

REVIEW ARTICLE

CURRENT CONCEPTS

Tuberculosis in Children

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WIDESPREAD IMPLEMENTATION OF THE STRATEGY OF DIRECTLY OBSERVED treatment short course (DOTS) during the 1990s resulted in improved global control of tuberculosis.¹ However, its effectiveness has been limited in areas where poverty and infection with the human immunodeficiency virus (HIV) or drug-resistant tuberculosis are prevalent, and the emphasis on a positive sputum smear as the diagnostic criterion actually excludes most children from care.² Tuberculosis remains a major but often unrecognized cause of disease and death among children in areas where the disease is endemic³; service delivery in such areas is hampered by the absence of pragmatic strategies to guide diagnosis and management. This article provides a brief overview of basic principles, current controversies, and recent advances related to the care of children with tuberculosis, with an emphasis on intrathoracic disease.

DISEASE BURDEN AND RECENT EPIDEMIOLOGIC SHIFTS

Poor ascertainment and reporting of cases of tuberculosis prevent accurate estimation of the global burden of disease from tuberculosis in children.⁴ Among the 4,452,860 new cases reported in 2010 by the 22 countries with the highest burden of disease from tuberculosis, only 157,135, or 3.5% (range, 0.1 to 15.0), were in children. Best estimates suggest that children (defined as persons younger than 15 years of age) account for approximately 11% of the burden of disease from tuberculosis,⁵ suggesting that just over 332,000 cases of tuberculosis in children went undiagnosed or unreported in these countries. Although overdiagnosis does occur, underdiagnosis is the rule in most areas where there is a high burden of disease and children with tuberculosis can access services only through referral hospitals. The problem of underdiagnosis in children is illustrated by the low pediatric caseload reported in four countries with a high disease burden, where rates exceeding 10% of all reported cases would be expected: Russia, 0.8%; India, 1.1%; Nigeria, 1.4%; and Brazil, 3.5%.¹ In areas such as North America and Western Europe, where there is minimal internal transmission and routine provision of postexposure prophylaxis, a smaller proportion of children is affected, and most cases of childhood tuberculosis occur in immigrant populations.^{6,7}

Coinfection with HIV has had a major epidemiologic effect, especially in sub-Saharan Africa. Apart from leading to an increase in the absolute number of patients with tuberculosis, it has induced a pronounced shift in the age and sex of patients toward young women of childbearing age.⁸ The effect of this demographic shift can be seen in the high rates of exposure to tuberculosis among infants born to mothers infected with HIV⁹ and in the high rates of tuberculosis among infants infected with HIV.¹⁰ Early initiation of antiretroviral therapy is the single most important intervention for reducing overall mortality and the risk of tuberculosis among HIV-infected infants,¹¹ with isoniazid preventive therapy providing additional benefit.¹²

The emergence of drug-resistant tuberculosis poses a major threat to global tuberculosis control.¹³ The initial complacency in addressing the problem was influenced by studies indicating that the acquisition of isoniazid resistance reduced the pathogenicity of the strain.¹⁴ However, the development of multidrug-resistant tuberculosis (characterized by resistance to isoniazid and rifampin) in children exposed to persons with infectious drug-resistant tuberculosis,¹⁵ as well as its clonal spread in New York City¹⁶ and the Russian prison system,¹⁷ has provided clinical evidence of the transmissibility of multidrug-resistant strains. Additional proof was provided by an explosive outbreak of extensively drug-resistant tuberculosis (multidrug-resistant bacteria with additional resistance to a fluoroquinolone and a second-line injectable agent) among patients with HIV infection in South Africa.¹⁸ Although the incidence of drug-resistant tuberculosis among children is unknown, pediatric cases provide a valuable epidemiologic perspective, since they reflect ongoing transmission within communities. In places where the rates of drug-resistant tuberculosis in children have been monitored, the rates among children were similar to those among adults from the same community.¹⁵ The World Health Organization (WHO) estimated that in 2008, 3.6% of incident tuberculosis cases globally were of the multidrug-resistant or extensively drug-resistant type, which suggests that there was a similar burden of this type of disease among children.¹³

NATURAL HISTORY OF DISEASE

An understanding of the natural history of tuberculosis is required to appreciate both the variations in susceptibility to disease and the diverse spectrum of clinical manifestations observed in children. Meticulous descriptions of tuberculosis in the literature published before the introduction of chemotherapy provide valuable insight into the sequence of events that follows primary infection with *Mycobacterium tuberculosis* (Table 1 and Fig. 1).^{19,20} An important observation documented in these earlier studies was the presence of transient hilar adenopathy, and even excretion of *M. tuberculosis*, in children who had never had progression to disease.²¹ This finding poses a major problem in case definition for studies, such as vaccine efficacy trials, that use active case-finding strategies in populations of asymptom-

atic children who have been exposed to persons with infectious disease.²² The recent formulation of an international consensus on reference standards and uniform research methodology should facilitate progress.²³⁻²⁵

The sequence of events that follows reinfection (which is common in areas where tuberculosis is endemic) remains poorly defined. In cases of recurrent tuberculosis, strain typing makes it possible to differentiate relapse from reinfection but cannot be used to quantify the risk of reinfection. Composite data analysis suggests that there is a 79% reduction in the risk of disease progression among previously infected immunocompetent adults as compared with previously uninfected adults after documented exposure²⁶; however, the epidemic contribution made by reinfection depends on the frequency of its occurrence in a particular environment.

