Pediatric Tuberculosis

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Essentials of diagnosis & typical features:

- All types: Positive tuberculin test in patient or members of household, suspicious chest x-ray, history of contact, and demonstration of organism by stain and culture.
- Pulmonary: Fatigue, irritability, and undernutrition, with or without fever and cough.
- Glandular: Chronic cervical adenitis.
- Miliary: Classic snowstorm appearance of chest x-ray; choroidal tubercles.
- Meningitis: Fever and manifestations of meningeal irritation and increased intracranial pressure. Characteristic CSF.

General Considerations:

Tuberculosis is a granulomatous disease caused by *Mycobacterium tuberculosis*. It is a leading cause of death throughout the world. Children under age 3 years are most susceptible. Lymphohematogenous dissemination through the lungs to extrapulmonary sites (including the brain and meninges, eyes, bones and joints, lymph nodes, kidneys, intestines, larynx, and skin) is more likely to occur in infants. Increased susceptibility occurs again in adolescence, particularly in girls within 2 years of menarche. High-risk groups include ethnic minorities, foreign-born persons, prisoners, residents of nursing homes, indigents, migrant workers, and health care providers. HIV infection is an important risk factor for both development and spread of disease.

Exposure to an infected adult is the most common risk factor in children. The primary complex in infancy and childhood consists of a small parenchymal lesion in any area of the lung with caseation of regional nodes and calcification. Postprimary tuberculosis in adolescents and adults occurs in the apices of the lungs and is likely to cause chronic progressive cavitary pulmonary disease with less tendency for hematogenous dissemination. *Mycobacterium bovis* infection is clinically identical to *M tuberculosis*. *M bovis* may be acquired from unpasteurized dairy products.

Clinical Findings:

1. **Pulmonary**— The most important aspect of the history is contact with an individual with tuberculosis—often an elderly relative, a caregiver, or a person previously residing in a region where tuberculosis is endemic—or a history of travel to or residence in such an area. Homeless and extremely impoverished children are also at high risk, as are those in contact with high-risk adults (AIDS patients, residents or employees of correctional institutions or nursing homes, drug users, and health care workers). Once exposed, pediatric patients at risk for developing active disease include infants and those with malnutrition, AIDS, diabetes mellitus, or immunosuppression (cancer chemotherapy, corticosteroids). In suspected cases, the patient, immediate family, and suspected carriers should be tuberculin-tested. Spread is mainly respiratory, so isolated pulmonary parenchymal tuberculosis constitutes more than 95% of presenting cases. The primary focus (usually single) and associated nodal involvement may not be seen radiographically. Because healing—rather than progression—is the usual course in the uncompromised host, a positive tuberculin test may be the only manifestation. However, for patients born outside the United States, a positive test may indicate only a previous Bacille Calmette-Guérin (BCG) immunization.

The tuberculous complications most often occur during the first year of infection. Thereafter, infection remains quiescent until adolescence, when reactivation of pulmonary tuberculosis is common. At any stage,

chronic cough, anorexia, weight loss or failure to gain weight, and fever are useful clinical signs if present. Except in cases with complications or advanced disease, physical findings are few. Most children with pulmonary tuberculosis are asymptomatic.

2. **Miliary**—Diagnosis is usually based on the classic **snowstorm** or millet seed appearance of lung fields on x-ray, although early in the course of disseminated tuberculosis, the chest x-ray may show no or only subtle abnormalities. The majority of patients have a fresh primary complex and pleural effusion. **Choroidal tubercles** are sometimes seen on fundoscopic examination. Other lesions may be present and produce osteomyelitis, arthritis, meningitis, tuberculomas of the brain, enteritis, or infection of the kidneys and liver.

3. **Meningitis**—Symptoms include fever, vomiting, headache, lethargy, and irritability, with signs of meningeal irritation and increased intracranial pressure, cranial nerve palsies, convulsions, and coma. **Choroidal tubercles are pathognomonic** when associated with these signs and symptoms.

4. **Glandular**—The primary complex may be associated with a skin lesion drained by regional nodes or chronic cervical node enlargement or infection of the tonsils. Involved nodes may become fixed to the overlying skin, suppurate, and drain.

