

Guidelines for the management of tuberculosis in children living in San Diego County 2003

San Diego Pediatric TB Task Force
Subcommittee on guidelines for the management of pediatric tuberculosis

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A. Describes diagnosis and treatment for latent TB infection (LTBI).

1. Definition of LTBI.

Latent tuberculous infection (LTBI) is defined by a positive tuberculin skin test in a person who has no evidence of disease by physical exam and a chest radiograph is either normal or reveals only granulomas or calcifications in the lung and/or regional lymph nodes. LTBI is the preferred term for tuberculous infection without disease. Tuberculous disease and LTBI can be caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) or *M. bovis*.

2. Diagnosis of LTBI.

Positive tuberculin skin tests (TST) may vary by size (mm of induration), based on risk factors, age, and exposure to active TB disease or unpasteurized dairy products. The Mantoux test containing 5 tuberculin units (TU) of purified protein derivative (PPD), administered intradermally, and read at 48-72 hours, is the preferred test. Multiple puncture tests are not recommended because they lack adequate sensitivity and specificity.

A positive TST as evidence of TB infection is defined as:

- a. **≥5 mm induration**
 - Children on immunosuppressive tx (eg. prednisone 2 mg/kg/day ≥ 2 weeks) or with an immunocompromising condition, including HIV
 - Close contact of known or suspect active TB case
 - Children with suspect active tuberculosis
 - Patients with fibrotic changes on chest x-ray suggestive of old TB disease

- b. **≥10 mm induration (most children in San Diego County given the relative high prevalence of TB)**
 - Children at increased risk of dissemination
 - Children < 4 years
 - Children with underlying chronic medical condition (ie. diabetes, end-stage renal disease)
 - Children at increased risk of exposure
 - Born in/travel to or exposure to adults born in high risk areas
 - Exposure to adults with risk factors for TB (homeless, HIV infected, illicit drug use, institutionalized, incarcerated, nursing home, migrant farm worker)

- c. **≥15 mm induration (The California TB Controllers Association assumes a TST induration of 10 mm as positive for any person living in California – California Department of Health Services/CTCA Joint Guidelines 1997)**
 - Children ≥ 4 yr of age without risk factors

Prior BCG vaccination does not alter criteria for interpretation of the TST or indications for skin testing.

3. Targeted testing for LTBI. (adapted from 2003 Red Book)

- a. Initial evaluation – Tuberculin skin testing recommended for:
 - Contacts of active TB cases
 - Children with suspected active TB disease
 - Recent immigrants from endemic countries
 - Travelers to endemic countries or close contact with persons indigenous to endemic countries
 - Children with a history of ingestion of unpasteurized milk or cheese
 - Children with HIV or other immunocompromising conditions
 - Children who have been incarcerated, homeless, or exposed to high risk adults

- b. Ongoing monitoring (if no documentation of prior positive TST)
 1. Annual skin testing recommended for:
 - HIV infected patient
 - Incarcerated adolescent

 2. Skin testing every 2-3 years
 - Exposure to adults with risk factors for TB (homeless, illicit drug use etc.)
 - Children with ongoing risk factors for TB exposure (travel to a TB endemic country, frequent ingestion of unpasteurized milk/cheese) especially patients with chronic disease

 3. Skin testing at age 4-6, then 11-16 years
 - Children with immigrant parents from endemic areas or contact with people from endemic areas
 - Children living in high-risk areas (e.g. large immigrant population) but no personal risk factors

4. Treatment of LTBI:

Prior to initiation of treatment for LTBI it is imperative to ensure active TB disease is ruled out. Providing single drug therapy to a child who proves to have active TB disease can lead to drug resistance and complicate subsequent therapy. If specimens for AFB culture have been obtained, await the final report (4-8 weeks). Young children often have low bacterial loads and extrapulmonary TB disease making recovery of organisms less

successful than in adult patients. Cultures may be negative despite findings of active TB disease. Expert consultation is recommended if the diagnosis of LTBI vs. active disease is unclear.

- a. Isoniazid (INH), 10-15 mg/kg/d (maximum dose of 300 mg), given daily for 9 months is the preferred treatment for LTBI.
- b. A twice a week DOT regimen is acceptable with INH 20-30 mg/kg/day (maximum dose 900 mg).
- c. HIV infected children should be treated daily for 9 months.
- d. INH resistant TB: Rifampin (RIF) 10 mg/kg/day (maximum dose 600 mg), given daily for at least 6 months.
- e. Routine monitoring of serum transaminases for INH therapy alone is not recommended unless the patient has underlying liver disease or clinical symptoms develop. (see below treatment of active TB disease)

5. Management of contacts of active TB cases:

a. Any child who is a close contact of an adult with active pulmonary TB should be evaluated for LTBI and/or TB disease.

