PART 9: SPECIFIC CLINICAL PROBLEMS

Chapter 332
TUBERCULOSIS AND LATENT TUBERCULOSIS INFECTION

Ann M. Loeffler, MD; Mark N. Lobato, MD

Tuberculosis (TB) is a serious disease caused by Mycobacterium tuberculosis. TB disproportionately affects young children as a result of their increased risk of progression to disease once infected by M tuberculosis and the increased likelihood of disseminated disease. In the United States, children who are at the highest risk for TB are children of color, children born in countries with a high prevalence of TB or into families from these countries, children who live with or in contact with adults who are at risk for TB, and children younger than 4 years.

DEFINITIONS

Tuberculosis

TB disease is caused by a member of the Mycobacterium tuberculosis complex, which includes Mycobacterium tuberculosis and M bovis, and is distinguished from latent TB infection (LTBI). Common clinical presentations of TB include pneumonia, intrathoracic or peripheral lymphadenopathy, meningitis, disseminated TB, and bone and joint disease. In the United States, children diagnosed with TB disease are often asymptomatic but have radiographic evidence of disease such as an infiltrate or intrathoracic adenopathy. Asymptomatic presentations of TB disease are treated with multidrug therapy because they will progress in most children if not treated. Table 332-1 provides epidemiologic data for TB in children. Among U.S. children with TB in 2006, 485 were <5 years of age, 322 were ages 5-14; 48% were Hispanic (most from Mexico), and 31% were black. A total of 25% of TB cases in children occurred in the foreign born: 15% of children were <5 years of age and 40% of children were 5-14 yrs of age. Thirty-six percent of the cases were reported from California, Texas, and New York. A total of 73% had pulmonary TB (with or without extrapulmonary TB).

Latent Tuberculosis Infection

Infection with Mycobacterium tuberculosis occurs when the organism is in a metabolically dormant state and replicating slowly within granulomata in the lung and other tissues. The patient usually has a positive tuberculin skin test (TST) result but no clinical or radiographic evidence...
of TB disease. Until new diagnostic tests become better studied in children and are more readily available, a positive TST result is used to define LTBI. An interferon-gamma release assay such as the QuantiFERON-TB test may also diagnose LTBI in children. Patients should be treated with isoniazid (isonicotinyl hydrazine [INH]) monotherapy daily for 9 months, unless they have a medical contraindication (including infection with a known INH-resistant strain). Because LTBI is not a reportable condition in most states, the number of children who have LTBI is unknown.

Tuberculosis Exposure
A person exposed to TB is one who has spent time in close proximity to a potentially contagious patient with TB disease. The exposed individual may or may not be infected. Young children can progress rapidly to TB once infected; thus they should be quickly evaluated and treated prophylactically while awaiting completion of the evaluation if they are exposed to TB.

DIFFERENTIAL DIAGNOSIS
TB symptoms mimic many different diseases. Because TB is uncommon in the United States among most populations, the clinician must maintain a high index of suspicion for TB, especially among children who fit the epidemiologic profile and who have risk factors for infection and disease. The differential diagnosis for TST results is outlined in Box 332-1. The differential diagnosis for forms of TB disease is provided in Box 332-2.

Tuberculin Skin Testing
Universal skin testing for TB is not recommended. Annual assessment for TB risk factors and testing of children with defined risk factors are the standard of care. Improper placement (eg, subcutaneous placement, improper storage of the PPD skin test material [eg, not refrigerated, prolonged storage in syringe]), and other circumstances can produce false results. Although initial TST results are frequently, but not always, smaller than those caused by M tuberculosis, the mechanism of a true positive TST reaction.

BOX 332-1 Differential Diagnosis for Tuberculin Skin Test Results

<table>
<thead>
<tr>
<th>TRUELY POSITIVE</th>
<th>FALSELY POSITIVE</th>
<th>FALSELY NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caused by infection with M tuberculosis complex</td>
<td>Cross-reaction with nontuberculous mycobacteria, such as M avium complex and M scrofulaceum. These reactions are frequently, but not always, smaller than those caused by M tuberculosis.</td>
<td>Recent infection with M tuberculosis (delayed-type hypersensitivity reaction takes 2-8 weeks after infection to develop)</td>
</tr>
<tr>
<td>Infancy</td>
<td>Cross-reaction with a recent or multiple vaccinations with BCG. In general, the public health strategy in the United States is to discount the history of BCG vaccination when deciding to administer or interpreting the TST. If a patient has received only a single BCG vaccination in the newborn period and several months have elapsed since the last BCG, then a positive TST reaction due to BCG is unlikely.</td>
<td>Improper placement (eg, subcutaneous placement, pressure by gauze or a Band-Aid leading to the absorption of PPD solution)</td>
</tr>
<tr>
<td>Improper storage of the PPD skin test material (eg, not refrigerated, prolonged storage in syringe)</td>
<td>Irritation from a circular Band-Aid or tape</td>
<td>Vaccination with a live virus vaccine within the previous 6 weeks</td>
</tr>
<tr>
<td>Improper placement (eg, subcutaneous placement, pressure by gauze or a Band-Aid leading to the absorption of PPD solution)</td>
<td>Injection with a substance other than PPD</td>
<td>Generalized or specific anergy associated with extensive or disseminated TB or as seen in immunocompromised patients, especially those infected with HIV</td>
</tr>
</tbody>
</table>

BCC, Bacille Calmette-Guérin; PPD, purified protein derivative; TB, tuberculosis; TST, tuberculin skin test.


