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Childhood Tuberculosis
An Overview

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Keywords

• Childhood tuberculosis • *Mycobacterium tuberculosis* • Tuberculin skin test • Interferon-γ release assay

Key points

- Tuberculosis (TB) is one of the oldest diseases known to mankind and still ranks as the second leading cause of death from infection worldwide.
- Transmission of *Mycobacterium tuberculosis* occurs person to person via inhalation of mucous droplets that become airborne when an individual with pulmonary or laryngeal TB coughs, sneezes, speaks, laughs, or sings.
- Even though TB incidence in the United States is low, pediatricians in this country should always consider TB as cause of a child's symptoms, especially those who traveled to endemic areas.
- The Centers for Disease Control and Prevention guidelines indicate that a tuberculin skin test (TST) or an interferon-γ release assay (IGRA) may be used to test for latent TB infection. An IGRA is preferred over the TST when testing people who are Bacille-Calmette-Guérin (BCG) vaccinated or are unlikely to return for TST reading.
- Multidrug-resistant TB strains are resistant to isoniazid and rifampin, while extensively drug-resistant TB is also resistant to fluoroquinolones and at least one of the second-line injectable drugs (amikacin, kanamycin, and capreomycin).
- BCG vaccine protects young children against severe forms of the disease (eg, TB meningitis) and disseminated TB. It has variable efficacy against pulmonary TB.

INTRODUCTION

Is it tuberculosis (TB) or another pulmonary process? Is it latent or active TB? If it is active TB, is it due to a susceptible or resistant strain? Will my pediatric patient tolerate the drug regimen that was prescribed without having side effects? How did this bacillus manage to survive millions of years in nature and thousands of years in our bodies and make best use of our immune

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system? Will there ever be a vaccine as good as the polio vaccine to eradicate TB? All these and more questions are addressed in this article, starting with a brief historical overview, then moving to the most recent World Health Organization (WHO) report that was released in 2014. Next is the pathogenesis section, with reference to Tobin's work and the utilization of the zebrafish model in trying to elucidate how this organism takes over our immune system in the smartest of ways to survive. This article then addresses the challenges that clinicians face in trying to make the correct diagnosis and choosing the right drug regimen in light of the finding that techniques to diagnose and check drug susceptibilities have been lacking in sensitivity. The emerging concern of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB is discussed as well. Finally, this article addresses what the future holds in regards to new vaccines in clinical trials.

HISTORY

TB is one of the oldest diseases known to mankind [1]. It is possible that the genus Mycobacterium originated more than 150 million years ago and that a progenitor of *Mycobacterium tuberculosis* (Mtb) was present in East Africa as early as 3 million years ago. It is likely that all modern members of the *Mycobacterium tuberculosis* complex (MTBC), including not only Mtb but also its African variants *M africanum* and *M canettii* as well as *M bovis* had a common African ancestor about 35,000 to 15,000 years ago [2]. Recent work based on phylogenetic analysis of Mtb strains goes further to suggest that Mtb has been infecting humans for more than 70,000 years [3].

Given the long historical relationship between TB and humans, it may seem surprising that TB still ranks as the second leading cause of death from infection worldwide. However, the long coevolution of the human immune system with Mtb may also explain the remarkable ability of this bacterium to evade the immune response.

In Egypt, TB was documented more than 5000 years ago with evidence of Pott deformities in Egyptian mummies in early Egyptian art. There are written texts as well describing TB in India and China 3300 and 2300 years ago, respectively [2]. In Greece, it was called phthisis, and Hippocrates wrote in his *Book I, Of the Epidemics*: "Consumption was the most considerable of the diseases which then prevailed, and the only one which proved fatal to many persons" [2]. In the middle ages, scrofula was treated with the "royal touch" by monarchs in Europe [2,4]. TB has claimed its victims throughout much of known human history. It reached epidemic proportions in Europe and North America during the eighteenth and nineteenth centuries.

It was René Théophile Hyacinthe Laennec who clearly elucidated the pathogenesis of TB early in the nineteenth century. Jean-Antoine Villemin demonstrated the infectious nature of TB in 1865 after inoculating a rabbit with pus taken from a tuberculous cavity [2]. On March 24, 1882, Hermann Heinrich Robert Koch made his famous presentation, *Die Aetiologie der Tuberculose*, demonstrating that the tubercle bacillus was the causative agent of TB [5].

From 1907 onward, a series of experiments led to the discovery of the tuberculin skin test (TST) with the initiation of Clemens Freiherr Von Pirquet, with Charles Mantoux then improving the technique and Florence Seibers developing the purified protein derivative (PPD) [2].