It is important to differentiate infection from disease, since infection is a common event and the approaches to managing the two conditions are very different. Disease progression is usually indicated by persistent, nonremitting symptoms, although the rate of progression is variable.²¹ In the vast majority of cases (>90%), disease occurs within 1 year after the primary infection, with the youngest children at greatest risk for progression. The risk profile is bimodal, with adolescents being at increased risk.²¹ Exploring the mechanisms underlying the increased risk and the sudden switch in phenotype toward adult-type cavitary disease that occurs with the onset of puberty should provide new insights into the immunopathogenesis of tuberculosis.²⁷

APPROACHES TO DIAGNOSIS

Children are usually evaluated for tuberculosis after presenting with symptoms or signs suggestive of disease (passive case finding) or as a result of contact investigation or routine immigration screening (active case finding). The clinical presentation of children whose infection is detected through active case finding differs from that of children whose infection is detected through passive case finding, with the former group often having infection but not disease or having disease in a very early phase. Among children in whom *M. tuberculosis* infection is detected, young children and those with recent exposure are at increased risk for progression to disease. Knowl-

Table 1. Clinical Syndromes Associated with Tuberculosis in Children.*

Disease Phase and Timing	Clinical Syndrome	Group at Greatest Risk	Immunopathogenesis	Results on Tuberculin Skin Test and IGRA	Manifestations on Imaging
Primary infection					
Incubation, 0–6 wk	Asymptomatic	All ages	No adaptive immunity	Negative	None
Immune conversion, 1–3 mo	Self-limiting symptoms (mild, viral-like); hypersensitivity reactions (fever, erythema nodosum, phlyctenular conjunctivitis)	All ages	Acquisition of adaptive immunity	Generally positive; infection may be lifelong; no test for reinfection	Transient hilar or mediastinal lymphadenopathy detected in 50–70% of cases; transient Ghon focus usually not detected
Early disease progression†					
2–6 mo	Uncomplicated lymph-node disease	<10 yr of age	Inadequate innate immunity, adaptive immunity, or both	Generally positive‡	Hilar or mediastinal lymphadenopathy without airway involvement; Ghon focus without cavitation
	Progressive Ghon focus	<1 yr of age or severely compromised immune system	Inadequate innate immunity, adaptive immunity, or both	Generally positive‡	Ghon focus with visible cavitation
	Disseminated (miliary) disease, tubercular meningitis, or both	<3 yr of age or severely compromised immune system	Inadequate innate immunity, adaptive immunity, or both	Generally positive‡	Discrete lung nodules (1–2 mm in diameter) on chest film, hepatosplenomegaly, retinal lesions with hydrocephalus, basal meningeal enhancement, brain infarcts or tuberculomas on CT of the head
4–12 mo	Complicated lymph node disease (airway compression, expansile caseating pneumonia, infiltration of adjacent anatomical structures [bronchus, esophagus, pericardium, phrenic nerve])	>1 yr of age	Exuberant lymph node responses, with inadequate innate immunity, or both	Generally positive‡	Hyperinflation, atelectasis, or collapse of lung; expansile consolidation of segment or entire lobe; tracheoesophageal or bronchoesophageal fistula; pericardial effusion; hemidiaphragmatic palsy
	Pleural disease (exudative effusion, empyema in rare instances, or chylothorax with ductus thoracicus infiltration)	>3 yr of age	Hypersensitivity response to tuberculo-protein	Generally positive‡	Effusion, sometimes large, usually in one lung; pleural thickening and loculations detected on ultrasonography
Late disease progression‡					
	Peripheral lymphadenitis (most frequent extrathoracic disease manifestation, usually in the neck)	1–10 yr of age	Inadequate local control	Generally positive‡	Ultrasonography usually not needed, but may reveal matting and adjacent soft-tissue edema
8–24 mo	Adult-type pulmonary disease (difficult to differentiate among primary infection, reactivation, and reinfection; reactivation may occur >20 yr after initial infection)	>10 yr of age, but can occur in children as young as 8 yr of age	Overly aggressive innate immunity, or both adaptive immunity, or both	Generally positive‡	Apical cavities in one or both lungs, minimal or no lymph-node enlargement (previously referred to as postprimary tuberculosis)

1-3 yr	Osteoarticular disease (e.g., spondylitis, arthritis, osteomyelitis)	>1 yr of age	Inadequate local control¶	Generally positive‡	Periarticular osteopenia, subchondral cystic erosions, narrowing of joint space
>3 yr	Urinary tract (kidney, ureter, bladder) disease	>5 yr of age	Inadequate local control¶	Generally positive‡	Renal calcifications, cavitation, hydronephrosis, calyceal dilatation, ureter stricture

* Adapted from Wallgren¹⁹ and Lincoln and Sewell.²⁰ Age ranges, risk groups, and timelines are intended to provide general guidance only; children infected with the human immunodeficiency virus are particularly susceptible to tuberculosis and may present with atypical features. For the phases of disease, the times shown are the interval between initial exposure and the onset of the disease phase. IGRA denotes interferon- γ -release assay.

† At least 90% of disease manifestations occur within 12 months after infection.

‡ Because test results may be negative in immunocompromised patients, a negative result cannot be used to rule out infection.

§ Late disease progression is generally rare, but adult-type pulmonary disease is common in adolescents.

