Screening for Tuberculosis in Infants and Children

Committee on Infectious Diseases

CURRENT STATUS OF INFECTION AND DISEASE

In 1992 the reported number of cases of tuberculosis (TB) was increased to 26 673 in the United States, an increase of 1.5% from 1991. Although a decline of approximately 5% to 6% occurred from 1981 to 1984, during the period of 1985 to 1992 the number of reported cases increased by 20.1%. The largest increase in TB cases by age group occurred in the 25- to 44-year-old cohort (54.5% increase in 1985 to 1992), whereas cases increased 36.1% among children 0 to 4 years old and 34.1% among children 5 to 14 years old.[1] This recent increase in the number of reported cases of tuberculosis and the changing epidemiology of this disease in children have necessitated a reevaluation of the appropriate use and type of skin test for the diagnosis.[2]

Within the general population there are groups at varying risk for infection and for progression to disease (Table 1). To achieve significant progress toward reducing the number of future cases of TB, it is necessary to have the following: 1) identification of high-risk groups, with Mantoux tuberculin skin testing of persons in those groups; 2) evaluation to determine the actual presence of disease in those persons identified as infected; and 3) provision of appropriate therapy for both those with positive Mantoux tests and those with active disease.[3] Therefore, the emphasis should be to identify targeted high-risk populations for annual skin testing rather than routinely screening all persons. Routine screening would include a vast number of individuals at low risk.

More than two thirds of reported TB cases now occur in nonwhite racial and ethnic groups. Approximately one quarter of all cases in the United States occur in foreign-born persons. The majority of adult cases reported annually in the United States comes from a group of persons who have been infected in the past. Infants and children who are exposed to adult contacts with infectious TB comprise a group of individuals at high risk for recent infection. Other high-risk groups include persons with human immunodeficiency virus (HIV) infection; substance abusers; low-income populations; residents of correctional facilities; and persons with specific medical risk factors such as diabetes mellitus, chronic renal failure, and immunosuppressive disorders.[1–4]

Because of current variability in incidence of TB in different regions of the United States, effective strategies for controlling infection and disease have evolved from periodic routine screening of the entire population, to aggressive identification and investigation of high-risk groups with annual testing. This is reflected in the recommendations published jointly by the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC),[5] those of the Advisory Council for the Elimination of Tuberculosis, and those of the American Academy of Pediatrics (AAP).[4] The CDC and ATS do not recommend routine skin testing in low-risk groups in communities with a low prevalence of tuberculosis except for one-time testing during childhood for epidemiologic reasons. For children in low-risk groups, the AAP had previously suggested two alternatives: (1) no testing or (2) skin tests at three times during childhood (12 to 15 months, 4 to 6 years, and 14 to 16 years of age). Annual tuberculin testing was recommended for high-risk children previously defined to include blacks, Hispanics, the socioeconomically deprived, and children living in neighborhoods where the disease rate was higher than the national average.[4] The following information and recommendations clarify indications for tuberculin skin testing, explain differences between multiple-puncture devices and the Mantoux tuberculin skin test, and give guidelines for tuberculin skin testing, including use of the Mantoux test and its interpretation.

TUBERCULIN SKIN TESTS

A positive tuberculin skin test reaction signifies primary infection with *Mycobacterium tuberculosis*. In most children tuberculin reactivity first appears 3 to 6 weeks, and occasionally up to 3 months, after initial infection. Tuberculin reactivity caused by *M tuberculosis* infection usually remains for the individual's lifetime, even after preventive chemotherapy is given.[5–7]

Two major techniques have been used for tuberculin skin testing: the Mantoux test and multiple-puncture tests (MPTs). The Mantoux test uses a standardized antigen containing 5 tuberculin units (TU) of purified protein derivative (PPD) administered intradermally. The MPTs have been used widely because of the speed and ease with which they can be administered even by unskilled personnel. The Aplitest (Parke-Davis, Morris Plains, NJ) and the Tine (Lederle Biologicals, Wayne, NJ) tests use metal prongs coated with dried antigen, usually PPD, although one type of the Tine test uses Old Tuberculin as the antigen. The Mono-Vacc Test (Connaught Laboratories, Swiftwater, PA) uses nine plastic prongs and liquid Old Tuberculin as the antigen.

Several problems with MPTs severely limit their usefulness. First, the exact dose of tuberculin antigen

TABLE 1. Infants, Children, and Adolescents at High Risk for Tuberculous Infection

Contacts of adults with infectious tuberculosis
Those who are from or have parents who are from regions of the world with a high prevalence of tuberculosis
Those with abnormalities on chest roentgenogram suggestive of tuberculosis
Those with clinical evidence of tuberculosis
HIV-seropositive children*
Those with immunosuppressive conditions
Those with other medical risk factors: Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
Incarcerated adolescents
Children frequently exposed to the following adults: HIV-infected individuals, homeless persons, users of intravenous and other street drugs, poor and medically indigent city dwellers, residents of nursing homes, migrant farm workers

* HIV, human immunodeficiency virus.