PART 9: SPECIFIC CLINICAL PROBLEMS

**BOX 332-2 Differential Diagnosis for Forms of Tuberculosis Disease**

**PULMONARY INFILTRATE**
- Community acquired pneumonia (ie, bacterial pneumonia, including lung abscess and necrotizing pneumonia; viral pneumonia)
- Atelectasis caused by reactive airways disease or other processes
- Other granulomatous diseases (eg, coccidiomycosis, histoplasmosis)

**INTRATHORACIC LYMPHADENOPATHY**
- Infections caused by fungus, virus, or bacteria
- Nontuberculous mycobacterial infections
- Malignancies
- Round pneumonia
- Other granulomatous diseases (eg, coccidiomycosis, histoplasmosis)

**SUBACUTE PERIPHERAL ADENOPATHY**
- Scrofula caused by nontuberculous mycobacteria
- Cat-scratch disease
- Toxoplasmosis
- Partially treated pyogenic infection

**MENINGITIS**
- Viral, bacterial, fungal, and chemical meningitis

and treatment of children with false positive TST results. At each well-child visit, the child should be screened with a risk-factor questionnaire. The child should undergo skin testing only if a new risk factor has been identified since the last TST. Foreign birth, foreign travel, and close contact with individuals with a positive TST result or TB disease predict increased risk of LTBI. Individual questionnaires should be modified based on local risks. A sample questionnaire is provided in Box 332-4, and the general strategy for targeted TB testing is outlined in Figure 332-1.

Prior bacille Calmette-Guérin (BCG) vaccination sometimes causes a small, transient TST reaction as a result of cross-reactivity among antigens. The effect of BCG vaccination on TST reaction is an ongoing challenge for clinicians. The Centers for Disease Control and Prevention and the American Academy of Pediatrics advise clinicians to discount the history of BCG when interpreting the TST. The following factors decrease the likelihood that the skin test reaction is caused by BCG:

- TST reaction (induration) >10 mm
- Previous receipt of a single rather than multiple BCG vaccines
- BCG given in the first month of life
- A long period since the BCG dose
- Receipt of no other recent TST

New blood tests may further clarify the impact of BCG on TST reactions and allow for more accurate TST cutoff points in individuals who have received BCG.

**BOX 332-3 Breakpoints for Interpretation of Tuberculin Skin Test Results**

A ≥5-mm induration is interpreted as positive in the following circumstances:

- Child is immunosuppressed (receiving immunosuppressive therapy) or immunocompromised, including HIV infection.
- Child is a recent contact of a person with TB or suspected TB disease.
- Radiograph or clinical evidence suggests TB disease.
- Fibrotic changes on chest x-ray are consistent with prior TB infection.

A ≥10 mm induration is interpreted as positive in the following circumstances:

- Child is <4 years of age.
- Child has medical conditions (lymphoma, Hodgkin disease, diabetes mellitus, chronic renal failure, malnutrition).
- Child or parent was born in a country with a high prevalence of TB.
- Child has frequent exposure to high-risk adults (HIV infected, homeless, residents of nursing homes, institutionalized, incarcerated, users of illicit drugs, migrant farm workers).
- Child has traveled to a high-prevalence country.
- Child is a resident of California.

A ≥15-mm induration is interpreted as positive in the following circumstance:

- Child is ≥4 years of age and has no risk factors

**MANAGEMENT**

**Tuberculosis Exposure**

A child exposed to an adult or adolescent with potentially contagious TB requires prompt and thorough evaluation to determine whether the child already has evidence of LTBI or TB disease. All exposed individuals should undergo a symptom review, TST, and a focused history and physical examination. These evaluations should be coordinated with the local health department. Children younger than 5 years and all immunocompromised individuals with significant exposure should receive window prophylaxis after TB disease has been ruled out by a normal chest radiograph and negative physical examination. Window prophylaxis is the practice of treatment with INH until a repeat TST given 8 to 10 weeks after their last exposure is performed and is negative.