¶ In cases of inadequate local control, manifestations are usually restricted to the local focus of disease, although disease can disseminate from any active focus.

edge of the child's status regarding the likelihood of exposure changes the pretest probability of disease and the positive predictive value of subsequent investigations.

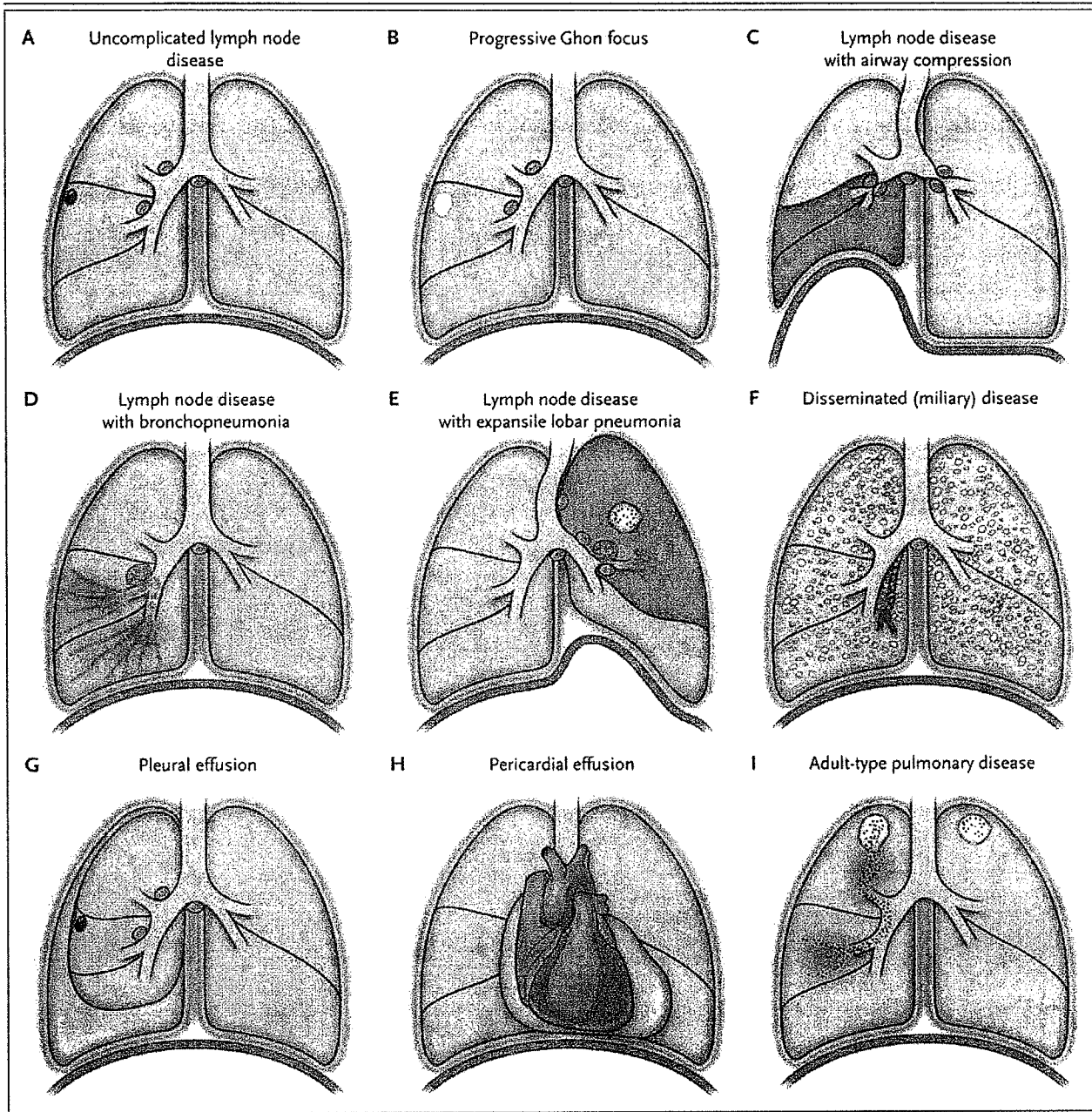
CLINICAL EVALUATION

Taking a careful patient history is essential for exploring the nature of the exposure and accurately characterizing the symptoms.²⁸ The diversity of the clinical presentation and the nonspecific nature of most symptoms complicate diagnosis. Constitutional symptoms often include failure to thrive (deviation from the expected growth-curve trajectory) and reduced playfulness; low-grade or intermittent fever is seen less frequently.²⁸ With airway involvement, the usual presenting symptom is a persistent, nonremitting cough or wheeze that is unresponsive to the treatment for likely alternative causes. Clinical signs are often subtle, and no diagnostic scoring system has been adequately validated²⁹; the sensitivity and specificity of the clinical diagnostic approaches for tuberculosis are particularly poor in children with HIV infection.³⁰

IMAGING STUDIES

In clinical practice, chest radiography is one of the most useful diagnostic studies. Both frontal and lateral views should be obtained, since a lateral view assists in the assessment of the mediastinal and hilar areas. The radiographic findings vary, but pronounced hilar adenopathy, with or without airway compression, is highly suggestive of tuberculosis. The International Union against Tuberculosis and Lung Disease compiled an atlas of illustrative cases.³¹ Unfortunately, the technical quality of the radiographs obtained in areas where tuberculosis is endemic is often poor or radiographic facilities are not available.