TABLE 3. Results of Multiple-Puncture Tests (≥2 mm) Compared With Mantoux Tuberculin Skin Test (≥10 mm) Used in a Single Study*

	Sensitivity, %	Specificity, %
Tine (PPD†)	96	40
Tine (OT‡)	85	69
Aplitest§	90	78
Mono-Vacc¶	68	90

* From Cantanzaro.[15]
† Purified protein derivative; Tine, Lederle Biologicals, Wayne, NJ.
‡ Old tuberculin; Tine, Lederle Biologicals, Wayne, NJ.
§ Aplitest, Parke-Davis, Morris Plains, NJ.
¶ Mono-Vacc, Connaught Laboratories, Swiftwater, PA.

introduced into the skin cannot be standardized. As a result, MPTs are not intended to be used as diagnostic tests. The need for a subsequent Mantoux test in a person with a positive MPT leads to the second problem, the booster phenomenon. Boosting represents an increase in reaction to a skin test caused by repetitive tests in a person previously infected with mycobacteria. The incidence of the booster phenomenon increases with age and is greater in geographic areas where exposure to nontuberculous mycobacteria is common or in children previously vaccinated with bacillus Calmette-Guérin (BCG).[8,9] Third, the MPTs have variable and, in some populations, high rates of false-positive and false-negative results compared with the Mantoux test. Although some studies have demonstrated sensitivities of 95% to 99% for various MPTs, other studies have yielded false-positive rates of 10% to 15% and false-negative rates of 10% to 30% in various populations (Tables 2 and 3).[10–15] Fourth, the widespread use of MPTs has led to the practice of allowing parents to interpret the skin tests and report the reactions to the physician's office by telephone or mail, causing inaccurate reading of the results. No other screening test used in pediatrics is interpreted routinely by nonprofessionals.

One of the reasons that periodic skin testing with MPTs is no longer a useful strategy for the general population is emphasized by the variable incidence of infection and disease, which is still low in most areas of the United States. The MPTs have a sensitivity of approximately 68% to 97%, but a specificity of 40% to 90% for correlation with a Mantoux reaction ≥10 mm.[11,12,15] As an example, if the prevalence of infection is 1% and 100 000 children are screened using MPTs, which have a sensitivity and specificity of 90%, the number of true positives would be 900, whereas the false positives would be 9900, giving a positive predictive value of 8%. Therefore, 10 800 children would require two additional visits for the placement of a confirming Mantoux skin test and for the subsequent reading of the test. The MPTs thus are not appropriate tests to use for diagnosis, and their use should be severely restricted, if not eliminated, as advised by the CDC and ATS. Furthermore, the efficiency and cost-to-benefit ratio of a strategy using MPTs followed by Mantoux testing compared with one of using the Mantoux alone in low-risk patients must be evaluated individually for a given clinical setting.

Prior BCG vaccination is never a contraindication to tuberculin testing. Recommendations for considering a Mantoux tuberculin skin test reaction as positive are the same, irrespective of prior BCG vaccination. No reliable method exists for distinguishing tuberculin reactions caused by BCG vaccination from those caused by natural infection.[5] Many persons who receive BCG vaccine never have a reactive tuberculin skin test. In those with a reaction, the size of induration is often <10 mm and wanes after 3 to 5 years.[16,17] For example, a reactive diameter ≥10 mm in a BCG-vaccinated child from a country with a high prevalence of tuberculosis indicates likely infection with *M tuberculosis* and necessitates further diagnostic evaluation and, usually, preventive chemotherapy.

A negative Mantoux tuberculin skin test never excludes tuberculous infection or disease. Approximately 10% of immunocompetent children with culture-documented tuberculosis do not react initially to 5 TU of PPD.[18,19] In addition, host-related fac-

TABLE 2. Sensitivity and Specificity of Multiple-Puncture Tests (MPT) Compared With Mantoux Tuberculin Skin Tests in Different Studies

	Multiple-Puncture Test Used	Sensitivity, %	Specificity, %	Reference
MPT (≥2 mm) and Mantoux (≥5 mm)	Tine	99	97	Maha[10]
	Tine	99	93	Furcolow et al[13]
	Mono-Vacc	98	86	Furcolow et al[13]
	Tine	89	99	French and Fulmer[14]
	Tine	98	76	Krasnitz et al[22]
	Rhodotest	68	72	Tala-Heikkila and Raitio[23]
MPT (≥2 mm) and Mantoux (≥10 mm)	Tine	96	66	Badger et al[12]
	Tine	97	77	Affronti et al[11]

TABLE 4. Probability Estimates of Tuberculous Infection According to the Mantoux Test Reaction Size*

Size of Mantoux Test Reaction, mm	Noncontacts of Adult Case, %	Contacts of Adult Case, %
0–4	1	10
5–9	5	45
10–13	25	85
14–21	50–80	96–100
21+	100	100

* Data from Reichman.[21] Values are estimated and vary with geographic locale, with individuals in high-risk grups included as noncontacts.