**Latent Tuberculosis Infection**

Management of LTBI is reasonably easy once TB disease is eliminated as a possibility. INH monotherapy should be initiated unless strong evidence exists of INH drug resistance in the source case (not merely LTBI acquisition in an area with a high level of INH
resistance). Dosing is 270 daily doses (or twice a week administered by directly observed therapy [DOT] within a 12-month period). Table 332-2 lists INH doses by weight. When a prolonged break occurs after a short initial treatment period, then therapy should be restarted, but short lapses are tolerated, especially if the regimen is well underway. If interruption of therapy is greater than 2 months, then the child should be reevaluated for possible TB disease before restarting INH. Vitamin-B6 (pyridoxine) supplementation is indicated only for exclusively breastfed infants, children and adolescents on milk- and meat-deficient diets, children who experience paresthesias while receiving isoniazid therapy, and those with HIV infection.\textsuperscript{3}

INH is available as 100-mg and 300-mg scored tablets and as a liquid suspended in sorbitol. The liquid formulation causes cramping and diarrhea in more

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**BOX 332-4 Tuberculosis Risk Assessment Questionnaire**

<table>
<thead>
<tr>
<th>Name: ________________________</th>
<th>DOB: ________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last tuberculin skin test (TST) date: __________________________</td>
<td>Results: ______ mm induration OR ______ not read by health care professional</td>
</tr>
<tr>
<td>If positive TST result in the past: Chest radiograph date and result: __________________________</td>
<td></td>
</tr>
<tr>
<td>1. Was your child born outside the United States? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Country: ____________________________</td>
<td></td>
</tr>
<tr>
<td>2. Since the last TB skin test, has your child traveled outside the United States? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Country or countries visited: ____________________________</td>
<td></td>
</tr>
<tr>
<td>Dates of travel and how long did they travel? ____________________________</td>
<td></td>
</tr>
<tr>
<td>Where did they stay (hotel, family, resort)? ____________________________</td>
<td></td>
</tr>
<tr>
<td>3. Since the last TB skin test, has your child been exposed to anyone with TB disease? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Name of their disease: ____________________________</td>
<td></td>
</tr>
<tr>
<td>Positive TST result with normal chest taking one medicine or no treatment OR TB disease taking many pills and different kinds of medicine?</td>
<td></td>
</tr>
<tr>
<td>Name of person: ____________________________</td>
<td>DOB: ____________________________</td>
</tr>
<tr>
<td>Where is the person being treated? ____________________________</td>
<td></td>
</tr>
<tr>
<td>4. Since the child’s last skin test, has your child had close contact with a person who has a positive TST result? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Nature of their disease: ____________________________</td>
<td></td>
</tr>
<tr>
<td>Positive TST result with normal chest radiograph taking medicine or no treatment OR TB disease taking many pills and different kinds of medicine?</td>
<td></td>
</tr>
<tr>
<td>Name of person: ____________________________</td>
<td>DOB: ____________________________</td>
</tr>
<tr>
<td>Where is the person being treated? ____________________________</td>
<td></td>
</tr>
<tr>
<td>Optional questions depending on local epidemiology:</td>
<td></td>
</tr>
<tr>
<td>Since the last skin test, has your child consumed unpasteurized milk or cheese (from Mexico or Central America)? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Since the last skin test, has your child been around people in jail, homeless or in shelters, people who have HIV, or use illegal drugs? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>Since the last skin test, has your child lived with a new person who was born or traveled outside the US? ______ Yes ______ No</td>
<td></td>
</tr>
<tr>
<td>INSTRUCTIONS FOR PROVIDERS: Test only children who have a new risk factor since their last TST. If the child has previously had a positive TST result, then do not administer another TST. Significant travel is considered travel to a country with a high prevalence of TB (eg, in Africa, Asia, Latin American, and Eastern Europe) for &gt;1 week AND had a substantial contact with indigenous people from such countries (did not stay in a resort).</td>
<td></td>
</tr>
</tbody>
</table>

than one half of children because of its osmotic load. The tablet can be crushed and mixed with or layered into a strong-flavored semisoft food in a spoon. Children should be examined monthly and questioned about symptoms of toxicity. INH-related transient increase of transaminases has been noted in children, with the effects increasing with increasing age; however, INH rarely causes clinical hepatotoxicity in children. Routine monitoring of liver transaminases is not indicated for asymptomatic children who do not have underlying liver disease and who are not receiving other hepatotoxic drugs.