Ultrasonography is useful in confirming the presence of pericardial or pleural effusions and abdominal lymphadenopathy. High-resolution computed tomography (CT) offers excellent anatomical visualization,³² but because of the high cost of CT and the high level of radiation to which the patient is exposed, as compared with other forms of imaging, it should be reserved for complicated cases. Both CT and magnetic resonance imaging (MRI) are particularly helpful in visualizing the intracranial effects of disease, although MRI is more sensitive to the detection of brainstem lesions and early perfusion defects in pa-



tients with tuberculous meningitis, and it also allows superior evaluation of the spine and soft tissues.³³

LABORATORY STUDIES

Table 2 provides an overview of the laboratory examinations used in the diagnosis of tuberculosis. (See the Supplementary Appendix, available with the full text of this article at NEJM.org, for a list of references that includes recent compre-

hensive studies that focus on children.) Microscopical examination of sputum smears is the cornerstone of diagnosis in most countries, but its usefulness is limited in young children with paucibacillary disease who are unable to expectorate. Both the tuberculin skin test and the interferon- γ release assay fail to differentiate *M. tuberculosis* infection from active disease. The WHO recommends that the assay not be used in place of the tuberculin skin test,³⁴ although the

Figure 1 (facing page). Clinical Syndromes of Intrathoracic Tuberculosis in Children.

Panel A shows hilar and mediastinal lymphadenopathy associated with an ipsilateral peripheral nodule, or "Ghon focus"; these nodules are often subpleural, with an overlying pleural reaction. Panel B shows a Ghon focus with cavitation, which is seen almost exclusively in infants and immunocompromised children; other elements of the Ghon complex are also visible. In Panel C, enlarged lymph nodes compress the airway, causing either complete obstruction with lobar collapse, as shown in the right middle and lower lobes, or partial obstruction with a ball-valve effect leading to hyperinflation, as shown in the left lung. Panel D shows necrotic lymph nodes erupting into bronchus intermedius, with endobronchial spread and patchy consolidation of the middle and lower lobes. In Panel E, necrotic lymph nodes compress and obstruct the left bronchus in the upper lobe and may infiltrate a phrenic nerve, causing hemidiaphragmatic palsy; endobronchial spread causes dense consolidation of the entire lobe, with displacement of the trachea and fissures and the formation of focal cavities. Panel F shows diffuse micronodules in both lungs, which may result from lymphohematogenous spread after recent primary infection or from the infiltration of a necrotic lymph node or lung lesion into a blood vessel, leading to hematogenous spread. Panel G shows a pleural effusion that is usually indicative of recent primary infection, with a hypersensitivity response to tuberculo-protein that leaked from a subpleural Ghon focus (often not visible) into the pleural cavity; in rare cases this effusion may also result from chylothorax or tuberculous empyema. Panel H shows a pericardial effusion that occurs when tuberculo-protein leaks from a necrotic subcarinal lymph node into the pericardial space; it may also occur after hematogenous spread. Panel I shows cavity formation in both upper lobes, with endobronchial spread to the middle lobe. Nodules or cavities in apical lung segments are typical of adult-type disease and are pathologically distinct from the other cavities shown.

two tests may be complementary, improving the sensitivity or specificity of the assessment in specific clinical circumstances.³⁵

Collecting specimens of spontaneously produced sputum in young children is problematic; gastric aspiration and sputum induction (with or without laryngopharyngeal suction) are feasible alternative methods of collection.³⁶ The "string test" (which involves the use of an esophagogastrroduodenal nylon yarn that can absorb swallowed sputum) works well in adults with HIV infection who have little sputum,³⁷ and preliminary test results in children seem promising.³⁸ Fine-needle aspiration biopsy is very useful in children with a peripheral lymph-node mass.³⁹ Although the Xpert-MTB/RIF assay (Cepheid) is

less sensitive than liquid cultures for the detection of *M. tuberculosis* in both children and adults, it provides results quickly, is highly specific, and detects resistance to rifampin. When two sputum samples are used, the assay detects three times as many cases as when microscopy is used⁴⁰ but only about 70% of the cases when liquid culture is used.^{41,42} Currently, access to the Xpert-MTB/RIF assay is limited, but the efforts of the Global Laboratory Initiative, a working group of the Stop TB Partnership, should increase its availability.

Each of the diagnostic approaches described has limitations. However, when a combination of clinical, radiologic, laboratory, and histopathologic findings are consistent with a diagnosis of tuberculosis and there is epidemiologic evidence of exposure to tuberculosis or immunologic evidence of *M. tuberculosis* infection, an accurate diagnosis is possible in most cases.⁴²

PRINCIPLES OF DISEASE
MANAGEMENT

Although every effort should be made to attain bacteriologic confirmation of disease, confirmation rates remain low, and treatment initiation should not be delayed in immunologically vulnerable children. Unfortunately, some tuberculosis-control programs will not initiate treatment without bacteriologic confirmation, citing the risk of adverse events from treatment and concerns about amplifying drug resistance. However, adverse events are rare in young children who are treated with first-line tuberculosis drugs, and they are at low risk for acquiring or transmitting drug-resistant tuberculosis. Despite differences between adult and pediatric tuberculosis (see Table S1 in the Supplementary Appendix), the principles of disease management are similar. The purpose of tuberculosis treatment is to cure the individual patient, whereas the intent of public health efforts is to terminate transmission and prevent the emergence of drug resistance. Rapidly metabolizing bacilli are quickly killed by bactericidal agents with high activity, thereby terminating transmission, ameliorating symptoms, and decreasing the risk of drug resistance (by reducing the population from which drug-resistant mutants emerge). The use of drugs with sterilizing activity is required to eradicate persistent subpopulations of intermittently metabolizing bacilli, thereby preventing relapse and effecting a