- Diagnostic work up should include:
 - TST: positive if ≥ 5 mm induration
 - CXR: PA and lateral

b. Therapy for LTBI should be started if:

- TST is positive (CXR negative and no other evidence of active TB disease) - treat for 9 months if using INH
- TST is negative but the patient is < 4 years or immunocompromised, (treatment may be considered for any household contact) – TST should be repeated 12 weeks after exposure to the infectious case has ended and therapy may be discontinued if TST remains negative. If TST is positive, therapy should continue to complete a 9-month course if using INH.

c. Find out drug susceptibilities of the source case (active disease case that the child was exposed to) in order to guide the choice of the most appropriate LTBI regimen. The TB control program can facilitate access of this information for all cases diagnosed within the county and other areas of the country. Susceptibility results may not be available for the source case for 3-6 weeks after diagnosis. In most cases, INH may be used while awaiting results. Consultation with an expert in the treatment of TB is recommended to treat infection with drug resistant organisms.

B. Describes diagnosis and treatment for tuberculosis (TB) disease

1. Definition of TB disease.

Tuberculosis disease is defined by the presence of signs, symptoms, and/or radiographic findings caused by MTB complex (*M.tuberculosis* or *M. bovis*). Disease may be pulmonary or extrapulmonary, e.g. central nervous system (CNS), bone and joint disease.

2. Diagnosis of TB disease.

The diagnostic work up for TB disease in children is tailored to the organ system most likely affected. Efforts should be made to collect clinical samples for AFB smear, histopathology, special stains, and AFB culture to assure confirmation of diagnosis and drug susceptibility. Nucleic acid amplification tests (NAAT) including polymerase chain reaction (PCR) and other methodologies are available but the sensitivity and specificity for TB have not been well defined outside of respiratory specimens, and to date none are FDA licensed for non-respiratory sites (consultation with an expert is recommended prior to ordering these tests). Diagnostic tests to consider include but are not limited to the following:

- a. Pulmonary TB
 - CXR (PA & lateral views)
 - Early am gastric aspirates or bronchoscopy fluid (< 12 years or unable to produce sputum)*
 - Sputum samples or bronchoscopy fluid (> 12 years or younger if able to produce sputum)*
- b. TB meningitis
 - Cerebrospinal fluid (cell count, protein, glucose, AFB culture)*
 - CT scan of the head with contrast
- c. Abdominal TB
 - CT scan of abdomen with contrast
 - Biopsy of mass/mesenteric lymph node*
- d. TB osteomyelitis
 - CT/MRI of affected limb
 - Biopsy of affected site*
- e. TB adenitis
 - Excisional biopsy or a fine needle aspirate (FNA) of the mass *

* All specimens should be sent for AFB smear and culture and susceptibility testing. Histopathology should be ordered when applicable. Nucleic acid amplification testing can also be considered on certain samples

In addition, all children evaluated for TB disease require a CXR to rule out pulmonary disease, regardless of other non pulmonary disease. For children under 24 months of age or if neurologic status is difficult to assess, a spinal tap should be considered to rule out meningitis.

3. Treatment of TB disease

Antibiotic therapy - TB disease requires a multidrug treatment regimen. Drug selection is dependent on drug susceptibility seen in the area the TB is acquired, disease burden, and exposure to previous TB medications. Therapeutic choices are **best** made according to the drug susceptibility of the organism cultured from the patient.

In San Diego County 2002, 12% INH resistance and 2% multi-drug resistance were reported from clinical isolates of *M. tuberculosis*. There were no cases of INH resistant organisms isolated from patients under 15 years of age however only 6 of 14 (43%) of reported cases in this age group had cultures available for susceptibility testing. (TB Control Program 2002 Annual Report) Most cases of pulmonary, meningeal, and osseous tuberculosis are likely due to *M. tuberculosis*. CDC recommendations include initial 4 drug therapy where *M. tuberculosis* drug resistance is reasonably likely. In San Diego, data show that cervical adenitis in young children and abdominal TB are more likely caused by the *M. bovis* species. All *M. bovis* isolates are intrinsically resistant to pyrazinamide (PZA), although rates of resistance to other drugs are found to be lower. Because the value of PZA cannot be demonstrated in *M. bovis* disease, a 9 month course of INH and Rifampin is the recommended regimen.

Directly Observed Therapy (DOT) is treatment in which the ingestion of every dose is monitored by a trained health care worker or trained third party (not a relative or friend) to document doses of medication given. DOT is extremely important to assure compliance and avoid subsequent emergence of drug resistance. In San Diego, the TB Control Program recommends DOT for all children with active TB disease and the program will assign health care workers to provide in-home DOT for all active TB cases.