Laboratory findings:

The **Mantoux test** (also known: tuberculin sensitivity test, Pirquet test) (0.1 mL of intermediate strength purified protein derivative [PPD] [5 TU] inoculated intradermally) is positive at 48–72 hours if there is significant induration (>10 mm). Parental reporting of skin test results are often inaccurate. All tests should be read by professionals trained to interpret Mantoux tests. False-negative results occur in malnourished patients, in those with overwhelming disease, and in 10% of children with isolated pulmonary disease. Temporary suppression of tuberculin reactivity may be seen with viral infections (e.g., measles, influenza, varicella, mumps), after live virus immunization, and during corticosteroid or other immunosuppressive drug therapy. For these reasons, a *negative Mantoux test does not exclude the diagnosis of tuberculosis*. When tuberculosis is suspected in a child, household members and adult contacts (e.g., teachers, caregivers) should also be tested immediately. Multiple puncture tests (**tine tests**) should not be used because they are associated with false-negative and false-positive reactions, and because standards for interpretation of positive results do not exist. The two commercially available reagents for Mantoux testing give discrepant results in some cases.

The **erythrocyte sedimentation rate** (ESR) is usually elevated.

Cultures of pooled early morning gastric aspirates from three successive days will yield *M tuberculosis* in about 40% of cases. Culture for M tuberculosis is critical for proving the diagnosis and for defining drug susceptibility. Biopsy may be necessary to establish the diagnosis. Therapy should not be delayed in suspected cases. The CSF in tuberculous meningitis shows slight to moderate pleocytosis (50–300 white blood cells, predominantly lymphocytes), decreased glucose, and increased protein.

The direct detection of mycobacteria in body fluids or discharges is best done by staining specimens with **auramine-rhodamine** and examining them with fluorescence microscopy; this method is superior to the Ziehl-Neelsen method.

Chest x-ray should be obtained in all children with suspicion of tuberculosis at any site or with a positive skin test. Segmental consolidation with some volume loss and hilar adenopathy are common findings in children. Pleural effusion also occurs with primary infection. Cavities and apical disease are unusual in children but are seen in adolescents and adults.

Differential Diagnosis:

Pulmonary tuberculosis must be differentiated from fungal, parasitic, mycoplasmal, and bacterial pneumonias; lung abscess; foreign body aspiration; lipoid pneumonia; sarcoidosis; and mediastinal cancer.

Cervical lymphadenitis is most likely due to streptococcal or staphylococcal infections. Cat-scratch fever and infection with atypical mycobacteria may need to be distinguished from tuberculous lymphadenitis.

Viral meningoencephalitis, head trauma (child abuse), lead poisoning, brain abscess, acute bacterial meningitis, brain tumor, and disseminated fungal infections must be excluded in **tuberculous meningitis**. The skin test in the patient or family contacts is frequently valuable in differentiating these conditions from tuberculosis.

Prevention:

A. **BCG Vaccine**: BCG vaccines are live attenuated strains of M bovis. Although neonatal and childhood administration of BCG is carried out in countries with a high prevalence of tuberculosis, protective efficacy varies greatly with vaccine potency and method of delivery. Because the great majority of children who have received BCG still have negative Mantoux tests, it is unwise to attribute the positive Mantoux test to the prior BCG vaccination.

B. **Isoniazid (INH) Chemoprophylaxis:**

Daily administration of isoniazid (10 mg/kg/d orally; maximum 300 mg) is advised for children who cannot avoid intimate household contact with adolescents or adults with active disease. Isoniazid is given until 3 months after last contact. At the end of this time, a Mantoux test should be done, and therapy should be continued for an additional 6 months if the test is positive. BCG is not recommended during the period of isoniazid chemoprophylaxis.

C. **Other Measures:**

Tuberculosis in infants and young children is evidence of recent exposure to active infection in an adult. The source contact (index case) should be identified, isolated, and given treatment to prevent other secondary cases. Reporting cases to local health departments is essential for contact tracing. Exposed tuberculin-negative children should usually receive isoniazid chemoprophylaxis. If a repeated skin test is negative 2–3 months following the last exposure, isoniazid may be stopped. Routine tuberculin skin testing is no longer recommended for children without risk factors who reside in communities with a low incidence of tuberculosis. Children with no personal risk for tuberculosis but who reside in communities with a high incidence of tuberculosis should be given a skin test at school entry and then again at age 11–16 years. Children with a risk factor for acquiring tuberculosis should be tested every 2–3 years. Incarcerated adolescents and children living in a household with HIV-infected persons should have annual skin tests.

Children who immigrate from a country with a high incidence of infection should receive a skin test upon entry to the United States or upon presentation to health care providers.