Table 2. Diagnostic Studies for Tuberculosis in Children.*

Type of Investigation	Examples	Uses	Strengths	Limitations
Microbiologic studies				
Detection of <i>Mycobacterium tuberculosis</i> bacilli	Light microscopy with use of Ziehl-Neelsen, Kinyoun, or Giemsa stains; fluorescence microscopy with use of light-emitting diode (e.g., Primo Star iLED) and auramine stain	Diagnosis of tuberculosis, monitoring of treatment response	High specificity; useful in all specimen types; rapid detection (<1 hr); low cost (fluorescence microscopy is the most cost-effective method); Primo Star iLED microscope is endorsed by the WHO; in adults, fluorescence microscopy has a sensitivity that is about 10% greater than that of light microscopy and a sensitivity that is 26–37% greater in patients coinfecting with HIV; specificity is similar to that of light microscopy and examination time is shorter	Sensitivity very low as compared with liquid culture; in young children, approximately 1–15% with a clinical diagnosis of tuberculosis and about 2–25% with confirmation on culture; highly operator-dependent; labor-intensive; no specification of acid-fast bacilli (a particular problem when nontuberculous mycobacteria may be present, e.g., in biopsy specimens from fine-needle aspiration of lymph nodes or gastric aspiration); no differentiation of viable and dead bacilli
Detection of <i>M. tuberculosis</i> growth	Solid medium: egg-based (e.g., Löwenstein-Jensen; Ogawa), agar-based (e.g., Middlebrook 7H10 or 7H11), and thin- or thick-layer plated agar Liquid medium (e.g., Middlebrook 7H9), with use of various growth-indicator methods, including fluorescent (e.g., MGIT 960), colorimetric (e.g., Bact/ALERT), microscopical (e.g., tuberculosis microscopical observation drug susceptibility test kit), radiometric (e.g., BACTEC 460), and manometric (e.g., VersaTREK)	Diagnosis of tuberculosis, species identification, drug-susceptibility testing, monitoring of treatment response	Solid medium: high specificity; capable of phenotypic and genotypic speciation and drug-susceptibility testing; useful in all specimen types except formalin-fixed tissue; can include colorimetric indicators of growth, such as nitrate reductase assay and colorimetric redox indicator assay, which are endorsed by the WHO; relatively low cost; less expensive than liquid culture Liquid medium: high sensitivity and specificity; traditional reference standard; useful in all specimen types except formalin-fixed tissue; less dependent on operator expertise than other options; most automated liquid-culture systems and microscopical observation tests for drug susceptibility testing are endorsed by the WHO; in children, sensitivity varies depending on disease severity and quality of specimen collection and processing	Solid medium: in young children with clinical diagnosis of intrathoracic tuberculosis, sensitivity is low (about 10–40%), depending on disease severity and specimen-collection method; slow turnaround time (2–12 wk); fastest turnaround provided by thin-layer agar Liquid medium: strict control of cross-contamination and quality required; contamination rates higher than with solid medium; high per-test cost relative to other options; slow turnaround time (2–8 wk)

<p>Detection of DNA specific to <i>M. tuberculosis</i></p>	<p>Positive or negative smear samples (sputum, gastric aspirates, and others) used for diagnosis but not for drug-susceptibility testing (e.g., Amplified MTD, artus MTB, GenoQuick MTB, GenoType MD, LightCycler MTB, Loopamp MTB, RealArt MTB, and TaqMan MTB)</p> <p>Positive or negative smear samples (sputum, gastric aspirates, and others) used for diagnosis and limited drug-susceptibility testing (e.g., Xpert MTB/RIF)</p> <p>Positive smear samples only (sputum, gastric aspirates, and others) and culture isolates used for diagnosis and expanded drug-susceptibility testing (e.g., GenoType MTBDRplus, GenoType MTBDRsl, and INNO-LiPA Rif.TB)</p>	<p>Diagnosis of tuberculosis, species identification, drug-susceptibility testing, monitoring of treatment response</p>	<p>Moderate sensitivity (50–85% for negative results on smears and positive results on culture of respiratory specimens [at higher end of range when at least two samples are collected] and >95% for positive results on smears); in children, sensitivity of Xpert MTB/RIF is 20%, fluorescence microscopy 9%, culture 25% in one to two IS samples from patients with clinical diagnosis of intrathoracic tuberculosis; substantial incremental yield for smear-negative disease (33–61%) as compared with culture; high specificity (>97%); fully automated and integrated platforms available (e.g., GeneXpert and COBAS); GenoType and Xpert MTB/RIF and are endorsed by the WHO; amplified-MTD and TaqMan MTB approved by FDA; can be used in all specimen types; rapid turnaround (2–12 hr)</p>	<p>Drug-susceptibility testing limited with most tests (except with line-probe assays, which require culture isolates); no differentiation of viable and dead bacilli; high risk of cross-contamination in open-tube-based systems; strict quality control essential; cost remains high, but ongoing innovation and economies of scale should continue to drive it down; polymerase-chain-reaction inhibitors may be problematic with use of certain specimens</p>
<p>Detection of mycobacterial antigens</p>	<p>Lipoarabinomannan, with assay in urine (e.g., Clearview TB ELISA and Determine TB-LAM Ag)</p>	<p>Diagnosis of tuberculosis disease</p>	<p>Sensitivity best in immunocompromised patients with HIV infection (CD4 count <50, 85%; CD4 count 50–100, 71%; CD4 count 101–150, 56%); high specificity (about 95%); rapid turnaround (3 hr); simple and user-friendly strip test; urine collection is noninvasive and safer to handle than sputum</p>	<p>Sensitivity generally very low (about 50%); no differentiation between <i>M. tuberculosis</i> and nontuberculous mycobacteria; availability of pediatric studies limited, some currently underway; current version requires an ELISA platform</p>
<p>Studies of histopathological features consistent with tuberculosis</p>	<p>Antigen MPB64, with immunochromatographic assay (e.g., Capilia TB, MGIT TBciD, and BIOLINE TB Ag MPT64)</p> <p>Tissue samples stained with hematoxylin and eosin or Papanicolaou stain</p>	<p>Species identification</p> <p>Diagnosis of tuberculosis</p>	<p>Confirms <i>M. tuberculosis</i> infection in positive cultures, with sensitivity >97% and specificity >99%; rapid turnaround (15 min); low cost, easy to use</p>	<p>May not detect some <i>M. bovis</i> BCG strains</p> <p>No pathognomonic histologic features, but very high specificity when both caseating granulomas and mycobacterial bacilli are identified</p>