Parents should be asked about the child’s adherence to therapy and results of skin testing of family members and other contacts. Figure 332-3 shows an example of a flow sheet for monitoring LTBI treatment. Every effort should be made to promote and facilitate adherence through enablers such as walk-in visits for refills (nurse visits) or school-based dosing or monthly monitoring. Incentives such as stickers and calendars, prizes, and end-of-treatment rewards can also be used to promote adherence (for an example, see www.maine.gov/dhhs/boh/ddc/treasure_chest_program Tb.htm). Children receiving antiepileptic drugs should be

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**Table:**

<table>
<thead>
<tr>
<th>TB Risk Factor?</th>
<th>TST Risk Factor?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>TST results negative based on breakpoints (Box 332-3)</td>
</tr>
<tr>
<td>Yes</td>
<td>TST results positive based on breakpoints (Box 332-3)</td>
</tr>
</tbody>
</table>

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**Figure 332-1** General strategy for targeted tuberculosis testing. LTBI, Latent tuberculin infection; TST, tuberculin skin test; DOT, directly observed therapy.
monitored closely because INH affects the drug levels of some of these medications. After completing the 270 doses of INH for LTBL, the family should be provided with a card or letter documenting completion of therapy and reminded that the child should not undergo tuberculin testing in the future. An end-of-completion radiograph is not necessary.¹

Figure 332-2 Evaluation of a child exposed to a person with contagious tuberculosis. INH, Isoniazid; TST, tuberculin skin test.

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¹BlackLining Enabled
Rifampin given for 180 daily doses is occasionally used as an alternative for a patient who is intolerant to INH or is known to be infected by an INH-resistant TB strain. Most side effects of INH can be overcome with adjustments of timing or symptomatic management. Rifampin may accelerate the metabolism or have other interactions with several important classes of drugs, including anticonvulsants, antiarrhythmics, antifungals, barbiturates, 

antibiotics, corticosteroids, oral contraceptives, oral hypoglycemics, and drugs used to treat HIV infection. Adjusting the dose of these drugs may be necessary if they are given concurrently with rifampin.

## EVALUATION

### History

Evaluation is intended to discern TB disease from LTBI, as well as to identify a possible source of infection, risks for drug resistance, and underlying medical conditions that might increase the risk of TB or complicate TB treatment (Figure 332-4).

In the United States, approximately one half of children diagnosed with TB disease either have no symptoms or their symptoms have been developing so subtly and insidiously that their parents have not noticed. Common symptoms include weight loss or failure to gain weight, anorexia, fever, and cough, as well as decreased energy, playfulness, or activity. Other symptoms may be noted for patients with extrapulmonary TB, lymph node enlargement, headache, personality changes, focal neurologic changes, or musculoskeletal pain. TB can produce fulminant or indolent symptoms, but symptoms are typically more chronic when caused by TB than when caused by bacterial or viral infections. Cough is often noted for weeks rather than days; lymph node swelling develops over weeks, with gradual and modest changes in the overlying skin. Occasionally, symptoms such as cough and fever are actually improving at the time of diagnosis.

The history should include information that would suggest an alternative diagnosis, such as reactive airways disease, bacterial or viral pneumonia, pyogenic lymphadenitis, or viral meningitis. Pertinent medical history includes previous TB skin test results, previous TB treatment, and results of any previous chest radiographs. The medical history should also include factors that would complicate TB therapy, including underlying liver disease and use of potentially hepatotoxic drugs. Patients infected with HIV or who have another immunocompromising condition are more likely than others to have TB and are more likely than others to have an atypical or extrapulmonary presentation of TB.

Close contact to a contagious person results in a significant proportion of household contacts becoming infected. If the family knows of a TB exposure, then the history should include the name, address, and the date of birth of the patient with TB, as well as the jurisdiction of treatment, susceptibility data, and treatment details.

If the family does not know anyone with TB disease, then family members should be asked whether they have close contact with an adolescent or adult with chronic cough, fever, or unexplained weight loss or if they have household contact with an individual with a positive TST result (especially a newly positive result). Because more than 50% of adult patients with TB disease are born outside the United States (primarily in Latin America, Asia, Africa, and Eastern Europe), contacts from these areas should be solicited. Children who were born in an area with a high incidence of TB or who have traveled to these areas are at increased risk of TB and LTBI. Family members should be asked where children were born, where they have traveled, how long they stayed, and with whom they stayed when traveling in TB-endemic areas.

Ingestion of foreign unpasteurized milk and milk products, such as Mexican-style soft cheeses (queso fresco) raises the possibility of infection with M. bovis. (although M. bovis has a propensity to cause peripheral and intraabdominal lymphadenitis, it can cause any TB manifestation, including pneumonia.)

Finally, if several family members have positive TST results, then the likelihood that the patient’s disease is TB increases. The primary care physician should immediately perform a TST on any family member who has not recently undergone such a test (and has never had a positive result in the past). To prevent possible continued transmission of TB, chest radiographs of adults with a previous or newly positive TST result or suspicious TB-like symptoms should be obtained.