Treatment of TB started with rest, fresh air, and home remedies. In the late nineteenth and early twentieth centuries, sanatoriums developed for the treatment of patients with TB. Then, the treatment was pulmonary collapse therapy and therapeutic pneumothorax, especially for treatment of cavitary disease. Streptomycin, the first antibiotic and first bactericidal agent effective against Mtb, was isolated in 1944. It was unlucky that the great writer George Orwell could not tolerate this drug and died of TB [4]. Isoniazid (INH), the first oral mycobactericidal drug, followed in 1952 and rifamycins in 1957. A new era of TB treatment had started with closure of the sanatoriums and implementation of effective public health measures [2].

EPIDEMIOLOGY

"Clearly we are still some distance from a world without tuberculosis" [6]. TB remains a major global health problem and ranks second as leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). There were 9.0 million new TB cases in 2013 and 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people). The estimates in children are 550,000 cases and 80,000 deaths [7]. In comparison with the most recent estimates, in 1989 there were 1.3 million new cases of childhood TB reported with 450,000 deaths. Although childhood TB usually represents less than 5% of disease in industrialized countries, the burden of disease borne by children in less developed, resource-poor countries may be as high as 39% [8,9]. Approximately one-third of the human population can be demonstrated to have immunologic evidence of current or past infection with Mtb [10].

In the United States, there were less than 10,000 cases reported in 2012 with an incidence rate of 3.2 new cases per 100,000 population in 2012 (as opposed to 122 globally). Sixty-three percent of TB cases and 88% of MDR-TB cases were foreign-born from countries where TB prevalence and drug-resistance rates are high [10].

With the emergence of drug-resistant TB, a new threat to the control of TB occurred. Globally, it is estimated that 3.5% of new cases and 20.5% of previously treated cases have MDR TB [11]. In 2013, there were an estimated 480,000 new cases of MDR-TB worldwide, and approximately 210,000 deaths from MDR-TB. XDR-TB has been reported by 100 countries. On average, an estimated 9.0% of people with MDR-TB have XDR-TB [7].

TB in children is common wherever TB is common in adults (ie, TB endemic settings). Studies done in child contacts in African communities have shown that one-third to two-thirds of child household contacts of TB cases have evidence of TB infection (ie, TST-positive) [12,13]. Of children with TB, 70% to 80% have the disease in their lungs (pulmonary TB, PTB).

The rest are affected by TB disease in other parts of the body (extrapulmonary TB). The HIV epidemic has increased the burden of childhood TB and made it more difficult to diagnose and treat [14].

In North America and Europe, childhood TB cases occurred mostly in high-risk populations, including immigrants and racial/ethnic minorities. Studies from low-income and middle-income countries have confirmed the long-recognized association of childhood TB with poverty, crowding, and malnutrition [8].

Risk factors for TB infection in children include closeness to a TB case and duration of the contact. Another risk factor is the smear positivity and presence of cavities on chest radiograph (CXR) of the source case. The first 2 years of life infer the greatest risk for developing TB disease in addition to HIV infection, immunosuppression, malnutrition, and other diseases. Most disease occurs within 2 years after exposure.

There has been much progress in the 15 years since 1995 with the Stop TB Strategy, whereby 36 million patients were cured. Case fatality rate halved from 7.6% to 4%. TB incidence, however, is declining much more slowly than predicted [14]. The rate of decline in TB approaches 2% per year, a number much lower than what is needed to eliminate TB by 2050. The HIV epidemic and the spread of MDR-TB and XDR-TB have slowed this decline. An estimated one-third of new TB cases are still being missed each year, and the unavailability of a rapid, low-cost, accurate diagnostic assay that can be used at the point of care is a major hindrance [15].

Children rarely develop sputum smear-positive TB and therefore they are often excluded from being reported; hence, the burden of disease in this population is underestimated [16,17]. In most settings, children with TB continue to be given low priority by National TB Control Programmes because they are less likely to transmit disease. Despite being a major contributor to childhood morbidity and mortality, childhood TB has been largely absent from the global public health agenda. In addition, scientific progress has been lagging [16].

National programs in low-income and middle-income countries are underfunded by about US $2 billion for both 2014 and 2015. "Tuberculosis suffers because it is a disease of poverty–there is very little interest in big pharma in diseases of this type because they know that since the big sales are going to be in developing countries, there is no income generation," explained Mario Raviglione of the WHO [18].

TRANSMISSION

Transmission of Mtb occurs person to person via inhalation of mucous droplets that become airborne when an individual with pulmonary or laryngeal TB coughs, sneezes, speaks, laughs, or sings. After drying, the droplet nuclei can remain suspended in the air for hours. Only small droplets (<10 μm in diameter) can reach alveoli. Droplet nuclei can also be produced by aerosol treatments, by sputum induction, and through manipulation of lesions [8].

