT) given the findings are still non-specific with additional cost and radiation, but it can better detect lymphadenopathy and may have a benefit if considering other etiologies that would warrant advanced imaging.

For abdominal TB, imaging (ultrasound, CT, MRI) may reveal lymphadenopathy, hepatosplenomegaly with tuberculomas, and thickening of the terminal ileum. CNS TB can be evaluated by magnetic resonance imaging (MRI) or CT, and can have several presentations including ring-enhancing tuberculomas, abscess, and leptomeningeal enhancement, especially in the basilar region.[18, 51]

Respiratory sample testing—The standard evaluation for TB includes the collection of respiratory specimens for Mtb testing.[1, 13] Sample types can include expectorated or induced sputum, or gastric aspirates. Three specimens should be obtained every 8–24 hours, with at least one early morning specimen. Children are often admitted for three morning fasting gastric aspirate samples. All samples should be sent for acid-fast bacilli (AFB) smear microscopy (Ziehl-Neelsen or fluorescent staining) and mycobacterial culture, and at least one specimen sent for nucleic acid amplification testing (NAAT). While positive results can be specific for TB, sensitivity is often low in children given their paucibacillary disease (Table 3). The majority of children have smear negative disease, and the yield of culture can be less than 40%,[17, 52] with slightly higher sensitivity and faster results in liquid mycobacterial growth in tube (MGIT) compared to solid culture media.[1] The NAAT known as Xpert MTB/RIF (Cepheid, Sunnyvale, USA) has a sensitivity of 65–73% with sputum or gastric aspirates; the next generation Xpert MTB/RIF Ultra has a lower limit of detection and new “trace” category that improved sensitivity to 70–73% in children.[53, 54] The yield of testing is lower in young children less than 5 years of age, and can be further impacted by the sample quality, type and number collected.[55, 56] Bronchoalveolar lavage may improve the quality of the specimen, but does not significantly increase yield and is invasive.

Non-sputum testing for intrathoracic TB—An IGRA or TST can be performed to evaluate for immunological evidence of TB infection. Given the moderate sensitivity of both TST and IGRAs, especially in vulnerable groups including young and immunosuppressed children, a negative result needs to be interpreted with caution and should not be used alone to rule out TB. Pleural effusions can have lymphocytic predominance, elevated protein, and elevated lactate dehydrogenase (LDH). Pleural fluid adenosine deaminase (ADA) ≥40 U/L has been associated with an 89–99% sensitivity and 88–97% specificity for TB.[1] Pleural TB can be difficult to diagnose, and pleural tissue biopsy can be valuable for pathological assessment of acid-fast bacteria, granulomas and culture. Urine-based testing with lipoarabinomannan (LAM) has had limited performance in children (Table 3), with sensitivity ranging from 28–73%[57–61] and specificity 61–91%.[57–61] Accuracy improves with HIV co-infection, and currently the WHO recommends urine LAM for children with HIV.[61] Next generation LAM assays are being developed (such as SILVAMP TB LAM, Fujifilm, Tokyo, Japan) that have improved sensitivity and can detect 42–65% of

confirmed TB in children,[62, 63] and may be considered in future guidelines. Stool-based testing has been suggested in young children as they swallow their sputum. Stool culture has limited performance, but NAATs, including Xpert MTB/RIF, have shown about 57–67% sensitivity,[53, 54, 64, 65] and has been included as an option for testing in recent WHO guidelines.[54]

Extrapulmonary TB specimen testing—Fine needle aspiration of lymph nodes and bone biopsies can be sent for pathology, AFB staining, mycobacterial culture, and NAAT. Similarly, joint fluid aspirations can be further assessed with AFB staining, culture and NAAT. For CNS TB, the cerebral spinal fluid (CSF) profile can have a mild leukocytosis with lymphocytic predominance, and most notably will have an elevated protein.[18] CSF culture can be low yield and often requires a large volume, but NAAT can be sent on the CSF with sensitivity of 67–85% and specificity 94–99%.[18, 53] CSF testing should also be performed in children under 2 years old regardless of neurologic symptoms given the risk of disseminated disease.[13]