Table 2. (Continued.)

<p>Studies of immune response to mycobacteria</p>	<p>Tuberculin skin test (stimulation with intradermal injection of purified protein derivative, e.g., Mantoux method) IGRA (stimulation with <i>M. tuberculosis</i>-specific antigens [e.g., ESAT-6 plus CFP-10, with or without TB 7.7], with detection by ELISPOT assay [e.g., T-SPOT.TB] or ELISA [e.g., QuantiFERON-TB Gold])</p>	<p>Identification of <i>M. tuberculosis</i> infection</p>	<p>Tuberculin skin-test sensitivity about 70–80% (lower in immunocompromised patients); low cost; sensitivity of IGRAs 75–90% (lower in immunocompromised patients); specificity unaffected by BCG vaccination; IGRAs may have higher sensitivity for detection of recent rather than remote infection; testing includes a negative control and requires only a single visit</p>	<p>Tuberculin skin-test specificity reduced by BCG vaccination, especially in infants; skin-test sensitivity is low in immunocompromised patients and second visit required after 48–72 hr; IGRA sensitivity low in immunocompromised patients; assay not well validated in children; indeterminate assay results are problematic; IGRA currently too complex and costly for routine use in settings with limited resources; neither tuberculin skin test nor IGRA can differentiate <i>M. tuberculosis</i> infection from active disease</p>
<p>Antibody tests</p>	<p>None</p>	<p>None</p>	<p>None with current tests; advances awaited</p>	<p>Values for sensitivity and specificity of current commercial serologic tests are highly variable; not recommended for the diagnosis of pulmonary or extrapulmonary tuberculosis</p>
<p>Studies involving body fluids: detection of biochemical markers consistent with tuberculosis</p>	<p>Adenosine deaminase, identified with colorimetric method</p>	<p>Diagnosis of tuberculosis disease, monitoring of treatment response</p>	<p>Sensitivity and specificity moderate to high in specimens from pleural and pericardial effusions, ascitic fluid, and CSF, especially for isoenzyme ADA2 of adenosine deaminase; has been used to monitor treatment response in CSF</p>	<p>May be negative in early stages of central nervous system tuberculosis; validated for certain body fluids only</p>
<p>Interferon-γ, identified on ELISA or ELISPOT assay</p>	<p>High sensitivity and specificity in specimens from pleural and pericardial effusions and ascitic fluid</p>	<p>High sensitivity and specificity in specimens from pleural and pericardial effusions, depending on threshold values</p>	<p>Further evaluation in children is needed; validated for certain body fluids only</p>	<p>Further evaluation in children is needed; validated for certain body fluids only</p>