### Table 332-2 Isoniazid Daily Dosing

<table>
<thead>
<tr>
<th>CHILD’S WEIGHT</th>
<th>MILLIGRAMS</th>
<th>100-mg TABLETS</th>
<th>300-mg TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>6.6-11</td>
<td>50</td>
<td>$\frac{1}{2}$</td>
</tr>
<tr>
<td>5-7.5</td>
<td>11-16.4</td>
<td>75</td>
<td>$\frac{3}{4}$</td>
</tr>
<tr>
<td>7.5-10</td>
<td>16.5-22</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>10-15</td>
<td>22-33</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>15-20</td>
<td>33-44</td>
<td>200</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20</td>
<td>&gt;44</td>
<td>300</td>
<td>0</td>
</tr>
</tbody>
</table>

*Maximal dose, 300 mg.
Physical Examination

The focused physical examination should emphasize vital signs, growth parameters, conjunctival examination, neck flexion, lymph node palpation, auscultation of heart and lungs, abdomen and flank palpation, spine and bone palpation, brief skin examination, and neurologic examination (depending on concerns for TB of the central nervous system). Children diagnosed as having LTBI will have no examination abnormalities that suggest TB disease. Even children with pulmonary TB may have no findings at physical examination. The findings on chest radiograph are frequently more useful than those found by physical examination or history.
**Laboratory Evaluation**

Routine testing for children suspected of having TB includes HIV serologic testing and mycobacterial cultures. Sputum specimens are challenging to collect from young children, but they can be collected by gastric aspiration (Box 332-5), induction, or bronchoalveolar lavage. Gastric aspirates are typically collected on three consecutive mornings after an overnight fast. Historically, yields are between 30% and 50%, with the highest yields being in the youngest infants and from the initial sample collected. If the patient is not otherwise ill enough to require inpatient management, then gastric aspirates can be collected in the outpatient setting.

In older children, sputum induction with hypertonic saline can be attempted; inducing sputum in infants is difficult. Bronchoalveolar lavage is used primarily when diagnostic possibilities other than TB are being strongly considered. Yield for bronchoalveolar lavage in culturing *M tuberculosis* in children is between 10% and 21%, and yields are less than that for gastric lavage in children.

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**Figure 332-4** Evaluation of a child with a positive TST result. *LTBI*, Latent tuberculin infection; *TST*, tuberculin skin test.
**BOX 332-5 Gastric Aspirate Procedure for Culture of Mycobacterium tuberculosis**

- For health care workers present during gastric aspirate procedures of a patient with suspected or confirmed infectious TB disease, at least N-95 disposable respirators should be worn.
- Collect all supplies and have everything ready: N-95 respirators, papoose board or sheet, No. 10 or larger French nasogastric or suction tube, 30-mL syringe with appropriate connector for tube; pen; sterile water; specimen cup or laboratory-prepared tube containing bicarbonate for bedside neutralization; requisition and label; helper.
- Child should not take anything by mouth for at least 6 hours before the procedure.
- Immobilize the child with a sheet with or without a papoose board.
- Measure the distance from the nose to the stomach.
- Insert a No. 10 French nasogastric tube through the nose into the stomach.
- Puff in the child’s face as the tube enters the throat to elicit a swallow reflex.
- Gently aspirate the tube with an appropriately fitted 30- to 60-mL syringe.
- If no significant yield, then advance and withdraw the tube slightly while aspirating.
- If yield is still less than 5 to 10 mL, then place any collected mucus into a container.
- Check tube position by auscultating the stomach while pushing air from the syringe into tube.
- Instill 20 mL of sterile water into the stomach and quickly aspirate again.
- If yield is less than 5 to 10 mL, then roll the child on the side, advance the tube, aspirating continuously to find the pool of mucus in the stomach.
- As tube is withdrawn, continuously aspirate the syringe.
- Place any yield, including any spontaneously vomited emesis, in the specimen container.
- Label the specimen and order AFB smear and culture.
- Promptly transport the specimen to the laboratory for processing (tell the laboratory if the specimen has already been neutralized).

Guided by the physical examination and clinical scenario, other specimens may be collected, including cerebrospinal fluid (CSF). CSF culture has a 50% to 75% yield in diagnosis of TB meningitis. Acid-fast bacillus (AFB) smear has an even lower yield, but it can be improved by centrifugation of large volumes of CSF. The use of the polymerase chain reaction technique has been disappointing, but it may play a role as an adjunct diagnostic method. AFB smear and culture of other tissues should be undertaken as indicated for lymph node tissue, abscess drainage, bone or synovial fluid, urine, blood, bone marrow, or other tissue. Specimens for AFB smear and culture should be submitted in a sterile cup (rather than on a swab) and without formalin preservative.

Regardless of the culture-collection method or specimen being collected, culture for *M tuberculosis* in children has suboptimal yields. Families should understand that AFB smears are not usually positive from specimens from children, that cultures must be incubated for several weeks before any results are available, and that cultures have less than 50% yield in most situations. Specimens are collected so that if cultures are positive and yield susceptibility data, then the treatment regimen can be optimized. In most cases, the diagnosis of TB in a child is a clinical diagnosis, influenced by the probability of exposure to a person with infectious TB, TST results, clinical symptoms and signs, and results of imaging tests. Although none of these elements is diagnostic for TB disease, the experienced TB clinician weighs all these factors along with the risk to the child of not treating TB when considering whether to begin treatment. Unless an alternative diagnosis is established, most often, once TB therapy is begun, the course should be completed.