1. Pulmonary TB:

- INH, RIF, PZA daily x 2 mo, followed by INH, RIF daily x 4 months
or INH, RIF, PZA daily x 2 mo, followed by INH & RIF twice a week x 4 months

Twice weekly therapy can be started after 2 weeks of daily therapy if the patient is tolerating medications. All intermittent dosing should be given by DOT.
Note: Twice a week INH and rifampin regimens are not recommended for persons with HIV infection.
- Add ethambutol (EMB) daily if drug resistance is suspected. Four drugs should be the initial regimen in all adolescents, children with prior anti-TB drug exposure, and children with large disease burdens. In a pre-adolescent child

with minimal disease, empiric therapy with 3 drugs should be sufficient unless the source case is at high risk for drug resistant TB.

- if *M. bovis* disease is suspected or proven, the treatment recommendation is INH, RIF daily x 9 months. Ethambutol should be added in the same situations for drug resistance as noted above. (Biweekly therapy with DOT may be considered after 2 weeks of daily therapy)
- In patients with pulmonary TB, repeat CXR should be considered 2-3 months into therapy to help evaluate response

2. Cervical adenopathy: (see pulmonary tuberculosis)

3. Abdominal TB: (see pulmonary tuberculosis)

4. Other extra-pulmonary TB, including meningitis/disseminated TB/bone and joint

INH, RIF, PZA, Streptomycin (or EMB) daily x 2 months then INH, RIF daily x 7-10 months,

or

INH, RIF, PZA, Streptomycin (or EMB) daily x 2 months, followed by 7-10 months of INH & RIF biweekly via DOT may be considered for non central nervous system disease but there are limited data on biweekly therapy for meningitis

*Steroids are indicated as part of the treatment of TB meningitis and endobronchial TB with severe airway compromise. For meningitis, prednisone 1-2 mg/kg or dexamethasone equivalent 0.6 mg/kg/day are administered for the first 3-4 weeks followed by a taper over 3-4 weeks depending on the patient's clinical course.

Table 1. Commonly Used Agents for Treatment of Tuberculosis in Pediatric Patients

| | Dosage forms | Daily dose (mg/kg/day) | Biweekly dose (mg/kg/dose) |
|--------------------|---|------------------------|----------------------------|
| Isoniazid (INH) | Tablets (100 mg, 300 mg), elixir (10 mg/ml) | 10-15 (max 300) | 20-30 (max 900) |
| Rifampin (RIF) | Capsules (150 mg, 300 mg), liquid can be made from capsules | 10-20 (600) | 10-20 (600) |
| Pyrazinamide (PZA) | Tablets (500 mg) | 20-40 (2g) | 50 (2 g) |
| Ethambutol*(EMB) | Tablets (100 mg, 400 mg) | 15-25 (2.5 g) | 50 (2.5 g) |
| Streptomycin | vials | 20-40 (1 g) | 20 (1 g) 20 |

* Ethambutol dosing is recommended to start at 15 mg/kg/day unless bactericidal activity is felt to be necessary.

b. Monitoring of drug toxicity:

Indications for baseline and routine monitoring of serum transaminases and bilirubin are recommended for:

1. Severe TB disease
2. Pregnancy/post partum
3. Clinical symptoms of hepatotoxicity
4. Underlying hepatic disease
5. Use of other hepatotoxic drugs (especially anticonvulsants)
6. HIV infection

Routine testing of serum transaminases in healthy children with none of the above risk factors is not necessary. Some experts recommend monitoring children treated with ethambutol for visual acuity and color discrimination.

c. Principles of antituberculous management:

1. Contact San Diego County TB Control(619-692-8610) to report suspected cases of tuberculosis within 24 hours of suspicion (required by California Health and Safety code) to facilitate contact investigation and treatment. Children diagnosed in a hospital may not be discharged until the patient's follow up management plan is approved by TB Control. Suspicion can be defined as whenever TB is a significant consideration in a differential diagnosis, and always includes situations where treatment for active disease is started or when a child is kept out of school while awaiting TB lab results.
2. Do not start LTBI therapy until active disease has been definitively excluded.
3. Achieve sterilization of the TB lesion in shortest time
4. DOT is recommended for treatment of active disease
5. Persons with tuberculous disease should be considered for testing for HIV infection, including pre and post test counseling
6. Drug resistance should be considered. Four drug initial therapy should be used for patients who are from populations with a high risk for resistant organisms including those with a source case with or at risk for drug resistance, adolescents, and in those for whom failure to cure the infection will lead to unacceptable morbidity and mortality (eg. all children with extensive initial disease, disseminated or central nervous system disease). Expert consultation should be sought before therapy initiation if the provider is unfamiliar with treatment of TB disease in children.
7. For any drug resistant organism, consultation with an expert in treatment of tuberculosis is recommended. Treatment with two bactericidal drugs to which the organism is susceptible is the minimum acceptable regimen. Additional drugs are needed in the initial phase until

cultures and susceptibilities are available and in order to shorten the overall length of therapy.

8. If the organism is INH resistant, 6 months of Rx is not generally recommended for LTBI.

9. Never add a single drug to a failing regimen. Seek expert consultation if a patient appears to be failing their TB regimen.

References:

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