Numerous factors are associated with the risk of acquiring Mtb infection, including the extent of contact with the index case, the burden of organisms

in the sputum, and the frequency of cough in the index case. Urban living, overcrowding, and lower socioeconomic status all are correlated with the acquisition of infection. An increased risk of developing infection has been demonstrated in multiple institutional settings, including nursing homes, correctional institutions, homeless shelters, as well as in refugee and orphanage settings [8].

PATHOGENESIS

The MTBC includes Mtb, *Mycobacterium bovis*, *Mycobacterium africanum, Mycobacterium canettii, Mycobacterium caprae, Mycobacterium microti*, and *Mycobacterium pinnipedii*. Mtb causes around 98% and *M bovis* causes around 1% to 2% of human TB. MTBC's complex cell wall contains mycolic acid that retains the stain with carbol fuchsin or auramine when decolorized by acid alcohol, hence the term acid-fast bacilli. The MTB genome contains 4,411,529 base-pairs with high guanine cytosine content (>65%) [10].

TB's varied clinical manifestations are due to the spectrum of immune responses in different human subjects; this can be asymptomatic with a positive TST to severe and fatal disease. Some studies have looked into the factors that influence development of TB. The highest risk of acquiring disease is greatest shortly after initial infection and is associated inversely with age from birth to 8 years of age. A second peak in the risk of developing disease occurs during late adolescence and early adult life. Exposure to a large infecting dose and immunosuppression are other risk factors. Children 0 to 5 years of age with recent infection have significant annual risk of developing disease [8].

A fundamental question in TB is the extent to which pathogenesis is a function of the pathogen, and to what extent it is a consequence of the immune responses of the host [19]. By evolving inside the macrophage, Mtb learned to take advantage of its inflammatory response. The initial phase is a silent infection; then, it is the formation of a granuloma in which the Mtb survives, and finally, the rearrangement of immunity between latent TB infection (LTBI) and active infection. During dormancy, no damage is done to the host; however, when immune disbalance occurs, Mtb becomes metabolically active, replicates to billions of organisms, damages the host, and gets transmitted to other subjects [20]. In approximately 90% of patients, the disease is controlled as LTBI; TB bacilli may remain viable within dormant lesions over many years and can be reactivated when the host immune system weakens [10,21].

The first checkpoint that Mtb has to overcome is the oxidative and nitrosative burst of the host. Mtb actively avoids the detrimental effects of the transient superoxide burst using its superoxide dismutase and cell surface glycolipids that possibly scavenge oxygen radicals [22].

Much of the understanding of TB's pathogenesis in recent years came from the zebrafish model (with similar immune system to that of humans). That model used *Mycobacteriummarinum*, Mtb's closest species. Cronan and Tobin provide a nice review of how both host and bacterial factors contribute to Mtb's pathogenesis. They also challenge the old understanding of the granuloma. During infection, Mtb is phagocytosed by macrophages; then other

immune cells (T cells, B cells, neutrophils) are recruited, forming the granuloma. Necrosis and then hypoxia result in caseum formation in the granuloma's inner core. Bacteria persist inside this granuloma and eventually are released when this granuloma ruptures [23]. Mtb binds to receptors on macrophages, including Toll-like receptors, Nod-like receptors, C-type lectin receptors, mannose receptor, DC-SIGN (dendritic cell-specific intracellular adhesion molecule 3–grabbing nonintegrin), complement receptors, Fc receptors, and DNA sensors. Once inside the macrophage, Mtb enters and inhibits maturation and fusion with lysosome of the phagocytic vacuole. At certain times and under certain conditions, phagolysosomal fusion and secretion of various cytokines (tumor necrosis factor, interferon [IFN], and interleukin-6 [IL-6]) occur, in addition to production of reactive nitrogen/oxygen species that aid in killing of the bacilli. Mtb-infected cells migrate to pulmonary lymph nodes, where an adaptive immune response is mounted with T-cell production of IFN and B-cell production of antibodies. Successful killing of Mtb occurs with activation of more macrophages by T cells through IFN release [24]. When partial success occurs, activated macrophages and other host cells (T cells, B cells, and fibroblasts) surround the Mtb-infected cells in an organized display, a granuloma, creating hypoxic, acidic, nutrient-poor conditions that are less permissive for Mtb replication. However, the lesions are not always sterilized, as Mtb uses several strategies to ensure its survival, including resisting toxic molecules produced by the host, modifying phagosome biogenesis to create an environment suitable for survival and growth, co-opting the trafficking of cells within the granuloma to expand the number of infected cells, and inhibiting macrophage apoptosis to preserve its host niche. Although the immune response in the lung is directed at eliminating the bacillus, activation of pathways that damage lung tissue results in fibrosis, scar formation, and impaired lung function. Hence, mycobacterial phagocytosis is not exclusively host driven; instead, it is a process tuned by the mycobacteria themselves to establish a productive niche for their growth and dissemination [23].