Other laboratory evaluations should be considered based on individual circumstances. Patients who have TB-HIV coinfection, severe TB disease, symptoms or signs of hepatitis, or known underlying liver disease or those who are receiving other hepatotoxic medications should have liver transaminase levels measured. The QuantiFERON-TB Gold test is an in vitro diagnostic test for detecting interferon gamma (IFN-γ) when a patient’s whole blood is incubated with specific TB proteins and controls. The detection of IFN-γ indicates a T-cell response by the patient’s lymphocytes and probable infection with *M tuberculosis*. Few data support its applicability to children, although studies are underway.

**Imaging Studies**

Any child whose TST result is positive or who is suspected of having pulmonary or extrapulmonary TB should have a chest radiograph performed. For the best-quality radiograph, the child should be in full inspiration and should not be rotated. For children younger than 8 years, both frontal and lateral views should be obtained. The lateral view is particularly helpful in distinguishing other central shadows from intrathoracic lymph nodes, which are spherical and can frequently be seen on both views. Ideally the films should be interpreted by a clinician or radiologist experienced in pediatric TB. Computed tomography is not indicated in the evaluation of an asymptomatic child with a normal chest radiograph and a positive TST result. A computed tomography scan can be helpful when the radiograph is equivocal and when looking for other causes of lung disease is necessary.

Findings on chest radiographs of children with TB are variable. Enlarged intrathoracic lymph nodes and infiltrate are the most common abnormalities. Intrathoracic adenopathy is frequently seen in children and is reported to be present in up to 85% of children.
under 3 years of age. Hilar, mediastinal, paraatracheal, and subcarinal nodes may be seen and are most often found on the right side. Isolated adenopathy should be treated as TB disease. Figure 332-5 shows the radiograph of a child with typical intrathoracic adenopathy caused by TB.

An infiltrate may be seen in any lung field and is seen in multiple lobes in one quarter of children. Parenchymal disease may be caused by several processes. A larger consolidation may be associated with advancement of the infection—the so-called progressive primary process—or it may be due to atelectasis or collapse-consolidation that results from lymph node obstruction. Lymph node obstruction can also cause air trapping behind the node with resultant wheezing and hyperinflation. Older children, especially adolescents, may have radiographic findings that are consistent with adult reactivation (postprimary) TB, including upper lobe disease with fibronodular infiltrates, volume loss, hilar retraction, and cavities.

Infection is sometimes spread to other parenchymal locations after erosion of a lymph node with spilling of infectious material (bronchogenic spread). This situation can cause a segmental lesion when the material is limited to one bronchus, or it may result in diffuse bronchopneumonia when the organism spreads throughout the lung.

Distribution of *M. tuberculosis* via hematogenous dissemination that causes disease to the lung and other organs is termed disseminated disease, although the term miliary disease was formerly used because of the small, round, millet-like appearance of the diffuse lesions. Figure 332-6 shows the radiograph of an infant with disseminated TB. Primary bacillemia occurs during the initial process of the proximal lymph nodes draining into the thoracic duct. The infection may also be disseminated secondarily if a necrotizing lymph node or airspace focus erodes into a blood vessel. These disseminated processes do not always appear radiographically in the classic disseminated pattern. Larger, patchy, reticulonodular lesions may

**Figure 332-5** Chest radiograph of a child with enlarged intrathoracic lymph nodes.

**Figure 332-6** Chest radiograph of infant with disseminated tuberculosis.
<table>
<thead>
<tr>
<th>TB MANIFESTATION</th>
<th>MINIMAL DURATION OF THERAPY</th>
<th>INITIAL REGIMEN</th>
<th>FOLLOW-UP REGIMEN</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB</td>
<td>6 mo</td>
<td>Isoniazid, rifampin, pyrazinamide, and ethambutol daily for 2 wk to 2 mo (three-drug therapy only if no risk of resistance)</td>
<td>Stop ethambutol as soon as the patient or reliable source case isolate is found to be drug susceptible. Document a follow-up chest radiograph 2 mo into therapy. If the isolate is sensitive and the patient is clinically well and radiographically improving or stable, then change to isoniazid and rifampin at 2 mo to complete a 6-mo course; twice-weekly therapy can be provided by directly observed therapy. Document chest radiograph at end of treatment—frequently not quite normal.</td>
<td>Four-drug initial therapy is provided if any risks exists of drug resistance, including previous TB treatment or exposure to a person with known drug-resistant TB. If a cavitary lesion was present on the chest radiograph and sputum culture is positive after 2 mo of treatment, then the total treatment should be extended to 9 rather than 6 mo.</td>
</tr>
<tr>
<td>Extrapulmonary (meningitis, bone or joint, disseminated)</td>
<td>9-12 mo</td>
<td>Same as pulmonary disease</td>
<td>7-10 mo of isoniazid and rifampin, either daily or twice a week by directly observed therapy.</td>
<td>Some clinicians use an injectable drug (eg, amikacin, kanamycin) for initial treatment of disseminated or meningeal disease. Strongly consider corticosteroid therapy for some types of extrapulmonary disease (eg, meningitis, pericarditis). Same as pulmonary disease</td>
</tr>
<tr>
<td>Other extrapulmonary (cervical adenopathy)</td>
<td>Same as pulmonary disease</td>
<td>Same as pulmonary disease</td>
<td>Same as pulmonary disease except no need to follow chest radiographs if initially normal</td>
<td>Same as pulmonary disease</td>
</tr>
</tbody>
</table>