Resistance testing—Culture-based methods can evaluate for phenotypic susceptibility to both first-line and second-line agents, but is slow and requires technical expertise.[66] Genotypic testing of known resistance-conferring mutations provides a faster approach, and includes evaluation of the *rpoB* mutation in rifampin resistance with Xpert MTB/RIF, as well as line probe assays (LPAs) and sequencing approaches that can assess mutations for first-line drugs and second-line options including aminoglycosides and fluoroquinolones. While faster, genotypic methods can have reduced sensitivity and there can be silent mutations that do not predict phenotypic resistance. Thus, when feasible, phenotypic approaches should still be done to further confirm drug resistance.

TREATMENT OF TB DISEASE

Treatment of Presumed or Drug-Susceptible Pulmonary Tuberculosis in Children—The purpose of TB treatment in children is to rapidly kill or inhibit multiplication of Mtb, which when combined with an immune response, prevents rapid dissemination of disease and results in cure. Treatment duration is typically six months to ensure eradication of both rapidly dividing and slowly metabolizing mycobacteria subpopulations, or persister mycobacteria, believed to cause relapse after treatment cessation.

First-line TB treatment includes three or four drugs: rifampin, isoniazid, pyrazinamide with or without ethambutol (RHZE). The 2-month initiation phase includes three or four drugs with the purpose of rapidly reducing mycobacterial burden. The subsequent 4-month continuation phase includes both rifampin and isoniazid, targeting elimination of persister mycobacteria. Dosing for first line drugs is provided in Table 4.

Both rifampin and pyrazinamide provide sterilizing activity of these slowly metabolizing mycobacterial subpopulations and in combination have allowed for a shorter treatment duration of 6 months. Isoniazid has two purposes, first to reduce the burden of rapidly metabolizing mycobacteria during the initiation phase and second to protect against the development of rifampin resistance during the continuation phase. Ethambutol prevents the

development of drug resistance among first-line companion drugs. Ethambutol is used when there is (1) unknown drug susceptibility patterns for the child or source case and either the risk of isoniazid mono-resistance or HIV prevalence is significant, (2) extensive “adult-type” or smear-positive pulmonary disease present or (3) severe form of extrapulmonary TB present. Drugs are not generally interchangeable; any need to modify the standard regimen due to drug resistance, allergy or intolerance, should be discussed with a pediatric TB specialist.

Because children often do not have microbiological confirmation of TB, the drug regimen is based on the drug susceptibility testing from the likely source case or epidemiology and the risk of drug-resistance. Risk factors for drug-resistant TB include prior TB treatment, contacts of patients with known drug-resistant TB or poor initial response to therapy (e.g., persistent smear positivity after appropriate treatment), and immigration from or travel to countries with a high prevalence of drug-resistant TB. When risk factors for drug resistance are present, every effort should be made to identify an isolate to guide treatment.

Treatment of TB Meningitis—Childhood tuberculous meningitis is associated with significant morbidity and mortality, and despite treatment only one in three children survive without neurologic sequelae.[67] Treatment with standard doses of RHZE results in low cerebrospinal fluid concentrations of both rifampin and ethambutol.[68–70] Adult trials have shown early intensified treatment with high dose rifampicin, either orally or intravenously, and levofloxacin, when isoniazid monoresistance is present, reduce morbidity and mortality.[69, 71–73] Modeling studies suggestion rifampin doses of at least 30mg/kg orally or 15mg/kg IV and levofloxacin dosing of at least 20–30mg/kg orally are likely necessary to attain similar exposures in children as were studied in adults.[74] Ongoing studies are evaluating this dosing and outcomes in children with tuberculous meningitis.