The idea that the granuloma is exclusively host-driven and static was challenged again using the zebrafish, *M marinum* model. In fact, the granuloma is a dynamic structure with cells moving into and within it. The granuloma is essential for mycobacterial survival. *M marinum* species lacking the RD1 virulence locus were found to be less virulent because of inefficient granuloma formation. In addition, multiple secretion systems were identified (ESX-1 system, which ESAT-6 is part of, and SecA2 system) and found to facilitate granuloma formation and lead to macrophage death and recruitment of more macrophages. ESAT-6 induces the inflammatory matrix metalloprotease, MMP-9, in adjacent epithelial cells, acting as a guidance cue for nearby macrophages, leading to further bacterial expansion and granuloma formation [23].

When the body's defense system fails, Mtb continues to grow intracellularly until it lyses the cell and either reinfects new cells or replicates extracellularly. Extracellular TB can be associated with high numbers of bacteria (eg, in lung cavities), which, due to their growth rate and metabolic state, likely have

varying susceptibilities to TB drugs in comparison with intracellular bacilli. In addition, the extracellular niche can be a source of drug-resistant organisms due to the high bacterial burden and known ability of Mtb to develop drug resistance [24].

One of the mechanisms by which Mtb survives is that it leads to macrophage necrosis rather than apoptosis. Apoptosis is associated with a reduction in the viability of intracellular Mtb and provides an important link to the establishment of T-cell immunity. The mechanisms by which virulent Mtb leads to macrophage necrosis are inhibition of plasma membrane repair, damage of inner mitochondrial membrane, and inhibition of formation of apoptotic cellular envelope [25]. Another process that aids Mtb's persistence is biofilm formation through the production of the *pks1* gene. This characteristic is common among TB isolates throughout the world [26].

Only a small fraction of individuals exposed to Mtb develop clinical TB. Over the past century, epidemiologic studies have shown that human genetic factors contribute significantly to this interindividual variability [27]. Studies have shown that certain genes affect susceptibility to TB. One of those is the STAT 4 promoter-region polymorphism found in a Moroccan population that may impact STAT 4 expression [28]. In the zebrafish model, Tobin and colleagues [29] found that mutations in the gene leukotriene A4 hydrolase (LTA4H), which catalyzes the production of the pro-inflammatory eicosanoid LTB4, were associated with hypersusceptibility to *M marinum*. Reduced LTA4H activity confers hypersusceptibility via an excess production of anti-inflammatory lipoxins. In humans, 2 intronic single-nucleotide polymorphisms (SNPs) at the LTA4H locus were associated with TB. Heterozygosity for the 2 SNPs was protective, while both homozygous states corresponded to increased disease severity. Tobin explains that therapies for TB must be directed against the host rather than the bacillus. Susceptibility to TB can be due to hypo-inflammatory or hyperinflammatory states, both ruled by the patient's genotype and causing either an increase or a decrease in LTA4H and both leading to macrophage lysis.

Because of the difference in their immune system, children are more susceptible than adults to progress from Mtb exposure to infection and disease [16]. In addition, children have a higher risk of extrapulmonary dissemination and death. Because of immaturity in their immune response, infants have a particularly high morbidity and mortality from TB [30].

Most patients with disseminated TB, whether children or adults, especially in endemic countries, have no known underlying immunodeficiency, inherited or acquired. However, a category of primary immunodeficiency that leads to disseminated mycobacterial disease is Mendelian susceptibility to mycobacterial diseases (MSMD), which is primarily seen in children. Cases of disseminated TB have been reported among children with MSMD, particularly in those presenting with IL-12Rβ1 deficiency, the most common known genetic cause of MSMD [31]. In addition to infecting the lungs, TB has the capability to disseminate to other organs. On Mtb infection, human macrophages express

numerous factors including vascular endothelial growth factor that controls the formation of new blood vessels. It was found that inhibiting angiogenesis in a murine model strongly decreased the spread of bacteria [6].

Description of the natural history of TB was documented before anti-TB drugs were introduced, and it gave an important description of disease progression. After inhalation of the bacilli, those reach a terminal airway, where a localized pneumonic inflammatory process occurs; this is called the parenchymal (Ghon) focus. From this focus, bacilli drain to regional lymph nodes and both the Ghon focus and the lymph nodes involved are termed the primary complex. During the incubation period and before adequate immune response, these bacilli disseminate systemically and infect other organs. Five phases of TB infection were described. Phase 1 occurred 3 to 8 weeks after primary infection with fever and formation of the primary complex. Phase 2 occurred 1 to 3 months after the primary infection, following the hematogenous spread with high risk for TB meningitis (TBM) or military TB. Phase 3 occurred 3 to 7 months after the primary infection, when pleural effusions in children older than 5 years or bronchial disease in children younger than 5 years occurred. The calcification of the primary complex occurred 1 to 3 years later, during phase 4. It is during this phase that osteoarticular TB in children younger than 5 years of age and adult-type disease in adolescents occur. Finally, during phase 5, which occurs after the age of 3 years, late manifestations of TB, including pulmonary reactivation, develop [32].