TABLE 5. Definition of Positive Mantoux Skin Test (5 TU-PPD) in Children*

Reaction ≥5 mm
- Children in close contact with known or suspected infectious cases of tuberculosis
  - Households with active or previously active cases if treatment cannot be verified as adequate before exposure, was initiated after period of child's contact, or reactivation is suspected
- Children suspected to have tuberculous disease
  - Chest roentgenogram consistent with active or previously active tuberculosis
  - Clinical evidence of tuberculosis
- Children with immunosuppressive conditions† or HIV infection

Reaction ≥10 mm
- Children at increased risk of dissemination from
  - Young age: <4 years of age
  - Other medical risk factors, including Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
- Children with increased environmental exposure
  - Born or whose parents were born in high-prevalence regions of the world
  - Frequently exposed to adults who are HIV-infected, homeless, users of intravenous and other street drugs, poor and medically indigent city dwellers, residents of nursing homes, incarcerated or institutionalized persons, and migrant farm workers

Reaction ≥15 mm
- Children ≥4 years of age without any risk factors

* The recommendations should be considered regardless of previous bacillus Calmette-Guérin (BCG) administration. TU-PPD, tuberculin units of purified protein derivative.
† Including immunosuppressive doses of corticosteroids.

tors such as young age, poor nutrition, immunosuppression, viral infection (especially measles, varicella, and influenza), and overwhelming tuberculosis can lower tuberculin reactivity.[8] Many adults coinfected with HIV and *M tuberculosis* have anergy for tuberculin.[20] Coinfected children also are frequently anergic. Other strengths of PPD skin test antigens (1 or 250 TU) should not be used.

Control skin tests to assess anergy are only indicated in patients with suspected or proven immunosuppression and those with possible severe, disseminated disease. Their use in otherwise healthy children with pulmonary disease and in annual tuberculin skin testing of high-risk children is unwarranted. In addition, standardized and reliable skin tests for assessing anergy in infants and children generally are not available.

INTERPRETATION OF THE MANTOUX TEST

Classification of tuberculin skin test responses must take into account epidemiologic and clinical factors. The interpretation of the reaction depends on the purpose for which the test was given and on the consequences of false classification.[5] The appropriate cutoff size of induration indicating a positive reaction varies with the person being tested and with related epidemiologic factors. In areas of the United States where nontuberculous mycobacteria (atypical mycobacteria) are common,[2,3] only 5% of children in the general population who have a 5- to 9-mm diameter of induration to a Mantoux tuberculin skin test are infected with *M tuberculosis* (Table 4). However, a child with the same reaction who is in contact with an adult with infectious tuberculosis has an almost 50% chance of being infected.[21] The critical information is whether or not the child is likely to have been exposed to an adult with tuberculosis.

All current guidelines (CDC, ATS, and AAP) accept a reaction ≥15 mm of induration as positive in any person (Table 5). A reaction of greater than or equal to 5 mm is interpreted as positive by the CDC and ATS in the following groups: (1) persons who have had close recent contact with individuals with infectious tuberculosis; (2) persons who have chest roentgenograms consistent with old healed tuberculosis; and (3) persons with HIV infection or persons with risk factors for HIV infection who have an unknown HIV status. To these groups, the AAP has added children with clinical (as well as roentgenographic) evidence of tuberculosis and children with immunosuppression from causes other than HIV infection. The group of high-risk patients is expanded by including as positive those in whom the tuberculin reaction is ≥ 10 mm diameter of induration (Table 5).

These guidelines for interpreting the Mantoux skin test present some problems for pediatricians. First, classifying children by risk group requires the willingness and ability of medical personnel to obtain a thorough history of the child and adults caring for the child. Second, children with identical reactions may be evaluated differently depending on the risk factors for tuberculosis. Third, the physician must have a clear understanding of the tuberculosis case rates and characteristics of tuberculosis within the community.

RECOMMENDATIONS

1. Routine annual skin testing for tuberculosis (Mantoux) in children with no risk factors residing in low-prevalence communities is not indicated. In such settings positive skin test reactions are most likely to be false-positive reactions.
2. Children at high risk (Table 1) should be tested annually using Mantoux tuberculin tests. All results (positive or negative) should be read routinely by qualified medical personnel.
3. Children who have no risk factors but who reside in high-prevalence regions and children whose history for risk factors is incomplete or unreliable

may receive periodic Mantoux skin tests, such as at the ages of 1, 4 to 6, and 11 to 16 years. Such a decision should be based on local epidemiology of tuberculosis.

4. A Mantoux skin test is considered positive at a reaction of ≥5 mm for the highest risk groups (Table 5):
   a. children in close contact with known or suspected infectious cases of tuberculosis;
   b. children suspected to have disease based on clinical and/or roentgenographic evidence; and
   c. children with underlying host factors that put them at extremely high risk for severe tuberculosis, including immunosuppressive conditions and HIV infection.
5. A Mantoux skin test is considered positive at a reaction ≥ 10 mm for children less than 4 years of age and those with medical diseases (other than immunosuppression) who are at increased risk for dissemination or for those at increased risk for disease because of environmental exposure (Table 5).
6. A Mantoux skin test is considered positive at ≥ 15 mm for all children including those with no risk factors.

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