In cases where drug susceptible TB is likely based on source case susceptibilities or epidemiology, rifampin, isoniazid and pyrazinamide are recommended. There are few randomized controlled trials to guide the selection of the fourth drug. CDC guidelines recommend ethambutol, however, given its poor CNS penetration, the AAP recommends either ethionamide or an aminoglycoside.[13] Ethionamide is a thioamide and pro-drug requiring activation by mycobacterial EthA with good CNS penetration.[75] Along with isoniazid, it inhibits mycolic acid synthesis via InhA. Gastrointestinal disturbance and reversible hypothyroidism are common during long term therapy, but are both often tolerated. Aminoglycosides, most commonly streptomycin, are IV and carry the risk of oto- and nephrotoxicity. In cases where drug resistance is identified or suspected or ethionamide is not available, initial treatment with a fluroquinolone and/or linezolid, which both penetrate the CNS well, may be beneficial.[72, 76, 77] Accumulating data in adults suggest levofloxacin may improve outcomes of TBM in drug-resistant tuberculous meningitis, including isoniazid mono-resistant TB.[72]

Adjuvant Steroids—Adjuvant corticosteroids reduce mortality from TB meningitis by 25% in people of all ages and pediatric studies have shown improved intellectual outcomes in children randomized to receive corticosteroids.[78, 79] Corticosteroids have also been shown to reduce the development of constrictive pericarditis and relieve obstruction most

commonly from lymphadenitis.[80] Finally, steroids are sometimes used in severe miliary disease to mitigate alveolocapillary block or in abdominal TB to reduce the risk of strictures.

Administering Tuberculosis Treatment to Children—Drug doses and formulations of first line therapy for pulmonary TB in children are shown in Table 4. First line TB medications can be crushed and mixed in sugar-free chocolate pudding or grape jelly to enhance acceptability in young children.[81] While medications in these compounds have been shown to be stable for up to 4 hours, practically any food the child prefers can be used to mask the taste as long as it is taken quickly after crushing and mixing with food. Rifampin and pyrazinamide can be compounded into suspensions, which is often necessary in very young children to obtain the appropriate dose given formulations available in the United States. Crushed isoniazid tablets should be used whenever possible; isoniazid solution causes nearly half of children to have significant GI upset. Pyridoxine supplementation often accompanies use of isoniazid to prevent peripheral neuropathy, but in children is limited to exclusively breast-fed infants, children with malnutrition and children living with HIV.

Monitoring TB Treatment—Monthly follow up to assess for treatment response, drug toxicity and adherence is typically sufficient. Drug-related hepatotoxicity is rare in children and routine assessment of serum transaminases is not recommended and limited to children with underlying liver disease. Caregivers should be counseled on early symptoms of hepatitis including nausea, vomiting, and abdominal pain which may prompt assessment of liver function testing. Treatment response is assessed clinically, by following symptoms, weight gain and development, radiologically, by following chest X-ray and other imaging, and microbiologically, with repeat sputa samples assessing for smear and culture conversion. The microbiological assessment is often not necessary in young children with paucibacillary disease who have negative smear and culture at diagnosis. Repeat radiographs are not mandatory, but are often helpful when a child has not shown significant clinical improvement and there are concerns about possible drug resistance. Notably, hilar adenopathy can take 1–2 years to resolve and should not be considered a poor response to therapy.

Therapeutic drug monitoring is used to determine drug concentrations at timed intervals to determine the appropriateness of drug dosing. This is not routinely recommended in TB care, but can be useful in children with malabsorptive conditions, those at risk for drug-drug interactions, renal insufficiency with or without renal replacement therapy, diabetes mellitus, and those with poor clinical response to first line therapy with known or assumed susceptibility to first line agents.[82]

Duration of Treatment—Treatment duration for drug-sensitive pulmonary TB disease in children is typically six months. This is extended in adult populations when there is cavitation on initial or follow up chest imaging and culture remains positive after two months of treatment. Certain extrapulmonary TB conditions require longer therapy including tuberculous meningitis (6–12 months) and tuberculosis of the bone, joint or spine (6–9 months). Treatment of TB with resistance to either rifampicin, isoniazid or pyrazinamide is also typically longer, including treatment of *M. bovis* which is inherently resistant to pyrazinamide.