CLINICAL MANIFESTATIONS

Persistent cough, associated with weight loss/failure to thrive, fever, fatigue, and reduced playfulness without improvement following other therapies, including antibiotics, antimalarial treatment, and nutritional support, should make a pediatrician highly suspicious of PTB. Specificity of these symptoms is highest in children 3 years of age or older (98.9%), decreases to 82.6% in those less than 3 years, and performs poorly in HIV-infected children [14]. Extrapulmonary TB occurs in 10% to 42% of patients, depending on race or ethnic background, age, presence or absence of underlying disease, genotype of the Mtb strain, and immune status. Extrapulmonary TB can affect any organ in the body, has varied and protean clinical manifestations, and therefore, requires a high index of clinical suspicion [33].

HIV coinfection poses special challenges to clinical management in patients with active TB. The risk of active TB increases soon after infection with HIV, and the manifestations of PTB at this stage are similar to those in HIV-negative persons. At CD4 counts of less than 200 per cubic millimeter, the presentation of TB may be atypical, with subtle infiltrates, pleural effusions, hilar lymphadenopathy, and other forms of extrapulmonary TB in as many as 50% of patients. At CD4 counts of less than 75 per cubic millimeter, pulmonary findings may be absent, and disseminated TB, manifested as a nonspecific, chronic febrile illness with widespread organ involvement and mycobacteremia, is more frequent, with high early mortality; polyclonal disease has also been

described. Such cases may be mistakenly diagnosed as other infectious diseases and are often identified only on autopsy [33]. Up to 25% of patients presenting for HIV care in endemic regions have undiagnosed active TB. Therefore, screening for TB is recommended for all patients with HIV infection to identify patients with active disease and before instituting INH preventive therapy (IPT) in the remainder [33]. Although an exuberant immune response in immunocompetent adolescents tends to result in adult-type, cavitating disease, in young children or individuals with HIV coinfection, poor cell-mediated immunity is thought to allow unrestrained proliferation of bacilli with progressive parenchymal lung damage (with or without cavity formation) and dissemination [30].

The following describes the disease classifications of PTB in childhood. The prechemotherapy literature documented the natural history of TB in childhood. These disease descriptions remain invaluable for guiding public health policy and research, because the introduction of effective chemotherapy radically changed the history of disease [32].

Pulmonary infection without progression to disease implies an effective immune response that has contained the tubercle bacilli and is characterized by infection with Mtb that is uncomplicated by clinical symptoms (other than self-limited, virallike illness) or radiological abnormalities (other than the primary complex). In pulmonary infection, the child has a positive TST, nonspecific viral respiratory symptoms, and enlarged lymph nodes on CXR. Over time, the lesions either disappear or calcify, indicating clinical quiescence. The prognosis of pulmonary infection was favorable, with the associated risk mainly dependent on the age at the time of primary infection.

Pulmonary disease is characterized by infection with Mtb that is complicated by marked clinical symptoms or additional radiological abnormalities apart from the primary complex. Approximately 70% of the primary foci are subpleural. Lobes are affected equally. Twenty-five percent of cases have multiple parenchymal foci. Pulmonary disease may be associated with a diverse spectrum of pathologic abnormality. Bronchial disease predominated in children aged less than 5 years with a range of bronchoscopic findings: no visible involvement, obstruction from external nodal compression, endobronchial nodal breakthrough with caseous drainage, granulation tissue with polyps, and fistula formation. Symptoms varied according to the degree of airway irritation and obstruction. Pleural effusions increased in incidence from 5 years of age onward. Pleural effusions varied in size from small to massive and had a characteristic clinical course, starting with an acute pleuritic pain in the chest, accompanied by a high fever in the absence of acute illness, an ill-defined loss of vigor, and a dry cough.

A Ghon focus with cavitation was rare. It occurred predominantly in black children aged less than 2 years. Clinical symptoms of Ghon focus cavitation included weight loss, fatigue, fever, and chronic cough. In those with cavitation, disease progressed to death within 1 year in most cases. Healing was rare, and even those that survived the initial illness ultimately died of TB or

associated complications. Cavitation following primary infection occurred frequently during adolescence, but in this age group, parenchymal breakdown probably reflected excessive rather than poor disease containment.