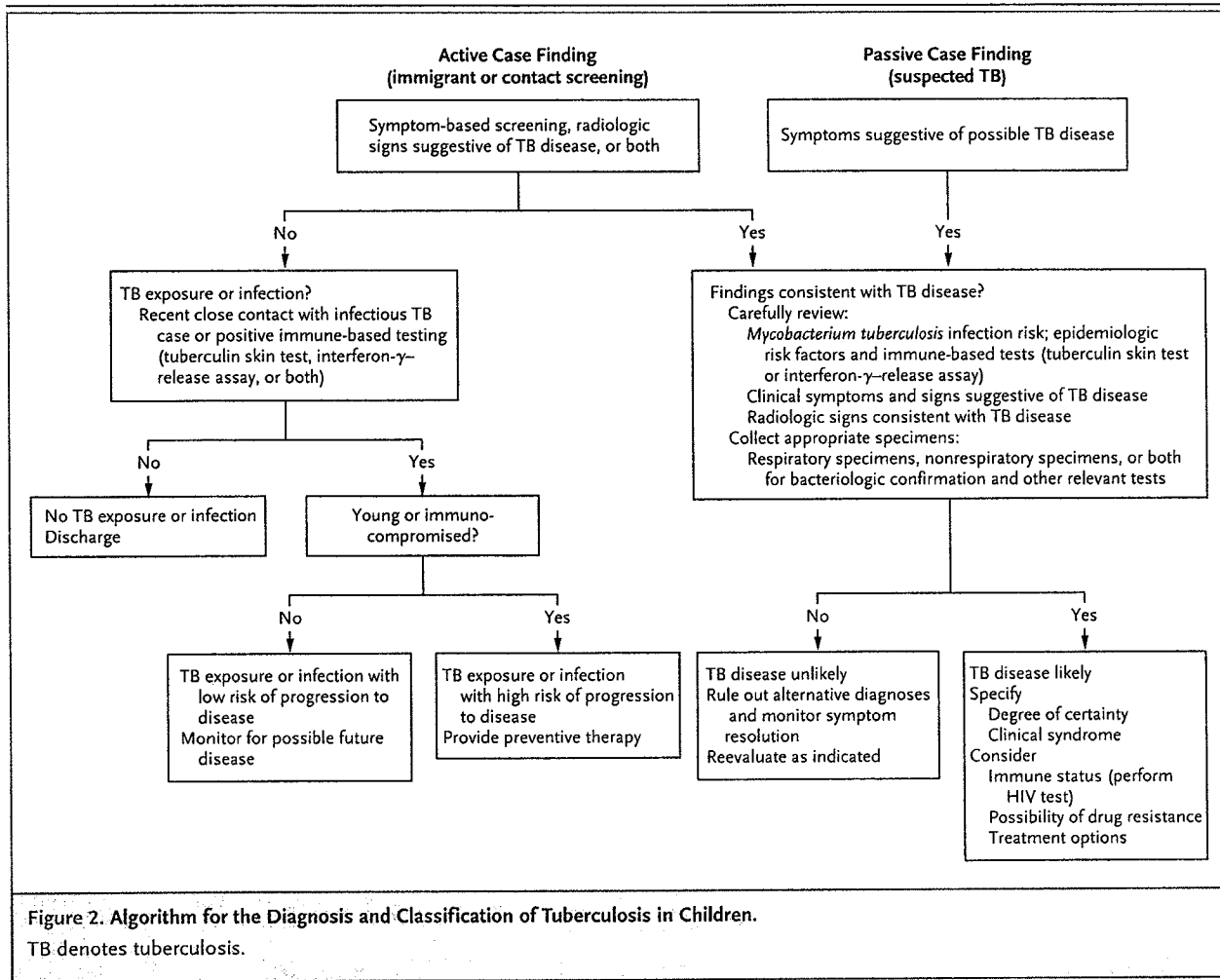
Composite measures	Protein, glucose, lactate, or lactate dehydrogenase	Rapid; easy to use; low cost	Results of individual tests lack accuracy, but a combined set of results consistent with disease is highly suggestive
Imaging studies: anatomical lesions consistent with tuberculosis disease	Radiography, CT, ultrasonography, MRI	Diagnosis of tuberculosis disease, monitoring of treatment response	Value of results depends on skills of operator and interpreter; findings in immunocompromised children are often atypical; CT is associated with high radiation exposure; CT and MRI are expensive and often inaccessible in settings with limited resources
		Often provide the initial suggestion of diagnosis, especially when other studies are unrevealing or unavailable; can reveal complications; chest radiography (anteroposterior and lateral views) is most helpful; CT may be useful in uncertain or complicated cases; ultrasonography useful in identifying intra-abdominal and retroperitoneal lymphadenopathy and for confirmation of pleural or pericardial effusions	

* Many new tests are in different phases of development and validation; see the Supplementary Appendix for further resources. BCG denotes bacille Calmette-Guérin, CSF cerebrospinal fluid, ELISA enzyme-linked immunosorbent assay, ELISPOT enzyme-linked immunosorbent spot, FDA Food and Drug Administration, HIV human immunodeficiency virus, IGRA interferon- γ -release assay, and WHO World Health Organization.

long-term cure. Pragmatic disease classification should guide case management (Fig. 2).

The most important variables to consider in disease management are bacillary load and anatomical location. Drug resistance should be considered in children from areas with a high prevalence of drug-resistant tuberculosis and in those who have had documented contact with a person with drug-resistant disease, with someone who died during treatment for tuberculosis or who is not adhering to therapy, or with someone who is undergoing retreatment for tuberculosis. Young children with uncomplicated disease who are from areas with a low prevalence of isoniazid resistance can be treated with three drugs (isoniazid, rifampin, and pyrazinamide) during the 2-month intensive phase of treatment, followed by isoniazid and rifampin only during the 4-month continuation phase.⁴³ However, children who have extensive or cavitary lung disease (either of which suggests a high bacillary load) or who are from areas with a high prevalence of isoniazid resistance should receive a fourth drug (ethambutol, which is safe in children of all ages) during the 2-month intensive phase of treatment.⁴³ Table S2 in the Supplementary Appendix summarizes the mechanism of action, main adverse effects, and recommended pediatric dosages of drugs prescribed for the first-line treatment of tuberculosis.