Treatment of Drug Resistant Tuberculosis in Children—Treatment of drug-resistant TB is often longer and requires at least 4 or 5 antituberculosis drugs. Drug choice should consider the drug resistance pattern of the child or source case isolate and drug penetration to the site of disease. Dosing and availability of child friendly formulations of second-line drugs are improving but still lacking. Up to date information on dosing and formulations can be found at the sentinel-project.org. Regimens to treat-drug resistant TB should be designed with a pediatric tuberculosis specialist.

Emerging advances for childhood TB diagnosis and treatment

Several new diagnostics for LTBI and TB disease are under evaluation.[83] For LTBI, skin-based testing has been developed that incorporates ESAT-6 and CFP-10 rather than the non-specific tuberculin mixture, and new platforms could allow IGRA testing closer to the point-of-care. For TB disease, pathogen-based tests include the measurement of cell-free DNA or other TB-specific antigens such as ESAT-6 and CFP-10 in plasma or urine. Host-based assays are also being assessed, including gene and protein-based signatures or the measurement of T-cell markers. In addition, there are efforts to optimize LAM and stool testing, and the use of oral swabs to make respiratory specimen collection less invasive. Image analysis with artificial intelligence has led to large advancements in computer-aided detection of TB in CXRs; further work is needed to extend it to children. For resistance testing, new molecular tests are being evaluated and next generation sequencing (NGS) may provide a broader assessment of all the possible mutations that can confer drug resistance. Lastly, there is a growing appreciation of the wider spectrum of TB, including incipient and subclinical TB,[84] and there are ongoing efforts to characterize and diagnose these different states to inform earlier and specific treatment regimens.

Continued advances in LTBI treatment are also anticipated. Worldwide, children 12 years and older have access to 1HP or one month of daily rifapentine and isoniazid for TB treatment. Ongoing studies in adults and children will clarify efficacy in different populations and the dosing, safety and tolerability of this regimen in children. A child-friendly formulation of rifapentine is not expected for at least 5–10 years. Ongoing studies of injectable bedaquiline in mice may prove useful in humans and could allow for a single injection to treat LTBI in both drug sensitive and drug resistant exposure. Finally, advances in TB vaccine research may also aid treatment and prevention of TB infection and TB disease.

Shortened treatment regimens in adults and children signify a major advance for TB treatment not seen for decades. For children, the SHINE trial found four months of RHZE – 2 months of intensive phase and 2 months of continuation phase – was non-inferior to the standard six-month RHZE regimen in children with minimal TB disease. Similarly, in adolescents and adults, a four-month regimen of rifapentine, isoniazid, pyrazinamide and moxifloxacin (RHZM) was non-inferior to the standard six month regimen of RHZE in all efficacy analyses and is already recommended by WHO.[85] Though some work needs to be done before these regimens are ready for implementation, there is great hope for shortened regimens, improved adherence and better treatment outcomes in the near future.

Beyond the development of new diagnostics and therapeutic regimens, we need to improve the care cascade for LTBI and TB disease to increase the proportion of children and adolescents who are screened, tested and treated. This requires greater engagement with providers and families to understand the individual, community and structural barriers to TB care. It is also important to improve early recognition of TB disease and encourage use of algorithms for clinical diagnosis.

Summary

The successful care of children and adolescents with TB requires 1) a recognition of the risk factors and clinical and radiographic signs of TB, especially when microbiological testing is negative, and 2) partnership with caregivers to safely complete the minimum 3 months of treatment for LTBI and 6 months for TB disease. Our approach to diagnosing and treating LTBI and TB disease is outlined in Boxes 1–4. Ongoing efforts seek to improve the performance and ease of TB diagnostics for children, with shorter treatment regimens and better formulations for LTBI and TB disease.

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Synopsis

Tuberculosis (TB) is one of the leading causes of mortality in children worldwide, but there remain significant challenges in diagnosing and treating TB infection and disease. We review the clinical approach to diagnosing and treating latent TB infection (LTBI) and pulmonary and extrapulmonary TB disease in children. We also discuss emerging diagnostics and therapeutic regimens that aim to improve pediatric TB detection and outcomes.