TB, Tuberculosis.

*Directly observed therapy by a trained health care worker is the standard of care for all children with TB.
be present and difficult to distinguish from other diffuse lung infections.

Pleural effusion and empyema are less common in children with TB compared with adults. Isolated, dense nodules with calcification, nonenlarged calcified lymph nodes, and isolated pleural thickening are considered signs of healed M tuberculosis infection and are not considered to be TB disease. Peribronchial cuffing or thickening is commonly associated with reactive airway disease and viral infection and, in isolation, is not consistent with TB.

The clinician should obtain a chest radiograph 2 months after therapy for TB disease has begun and again when therapy has ended. Radiographic abnormalities in children with TB resolve slowly, and enlargement of lymph nodes may persist for a long period. The chest radiograph is not normal in more than one half of children at the end of therapy. However, they continue to improve gradually. The radiograph at the completion of therapy should be greatly improved compared with the original radiograph, which will serve as a baseline for monitoring future changes. The chest radiograph need not be repeated for children receiving or completing LTBI treatment unless they develop symptoms compatible with TB disease.

**Treatment of Tuberculosis Disease**

In all states, Puerto Rico, and US territories, providers are legally mandated to report persons suspected of having or confirmed to have TB to the local health department. Reporting is an important public health function because the health department assumes responsibility for collaboration in case management, provides DOT, and tests exposed contacts.

Children with TB disease should be managed in a dedicated TB clinic or by the most experienced pediatric TB clinician available. In areas where this treatment is not feasible, close and ongoing consultation with an experienced clinician should be sought.

Children with clinical or radiographic evidence of active TB, regardless of the TST result, should be evaluated immediately, as outlined in Figure 332-4. Specimens for AFB smear and culture should be collected. TB disease is hard to diagnose definitively in children because culture confirmation is frequently lacking or can be delayed for several weeks. Children who have a positive TST result, who have known exposure to TB or risk factors for TB exposure, who have radiographic changes consistent with TB, or who have relatively few symptoms compared with their radiographic changes are more likely to have TB as opposed to alternative diagnoses such as community-acquired pneumonia or reactive airways disease.

Table 332-3 shows recommended treatment regimens for TB disease in children. A four-drug empiric regimen (INH, rifampin, pyrazinamide, and ethambutol) is recommended for individuals who are at higher risk for having INH-resistant TB, including exposure to an individual from an area of high prevalence of drug-resistant TB, with known drug-resistant TB, or previous treatment for TB. DOT by a health care professional (not parents) is recommended for treatment of TB in children and adolescents. After 2 months of treatment, a repeat chest radiograph should be performed. For children from whom sputum can be obtained, follow-up sputum should be obtained to document culture conversion. If the patient has been adherent to therapy, is clinically well, has an improving or at least stable radiograph, and no reason exists to suspect drug resistance, the regimen can then be changed to two drugs (INH and rifampin) after completing 2 months of pyrazinamide so as to complete a 6-month course. Twice-weekly dosing by DOT can be used after the induction phase of daily treatment if the child is tolerating the regimen well and has shown considerable clinical improvement. The number of doses actually observed should be counted when considering whether a patient has completed therapy. Patients receiving daily doses for the first 2 months will typically receive 40 observed doses (Monday through Friday for approximately 8 weeks) followed by 36 twice-weekly doses in the following 18 weeks.

Treatment of INH-monoresistant TB disease requires at least 6 months of rifampin, pyrazinamide, and ethambutol. Treatment of drug-resistant TB should be performed in consultation with an expert in this area. (See Farhart M et al and Menzies for details.)

The most important element of TB therapy is the actual ingestion of the drugs. Children are difficult to dose with TB drugs, given that the formulations are not particularly child friendly. See dosing suggestions in the previous section on Latent Tuberculosis Infection.

The parents and public health staff should be warned that they might have to endure a several-week period of trial and error. Patients should be monitored monthly during therapy. Routine laboratory evaluation need not be performed unless the patient has symptoms of toxicity or underlying liver disease or unless the patient is taking other medications, which might interfere with the TB drugs or cause similar toxicities.