Enlarged regional lymph nodes on CXR rarely caused symptoms except when they were associated with bronchial disease, or when excessive nodal caseation caused persistent fever and weight loss. The subcarinal nodes were most commonly involved, and rarely, pericardial effusion developed following nodal erosion with caseous discharge into the pericardial space.

Adult-type disease resulted from primary infection, endogenous reactivation, or exogenous reinfection. Adult-type disease was most common after recent primary infection in children older than 10 years of age. The interval from primary infection to adult-type disease was widely variable (3 months to 20 years), mostly dependent on the age at primary infection. The shortest time intervals and highest risk followed primary infection during adolescence, especially in girls of perimenarchal age. The disease started off with minimal symptoms, such as cough, loss of appetite, and fatigue. With disease progression, typical TB symptoms of chronic cough, chest pain, lethargy, anorexia, and weight loss became evident. Children with advanced disease became anemic, developing an oscillating fever and hemoptysis. A frequent complaint, even in the absence of fever, was night sweats. The prognosis of adult-type disease was poor, with 50% to 60% mortality within 5 to 10 years. These children were sputum smear-positive and able to transmit infection.

With hematogenous spread, bacilli seed to susceptible organs, especially the spleen, bone, kidney, and cerebral cortex, and possibly to the lung apices (Simon foci). Infection in a child less than 2 years of age carried a significant risk of serious disease. TBM was present in more than 30% of children who presented with TB before 2 years of age. The risk of TBM after 3 years of age was extremely low, and those who did develop TBM had significant preceding symptoms. Infants were most vulnerable to developing miliary disease. The symptoms included prolonged pyrexia, lassitude, anorexia, and weight loss. Children appeared acutely ill, with minimal physical signs apart from possible tachypnea and hepatosplenomegaly. Radiological mottling followed 7 to 21 days after febrile onset, starting as barely visible nodules that slowly progressed to large, poorly defined patches. The initial miliary lesions were often difficult to visualize, with 30% to 40% of autopsy-proven miliary lesions missed on CXR before death. Bone marrow biopsy and ophthalmoscopy were useful diagnostic aids. The prognosis of miliary disease was poor. Clinical progression with persistent fever, increased irritability, and weight loss frequently terminated in TBM. The majority died within 6 months, but chronic forms were occasionally seen whereby children eventually died from toxemia, malnutrition, or amyloidosis [32].

DIAGNOSIS

Even though TB incidence in the United States is low, pediatricians in this country should always consider TB as cause of a child's symptoms, especially

if there's a history of TB exposure. Those who traveled from endemic areas should be routinely screened for TB on arrival [34].

In making the diagnosis of TB, a pediatrician should pay careful attention to history of TB contact in addition to symptoms suggestive of TB as described in the previous section. Assessment of growth is extremely important. Then, TST, bacteriologic confirmation whenever possible, and HIV testing must be done [14]. Unfortunately, in many countries, TST and culture may not be readily available; however, neither is required to make a decision to treat.

While taking history, it is important to note the closeness of contact with a TB patient as well as duration of this contact. If the pediatrician is unable to identify a confirmed contact, then he or she should always ask if anyone in the household has been coughing and request immediate assessment of that person for possible TB.

The following sections discuss the proper up-to-date recommendations in making diagnosis of LTBI and active TB.

Latent tuberculosis

Testing for LTBI should be targeted and restricted to persons at high risk for LTBI and progression to active TB disease. It is indicated for groups in which the prevalence of latent infection is high (eg, foreign-born persons from regions in which TB is endemic), those in whom the risk of reactivated disease is high (eg, patients with HIV infection or diabetes, and patients receiving immunosuppressive therapy), and recent contacts of patients with TB [33]. Two tests exist for making the diagnosis of LTBI, namely, the TST and IFN-γ release assay (IGRA).

A major obstacle to the development and assessment of LTBI tests is the lack of a gold standard to measure sensitivity and specificity [35].

Active TB should be ruled out in patients with a positive diagnostic test for LTBI before the initiation of therapy for the treatment of LTBI [36].

Before 2001, the TST was the only test for TB. TST requires proper administration by the Mantoux method with intradermal injection of 0.1 mL of tuberculin-PPD into the volar surface of the forearm. False-positive TSTs can result from contact with nontuberculous mycobacteria (NTM) or Bacille-Calmette-Guérin (BCG) vaccine [37]. The degree of BCG cross-reactivity depends on many factors, including the strain of BCG used, the patient's age and nutritional status at the time of vaccination, frequency of skin testing, and years since the vaccination was given. In most studies of children vaccinated with BCG during the newborn period, only 5% react to tuberculin testing at 12 months and 80% to 90 % lose such reactivity within 2 to 3 years. Although BCG vaccination of older children or adults results in greater initial and more persistent cross-reactivity, most of these individuals lose cross-reactivity within 10 years of receiving the vaccination. Exposure to NTM varies geographically and generally results in smaller, transient indurations than those of TB [8].