Key points

- LTBI diagnosis requires assessment of risk factors, immunological evidence of infection, and exclusion of symptomatic TB disease
- LTBI treatments have moved away from the traditional 9 months of isoniazid towards shorter rifamycin-containing regimens
- The integration of clinical, radiographic, and microbiological data is needed to support a diagnosis of TB disease
- Multi-drug therapy for at least 6 months is currently used to treat TB disease, with additional considerations in formulation and administration required for children
- New diagnostics for more accurate and faster detection, and shorter treatment courses for LTBI and TB disease seek to improve TB outcomes in children

Clinical Care Points 1:

Summary of our approach to the diagnosis of TB Infection

- We assess risk factors that increase the risk of TB infection or progression to TB disease, in particular birth in, residence to or travel to a TB endemic setting, immunosuppression, or contact with an individual with TB disease.
- LTBI testing should be done on all children with risk factors. We perform IGRAs on all children 2 years and older; if the child is under 2, we perform a TST, but if it is not available or feasible, or there is concern for false positivity, we use an IGRA.
- We do not perform both TST or IGRA unless one test is invalid/ indeterminate, there is concern for false negativity, or to evaluate for other etiologies including NTM infection.
- We consider positive results for a TST or IGRA a true positive in children with TB risk factors unless there is a clear alternative explanation.
- We exclude TB disease by symptom screen, physical exam, and two-view CXR. If there is no evidence of TB disease, we proceed with LTBI treatment. If there are clinical signs of TB or radiographic abnormalities, we would next consider the collection of respiratory specimens for TB disease evaluation.

Clinical Care Points 2.

How we approach LTBI Treatment in Children

- Regimen choice should consider age, formulation, likely adherence and possible drug-drug interactions with rifamycins.
- Vitamin B6 is indicated for exclusively breast-fed infants, children with malnutrition and children living with HIV.
- None of the newly recommended short-course regimens require directly observed therapy, including 3HP.
- Parents should be counseled about the early symptoms of hepatoxicity (nausea, poor appetite, emesis, and abdominal pain) and should immediately return to care should they develop.
- Children should be followed by their pediatrician monthly to evaluate for drug toxicity and adherence. All medications should be weight-adjusted monthly.
- In most situations, liver function testing is only indicated when the child is symptomatic of hepatitis.
- Children exposed to drug-resistant TB should be referred to a pediatric TB expert.

Clinical Care Points 3:

How we approach TB diagnosis in children

- We screen for TB risk factors and symptoms, and perform a complete physical exam, including growth assessment.
- We obtain an IGRA or TST, two-view CXR, and three respiratory specimens for AFB smear and culture, and at least one for Mtb NAAT.
- For TB lymphadenitis, we obtain fine need aspirations on an enlarged lymph node for pathology, AFB staining, mycobacterial culture, and NAAT.
- A CT or MRI should be obtained for concerns for CNS TB, and CSF sent for NAAT in addition to a standard CSF profile.
- Without microbiological confirmation, we will still diagnose a child with TB if they have risk factors, signs and symptoms of TB without a clear alternative etiology.

Clinical Care Points 4.

How we approach TB Treatment in Children

- First we assess the child's risk for drug-resistant TB.
- Assuming no risk factors for drug resistance, three or four drug therapy with rifampin, isoniazid, pyrazinamide with or without ethambutol is started as empiric therapy.
- During the 2-month initiation phase, all 3 or 4 drugs are used to rapidly decrease the mycobacterial burden. During the continuation phase, rifampin and isoniazid are used to eradicate persister mycobacteria.
- Vitamin B6 is indicated for exclusively breast-fed infants, children with malnutrition and children living with HIV.
- Children should be followed monthly to evaluate for treatment response, drug toxicity and adherence. All medications should be weight-adjusted monthly.
- Directly observed therapy is the standard of care in all settings.
- In most situations, liver function testing is only indicated when the child is symptomatic of hepatitis.
- Therapy can be extended beyond six months with certain forms of TB, poor response to therapy, with cavitation and persistently positive smears at month two, or if there is poor adherence.