Treatment:

A. Specific measures:

Most children with tuberculosis are hospitalized initially. If the infecting organism has not been isolated from the presumed contact for susceptibility testing, reasonable attempts should be made to obtain it from the child using "morning gastric aspirates", sputum, bronchoscopy, thoracentesis, or biopsy when appropriate. Therapy is given daily for 2–4 weeks and then reduced to 2–3 times per week for the duration of the course. Directly-Observed Therapy (DOT) of all doses of anti-tuberculous therapy by a trained health care professional is essential to ensure compliance with therapy.

All children with positive skin tests without overt disease should receive 9 months of isoniazid (10 mg/kg/d orally; maximum 300 mg) therapy. In children with overt pulmonary disease, therapy for 6 months using isoniazid (10 mg/kg/d), rifampin (15 mg/kg/d), and pyrazinamide (25–30 mg/kg/d) in a single daily oral dose for 2 months, followed by isoniazid plus rifampin (either in a daily or twice-weekly regimen) for 4 months appears effective for isoniazid-susceptible

organisms. For more severe disease, such as miliary or CNS infection, duration is increased to 12 months or more, and a fourth drug (streptomycin or ethambutol) is added for the first 2 months. In communities with resistance rates greater than 4%, initial therapy should usually include four drugs.

1. **Isoniazid**—The hepatotoxicity from isoniazid seen in adults and some adolescents is rare in children. Transient elevation of aminotransferases (up to three times normal) may be seen at 6–12 weeks, but therapy is continued unless clinical illness occurs. "Routine monitoring of liver function tests is unnecessary" unless prior hepatic disease is known or the child is severely ill. Peripheral neuropathy associated with pyridoxine deficiency is rare in children, and it is "not necessary to add pyridoxine" unless significant malnutrition coexists.

2. **Rifampin**—Although it is an excellent bactericidal agent, rifampin is never used alone owing to rapid development of resistance. Hepatotoxicity may occur but rarely with recommended doses. The orange discoloration of secretions is benign but may stain contact lenses or clothes.

3. **Pyrazinamide**—This excellent sterilizing agent is most effective during the first 2 months of therapy. With the recommended duration and dosing, it is well tolerated. Although pyrazinamide elevates the uric acid level, it rarely causes symptoms of hyperuricemia in children. Use of this drug is now common for tuberculous disease in children, and resistance is almost unknown. Oral acceptance and CNS penetration are good.

4. **Ethambutol**—Because color blindness and optic neuritis are the major side effects in adults, ethambutol has usually been given only to children whose vision can be reliably tested every 2 months. This complication is rare and usually occurs in those receiving more than the recommended dosage of 25 mg/kg/d. Documentation of optic toxicity in children is lacking despite administration worldwide. Therefore, many four-drug regimens for children now include ethambutol.

5. **Streptomycin**—Streptomycin (20–30 mg/ kg/d, given intramuscularly in one or two doses) should be given for 1 or 2 months in severe disease. The child's hearing should be tested periodically during use.

*"Recommendations for antituberculosis chemotherapy, based on disease stage, are continuously being updated. The most current edition of the AAP **Red Book** is a reliable source for these protocols."*

B. Chemotherapy for drug-resistant tuberculosis:

The incidence of drug resistance is increasing and reaches 10–20% in some areas. Transmission of multiply drug-resistant strains to contacts has occurred in some epidemics. All patients with resistant strains should be given at least two effective drugs. In areas with rates of resistance greater than 4%, initial therapy should include four drugs pending susceptibility testing. Consultation with local experts in treating tuberculosis is important in these difficult cases. Therapy should continue for 12 months or longer.

C. General measures:

1. **Corticosteroids**—These drugs may be used for suppressing inflammatory reactions in meningeal, pleural, and pericardial tuberculosis and for the relief of bronchial obstruction due to hilar adenopathy. Prednisone is given orally, 1 mg/kg/d for 6–8 weeks, with gradual withdrawal at the end of that time. The use of corticosteroids may mask progression of disease. Accordingly, the clinician needs to be sure that an effective regimen is being used.

2. **Bed rest**—Rest in bed is indicated only while the child feels ill. Isolation is necessary only for children with draining lesions or renal disease and for those with chronic pulmonary tuberculosis. Most children with tuberculosis are **noninfectious** and can attend school while receiving treatment.

Prognosis:

If bacteria are sensitive and treatment is completed, most children are cured with minimal sequelae. Repeat

treatment is more difficult and less successful. With antituberculosis chemotherapy (especially isoniazid), there should now be nearly 100% recovery in miliary tuberculosis. Without treatment, the mortality rate in both miliary tuberculosis and tuberculous meningitis is almost 100%. In the latter form, about two thirds of patients receiving treatment survive. There may be a high incidence of neurologic abnormalities among survivors if treatment is started late.