The reaction to tuberculin typically begins 5 to 6 hours after the patient receives the injection and reaches maximal induration at 48 to 72 hours. In

some individuals, the reaction may peak after 72 hours. In these instances, the TST should be measured again and interpretation of the test should be based on the larger, later reading. Rarely, vesiculation and necrosis may occur. In these cases, repeat tuberculin testing should be avoided. Forty-eight to 72 hours after the injection is given, the diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters. A trained health care professional should read all skin tests. A nonreactive TST does not exclude LTBI or TB [8].

Cutoff values for TST exist. The test is considered positive depending on the risk factors present (Table 1) [8]. There are factors that might lead to false negative TST results, including viral infections (measles, mumps, chicken pox, HIV), bacterial infections (typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming TB, TB pleurisy), fungal infections (South American blastomycosis), live virus vaccines (measles, mumps, polio, varicella; TST can be performed either on the same day that the vaccination with live virus is given or 4–6 weeks later), metabolic derangements (chronic renal failure), low protein states (severe protein depletion, afibrinogenemia), diseases affecting lymphoid organs (Hodgkin disease, lymphoma, chronic leukemia, sarcoidosis), drugs (corticosteroids and other immunosuppressive agents), age (newborns, elderly patients with "waned" sensitivity), stress (surgery, burns, mental illness, graft-versus-host reactions), improper storage of tuberculin, contamination, improper administration such as subcutaneous injection, or error in reading the test [8].

IGRAs detect sensitization to Mtb by measuring IFN-γ release in response to antigens representing Mtb. In 2001, the QuantiFERON-TB test (QFT; Cellestis Inc, Valencia, CA, USA) became the first IGRA approved by the US Food and

Table 1
Definitions of a positive tuberculin skin test results in infants, children, and adolescents

Induration	Risk Factors
>5 mm	Children close to a known or suspected contagious TB case
	Children with CXR findings consistent with active with active or previously active TB
	Children with symptoms suggestive of TB disease
	Immunocompromised children
>10 mm	Children at increased risk of disseminated disease:
	Children less than 4 years of age
	Children with diseases including Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure,
	or malnutrition
	Children with increased exposure to TB disease based on country of birth, exposure to high-risk adults (including drug users, HIV-infected adults)
	Children who traveled to high-prevalence regions of the world
>15 mm	Children who are 4 years or older who do not have any other risk factors

Data from Mandalakas AM, Starke JR. Current concepts of childhood tuberculosis. Semin Pediatr Infect Dis 2005;16:93–104.

Drug Administration (FDA). It used the PPD, was found to be less specific than TST, and was subsequently removed in 2005. In 2005, the QuantiFERON-TB Gold test (QFT-G) was introduced and in 2007 the QuantiFERON-TB Gold In-Tube test (QFT-GIT) was introduced. In July 2008, T-Spot became the fourth IGRA to be approved by the FDA. With the newer IGRAs, there was improved specificity as they assessed MTB-specific peptides (ESAT-6) and (CFP-10). However, ESAT-6 and CFP-10 are present in *M kansasii, M szulgai*, and *M marinum* [37].

Several studies have been done trying to assess the sensitivity and specificity of IGRAs. In a meta-analysis published in *The Pediatric Infectious Disease Journal*, the investigators found that there was not enough evidence to support the use of IGRAs over TST for LTBI in children. They even concluded that IGRA sensitivity was low in high-burden TB settings compared with low-burden TB settings [38].

In a small French study where TB incidence is low, the sensitivity of IGRA in immunocompetent children older than 2 years of age was high [39].

In a study conducted in the United States on immigrant children (Mexico, the Philippines, and Vietnam), it was found that IGRA should be used for screening children 2 years and older instead of TST because most of these children are BCG vaccinated. The benefits of such practice whereby fewer children are QFT-positive include decreasing radiation exposure, lowering cost, and decreasing LTBI treatment [35].

Studies on the utility of IGRA in children less than 5 years of age are scarce and only recently published. One of these studies showed good sensitivity and specificity of IGRA and a low rate of indeterminate results in the first 2 years of life, supporting its use at this age [40]. Another study was done in children less than 5 years of age that showed that IGRA performed well in this age group; however, in this study, there was discordance between IGRA and TST, which led the authors to conclude that both tests should be considered in high-risk populations [41].

Now that it is known that IGRA is more specific than TST, a study done in US college students who have been in TB-endemic areas showed that IGRA was not superior to TST in that population and was actually less specific. The investigators recommended adopting a higher cutoff value of 1.0 IU/mL or higher for those at lower risk of exposure to TB, such as matriculating health care professional students from low prevalence countries such as the United States, and the current manufacturer's recommended cut point of TB-nil 0.35 IU/mL or higher for those at higher risk of exposure, such as students coming from countries with high TB burden [42].