In the absence of drug resistance, the most frequent cause of a poor response to treatment is nonadherence to the regimen. Although empirical evidence of the value of DOT is limited, as a method of medication administration, it is preferable to unsupervised administration and to administration by a parent.⁴⁴ In most instances, a recurrence of tuberculosis more than 12 months after treatment represents reinfection. Standard first-line treatment is appropriate in the absence of exposure to a person who is believed to have drug-resistant tuberculosis. Use of an escalated retreatment regimen that includes streptomycin is discouraged.⁴³ When there is a poor clinical response in a patient with a history of adherence to treatment, a reevaluation of the diagnosis should be conducted, including consideration of the immune reconstitution inflammatory syndrome (IRIS) and drug resistance. Principles for the management of drug-resistant tuberculosis in children have been summarized elsewhere,⁴⁵ and excellent outcomes have been reported.⁴⁶



Immune recovery after the initiation of antiretroviral treatment for HIV-coinfected individuals or nutritional rehabilitation may unmask subclinical disease or induce paradoxical deterioration, despite adequate treatment for tuberculosis. A finding of IRIS does not indicate treatment failure, and treatment should not be interrupted; patients with severe IRIS may require a course of glucocorticoids. Despite the risk of IRIS, data on adults indicate that antiretroviral therapy is most effective when initiated within 8 weeks after the start of tuberculosis treatment, or for patients with severely compromised immune systems, within 2 to 4 weeks after the start of treatment.⁴⁷ The only exception would be patients with central nervous system tuberculosis, in whom IRIS can have devastating consequences.⁴⁸ With HIV-associated tuberculosis, treatment should be given daily, and

a prolonged course may be required, depending on the degree to which the patient's immune system has been compromised and the extent of disease.^{49,50}

PREVENTION AND CONTROL

Transmission of tuberculosis within health care facilities is a particular concern in settings where immunologically vulnerable children may be exposed. In hospitals and clinics, careful consideration should be given to areas where patients are treated and to air-exchange patterns. It is also important to recognize that symptomatic parents or caregivers may pose transmission risks.⁵¹ Vaccination with bacille Calmette–Guérin (BCG) reduces the risk of disseminated (miliary) disease and tuberculosis meningitis in young children but offers

no consistent protection against adult-type tuberculosis.⁵² No benefit of BCG vaccination has been established in HIV-infected children, and it is contraindicated in such children because of the risk of disseminated BCG disease.⁵³ The development of a safe and effective vaccine remains a top priority among global health researchers.

With good adherence, a 6-month course of isoniazid preventive therapy provides excellent protection against tuberculosis disease.⁵⁴ Despite universal recommendations regarding the provision of preventive therapy and strong evidence of the greatly increased risk of tuberculosis and the increased mortality among children in close contact with persons who have tuberculosis,⁵⁵ the implementation of preventive strategies remains poor. Pragmatic solutions are required to close the pronounced gap between policy and practice.⁵⁶ Parents are often reluctant to provide preventive treatment for an otherwise well child, and the long duration of preventive therapy is a source of further discouragement. One study showed that a 3-month course of preventive therapy with isoniazid and rifampin was similar in efficacy to a 9-month course of isoniazid alone.⁵⁷ A regimen of 12 doses of weekly rifampin and isoniazid has been shown to be efficacious in adults,⁵⁸ but this regimen is not yet recommended for children younger than 12 years of age because specific data on safety and efficacy in this age group are required. The efficacy of abbreviated regimens has not been well studied in children with HIV infection. A disadvantage of the regimens that include rifampin or rifampin is the interactivity of these drugs with the protease inhibitors included in the antiretroviral therapy provided for infection with HIV^{49,50}; rifabutin is less reactive, but its use in preventive therapy regimens has not been evaluated.

Although the value of postexposure prophylaxis is universally acknowledged, the value of preexposure prophylaxis remains in question. Successive randomized, controlled trials of preexposure prophylaxis in children with HIV infection have had contradictory findings. The first of these trials, involving children with minimal access to antiretroviral therapy, was discontinued because of increased mortality in the placebo group.⁵⁹ The reduction in mortality among those receiving isoniazid preventive therapy was confined to the first 2 to 3 months of treatment,

raising the possibility that subclinical tuberculosis was present at trial entry. The second trial enrolled young infants (3 to 4 months of age) who had been exposed to HIV but had no known exposure to tuberculosis.⁶⁰ The infants were randomly assigned to receive open-label isoniazid or placebo; those who were infected with HIV also received early antiretroviral therapy. All infants were closely monitored for subsequent exposure to tuberculosis. The investigators found no significant difference in the incidence of tuberculosis or mortality between the treatment and placebo groups, suggesting that preexposure prophylaxis against tuberculosis has little value if HIV-infected infants are enrolled in management programs early, with meticulous monitoring for tuberculosis exposure and provision of postexposure prophylaxis. However, the value of preexposure prophylaxis in areas where monitoring for tuberculosis exposure is likely to be poor remains unresolved.^{49,54}

With the use of isoniazid preventive therapy after the completion of tuberculosis treatment in HIV-infected adults, it has been estimated that 83 recurrences can be prevented for every 1000 cases treated.¹² The WHO recommends isoniazid preventive therapy for 6 to 36 months after the completion of tuberculosis treatment in all patients with HIV infection, including children who live in areas with a high prevalence of tuberculosis. However, the added value of preventive therapy as compared with ongoing screening for tuberculosis exposure and meticulous postexposure prophylaxis has not been evaluated.

It is possible to drastically reduce the morbidity and mortality associated with pediatric tuberculosis if case detection is improved and preventive therapy and curative treatment are made more accessible globally. Many challenges and research priorities remain (Table S3 in the Supplementary Appendix), but while we await the development of new vaccines, better diagnostics, and shorter treatment regimens, much can be achieved with pragmatic approaches and sensible application of existing tools.

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