Table 1.

Summary and comparison of TB Screening Questions for LTBI Children

Category	AAP Red Book[13]	California Pediatric TB Risk Assessment[86]	Pediatric Tuberculosis Collaborative Group[14]
Birth or significant time spent in TB endemic setting	Was your child born in a high-risk country?[a]	Birth, travel, or residence in a country with an elevated TB rate for at least 1 month	Was your child born outside the United States?
	Has your child traveled to a high-risk country?[a] How much contact did your child have with the resident population?		Has your child traveled outside the United States?
Immunosuppression [b]	Immunosuppressed populations	Immunosuppression, current or planned	
Known or Suspected TB Contact or High Risk of Exposure	Has a family member had a positive tuberculin skin test result?	Close contact to someone with infectious TB disease during lifetime	Has your child been exposed to anyone with TB disease?
	Has a family member or contact had tuberculosis disease?		Does your child have close contact with a person who has a positive TB skin test?

[a] Countries other than the United States, Canada, Australia, New Zealand, or Western and North European countries

[b] HIV, organ transplant recipient, steroids (prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥2 weeks), anti-TNF-alpha inhibitor, or other immunosuppressive medication

Table 2.

Regimens, Dosing, Formulations, Efficacy, Adverse Reactions and Significant Drug-Drug Interactions for LTBI Treatment

Regimen	Dosage	Formulations	Recommended populations	Efficacy with 9H as a reference	Hepatotoxicity in children	Other adverse Events	Significant drug-drug interactions
Rifapentine plus isoniazid weekly for 3 months (3HP)	**Children (2–11 years old):** Isoniazid 25 mg/kg Rifapentine 10.0–14.0 kg, 300 mg 14.1–25.0 kg, 450 mg 25.1–32.0 kg, 600 mg 32.1–49.9 kg, 750 mg ≥ 50.0 kg, 900 mg **Adults and children (≥ 12 years old):** Isoniazid 15 mg/kg Rifapentine as above **Maximum doses:** Isoniazid 900 mg Rifapentine 900 mg	RPT: 150mg film-coated tablet; may be taken whole or crushed (should be maintained in blister packs until ready to use) INH Tablet: 100mg (scored) or 300mg tablet; may be crushed	Adults and children ≥ 2 years old, People living with HIV	Non-inferior to 9H: Cumulative Rate Difference: −0.74% (UL 95%CI: 0.32%, predefined NI Margin 0.75%)[30]	No hepatotoxicity identified in children during trials)[30] or programmatic roll out to date.[33, 34, 87]	Hypersensitivity reactions with influenza-like syndrome, rash, drug-induced liver injury, hypotension, syncope	Protease inhibitors, integrase inhibitors, maraviroc; anticonvulsant agents, azole antifungal agents, macrolides and tetracyclines, hormone-replacement therapy, and warfarin
Rifampin daily for 3–4 months (4-R)	**Children**: 15–20 mg/kg * **Adults**: 10 mg/kg **Maximum dose**: 600 mg	Oral Capsule: 150mg and 300mg; may be opened and used as sprinkles Oral Suspension (10mg/mL) *	Adults and children of all ages Limited data for people living with HIV (not recommended in the US)	Similar Efficacy to 9H: Rate difference: −0.37 cases per 100 person-years (95%CI: −0.88 to 0.14)[36]	Range: 0–0.1 %[34, 36, 88–90]	Nausea, decreased appetite, orange discoloration of bodily fluids	Dolutegravir (dose should be increased to twice daily), protease inhibitors, rilpivirine, elvitegravir, maraviroc; oral contraceptives, azole antifungal agents, calcium channel blockers
Rifampin plus isoniazid daily for 3 months (3HR)	**Children**: Isoniazid 10–20 mg/kg Rifampin 15–20 mg/kg **Adults**: Isoniazid 5 mg/kg Rifampin 10 mg/kg **Maximum doses:** Isoniazid 300 mg Rifampin 600 mg	RIF Oral Capsule: 150mg and 300mg; may be opened and used as sprinkles INH Tablet: 100mg (scored) or 300mg tablet; may be crushed Worldwide: 75/50 RH dispersible tablet available	Adults and children of all ages, People living with HIV	Similar Efficacy to 9H[91]	Hepatitis found in in 0–0.5% of children; transient liver enzymes found in up to 6% of children[91–96]	Nausea, decreased appetite, orange discoloration of bodily fluids, drug-induced liver injury	Dolutegravir (dose should be increased to twice daily), protease inhibitors, rilpivirine, elvitegravir, maraviroc; oral contraceptives, azole antifungal agents, calcium channel blockers
Isoniazid daily for 9 months	**Children**: 10–15 mg/kg ** **Adults**: 5 mg/kg **Maximum dose**: 300 mg	INH Tablet: 100mg (scored) or 300mg tablet; may be crushed	Adults and children of all ages, People living with HIV	-	~1%	Drug-induced liver injury	Azole antifungal agents, MAO inhibitors, phenytoin, SSRI antidepressants, valproic acid, acetaminophen