An end-of-therapy chest radiograph should be obtained. Most children do not have a normal radiograph at the end of therapy, but significant improvement is expected.

Corticosteroids have been shown to be beneficial in central nervous system disease, particularly stage 2 and 3 (altered mental status). Some clinicians would use steroids for any child with symptomatic TB meningitis. Steroids are also frequently used for TB pericarditis. Two reports support the use of steroids in children with symptomatic airways compression caused by lymphatic disease. Prednisone is generally used at a dose of 1 to 2 mg/kg/day given for 4 to 8 weeks and then tapered over several weeks.

**CONCLUSION**

TB is a focal problem in the United States, disproportionately affecting immigrant, Hispanic, and black populations. TB risk assessments at well-child and other visits have replaced universal screening of children by TST. Only children who have a new risk for TB exposure since the last TST or who have features suggestive of TB disease should undergo the TST. All children diagnosed as having LTBI should be treated and closely monitored for adherence and toxicity. Clinics should develop or modify systems to remove barriers to completion of therapy, including walk-in nurse visits, minimal paperwork, easy chart forms, and incentives. Many children with TB in the United States are asymptomatic at the time of diagnosis. TB
The authors thank Phil LoBue, MD, Ann Lanner, and Michael Iademarco, MD, Centers for Disease Control and Prevention, for their input on this chapter.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry.

WHEN TO REFER

- All patients suspected of having active TB should be reported to the local health department according to state statute (eg, within 1 working day).
- In many jurisdictions, young children with LTBI should be reported to the local health department, according to local regulations.
- Ideally, an experienced pediatric TB clinician should manage children with TB disease. If local resources are not available, then close and ongoing consultation with a pediatric TB expert should be established.

WHEN TO ADMIT

- Children should be admitted to the hospital for culture collection if local resources are not available for outpatient culture collection.
- Few children require admission to the hospital based on clinical severity of TB disease. Patients with increased work of breathing, meningitis, or complicating simultaneous conditions or patients who require diagnostic evaluation should be admitted.

REFERENCES


AAP POLICY STATEMENTS


TOOLS FOR PRACTICE

Engaging Patient and Family

Medical Decision Support
- Division of Tuberculosis Elimination (Web page), Centers for Disease Control and Prevention (www.cdc.gov/tb/default.htm).
PART 9: SPECIFIC CLINICAL PROBLEMS


Despite its essential role in the survival of the fetus during prenatal life, the umbilicus, the external vestige of the umbilical cord, is frequently ignored or overlooked by the pediatric primary care physician. However, aberrations in either the formation or the position of this structure can offer helpful clues to underlying disease in the young child. Major congenital anomalies of the ventral abdominal wall, such as omphalocele, gastrochisis, and extrophies of the bladder and cloaca, are described in detail elsewhere. This chapter deals with minor anomalies in configuration, placement, and formation of the umbilicus. In addition to the conditions described here, the umbilicus can be the site of both tumors (either vascular or teratomatous neoplasms) and infections (omphalitis).

To understand the causes and significance of anomalies of the umbilicus, a review of some basic fundamentals of the embryologic development of the umbilical cord is necessary.

EMBRYOLOGIC DEVELOPMENT OF THE UMBILICAL CORD

Appearing within the first 6 weeks of gestation, the umbilical cord is derived from the fusion of 3 separate embryonic structures: (1) the primitive or primary yolk sac, which contains the allantois and a portion of the vitelline duct, transient structures that ultimately form the central portion of the embryonic gut, the urinary bladder, the urachus, and the umbilical blood vessels (usually 2 arteries and 1 vein); (2) the secondary yolk sac, composed of the remainder of the vitelline duct; and (3) the mesenchyme of the connecting body stalk of the embryo, the tissue that produces Wharton jelly, which is the packing substance that holds the cord together. After fusion is complete, these unified structures become covered by the amnion and are ultimately surrounded by amniotic fluid.

Many of these embryonic structures that form the umbilical cord are present for only brief periods during embryogenesis. After the 7th week of gestation, the vitelline duct regresses and is ultimately completely resorbed. Similarly the allantois, which is contiguous with the urinary bladder, degenerates, forming a fibrous cord called the *urachus*, which connects the apex of the bladder with the umbilicus. Anomalies may result when these structures fail to undergo normal regression, causing them to persist into postnatal life.

ANOMALIES

Abnormalities of Position and Morphology

Anatomically, the level of the umbilicus is usually at the top of the iliac crest ventral to the 3rd or 4th lumbar vertebra. Variations in the position of the umbilicus can result from abnormalities in the way in which the abdominal wall itself has formed and, as such, may be a clue to the diagnosis of specific dysmorphic syndromes. For example, as described in Table 333-1, the umbilicus has been noted to be low set in achondroplasia (in which disproportionate growth of the trunk accounts for the aberration in position), in bladder and umbilical anomalies.