* Some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers

** CDC recommends dosage of 10–20mg/kg

Table 3.

Accuracy of Diagnostics for TB disease in Children

	Sensitivity Range	Specificity Range
AFB Smear Microscopy[1, 18, 97]	7–29%	≥90%
Mycobacterial culture[52]	1.5–65%	100%
Xpert MTB/RIF or Ultra[a]		
Respiratory Specimens[b,53, 54]	65–73%	97–100%
Stool[53, 54, 64, 65]	57–67%	98–99%
Lymph Node[18, 53]	80–94%	99%
Cerebral Spinal Fluid[18, 53]	67–85%	94–99%
Urine Lateral-Flow Lipoarabinomannan (LAM)[a,57–61, 98, 99]	28–73%	61–91%

[a.] Based on a Microbiological Reference Standard

[b.] Includes expectorated sputum, induced sputum, or gastric aspirate

Table 4.

Dosing, Formulations and Adverse Reactions for First Line Treatment of Pediatric Pulmonary TB Disease

Drug	Dose	Formulations[&]	Adverse Reactions
Rifampin	10–20 mg/kg[+] (max 600–900 mg)	Oral Capsule (150mg, 300mg)[#] Oral Suspension (10mg/mL)[*] IV injection	Hepatotoxicity Hypersensitivity Red/orange-tinged secretions GI upset Rash
Isoniazid	10–15 mg/kg (max 300 mg)	Oral Tablet (100mg, 300mg) Oral Solution (50mg/5mL)[^] IM injection (100mg/mL)	Hepatotoxicity Peripheral neuropathy Hypersensitivity GI upset Rash
Pyrazinamide	30–40 mg/kg (max 2000 mg)	Scored Tablet (500 mg) Oral Suspension (100mg/mL)[*]	Hepatotoxicity Hyperuricemia GI upset
Ethambutol	15–25 mg/kg (max 1600 mg)	Oral Tablet (100mg, 400mg) Oral Suspension (50mg/mL)[*]	Optic neuritis[+] Hypersensitivity

[*] Requires compounding pharmacy.

[^] Often poorly tolerated (GI upset), most patients prefer crushed tablet mixed with food, formula or breast milk

[#] Often given as sprinkles by opening the capsule

[+] Author recommends highest tolerated dose within range, as formulations allow.

[&] Fixed dose combinations not available in the United States

[+] Ethambutol has been associated with optic neuropathy whose early symptoms cannot be easily reported or detected in young children. The World Health Organization reviewed ethambutol toxicity and found doses of 20mg/kg (range 15–25 mg/kg) daily for two months was not associated with ocular toxicity and could be given without ophthalmology follow up.