The Centers for Disease Control and Prevention guidelines indicate that a TST or an IGRA may be used to test for LTBI. An IGRA is preferred over the TST when testing people who are BCG vaccinated or are unlikely to return for TST reading. The TST is preferred for serial testing programs, such as those involving health care workers, because the IGRA has a high false positive rate in this setting in the United States [36]. The TST is less expensive and is therefore preferred in low-income regions [33].

The American Academy of Pediatrics has also published in its Red Book recommendations on the use of TST versus IGRA in children (Table 2).

Newer concerns have also emerged about IGRAs. Considerable fluctuations with serial testing in individual patients have been reported; some might be attributed to new infection, to boosting following a TST, or response to antimycobacterial treatment. Most of these fluctuations, however, remain unexplained. Hence, well-controlled studies are needed to define the causes of individual variations in IFN-γ response and to develop criteria to differentiate nonspecific variation from that associated with new or resolving infection [43,44].

One must conclude with the WHO 2011 report on use of IGRA in high-TB endemic areas. In this report, the WHO recommends against use of IGRAs instead of TST in low- and middle-income countries for the diagnosis of LTBI in children (irrespective of HIV status) [45].

Active tuberculosis

Diagnosing TB in children can be challenging because it can mimic many common childhood diseases like pneumonia, malnutrition, and HIV. In attempting to reach a definite diagnosis after TB is considered, clinicians are faced with another challenge of the paucibacillary nature of the disease in this age group. Sputum production is often faint and mostly swallowed rather than expectorated. Gastric samples require that children be hospitalized and fasting for 3 nights. Even when a good sample is produced, only in 10% to 15% of the samples is the acid-fast bacilli smear positive and in 30% the culture is positive. Ways to improve sputum production include use of nebulized hypertonic saline that yields more TB compared with gastric washings [30].

Table 2
Use of interferon-γ release assay and tuberculin skin test in children

TST preferred, IGRA acceptable	• Children who are younger than five years of age
IGRA preferred, TST acceptable	• Children older than five years who had the BCG vaccine or those unlikely to return for TST reading
TST and IGRA should be considered when	• T The initial and repeat IGRA are indeterminate • The initial TST or IGRA is *negative* and: ◦ There is moderate to high clinical suspicion for TB disease ◦ There is high risk of progression and poor outcome • The initial TST is *positive* and: ◦ History of BCG vaccination in a child older than five years of age ◦ The additional evidence is needed to increase compliance ◦ Nontuberculous mycobacterial disease is suspected

Data from Daley CL, Reves RR, Beard MA, et al. A summary of meeting proceedings on addressing variability around the cut point in serial interferon-gamma release assay testing. Infect Control Hosp Epidemiol 2013;34:625–30.

In the absence of bacteriologic confirmation, the diagnosis of childhood TB is often based on the triad of (1) close contact with an infectious index case, (2) a positive TST result, and (3) observation of suggestive signs on a CXR. This triad is less helpful in areas of endemicity, whereby a positive TST result is not uncommon and where exposure to Mtb is often undocumented. In TB-endemic countries, the diagnosis of childhood TB depends mainly on clinical characteristics and the subjective interpretation of the CXR; however, CXR has well-recognized limitations and is unavailable in many resource-limited countries.

Clinical scoring systems designed to aid diagnosis have not been validated against the standard of culture-confirmed diagnosis, and the diagnostic accuracy of these systems varies markedly [46]. It is important to emphasize that neither IGRAs nor the TST have high accuracy for the prediction of active TB [47].

Since declaration of TB as a public health emergency in 1983, the diagnostic tests developed have shown improvement in sensitivity and specificity. The initial tests used had many limitations: direct-smear microscopy was insensitive; TST did not distinguish latent from active disease; solid culture was slow with results arriving too late to influence clinical decisions; and CXRs were unable to differentiate between TB and other pulmonary pathologic conditions [48]. Acid-fast stain with microscopic examination is the easiest, quickest, and least expensive diagnostic procedure. However, this method cannot differentiate TB and NTM. There must be 5000 to 10,000 bacilli per millimeter of specimen present to allow detection of the bacteria in stained smears, resulting in only moderate sensitivity in children. Thus, negative smears do not preclude the presence of TB in children [8].

Newer tests are found in later discussion.

Culture

Traditional culture media often require 4 to 6 weeks for positivity and another 2 to 4 weeks for susceptibility testing [8]. The microscopic-observation drug-susceptibility assay (MODS) and the automated liquid culture methods have increased the sensitivity of culture and are faster than Lowenstein–Jensen and other solid media, with the added advantage of obtaining drug-sensitivity information. Both MODS and liquid culture have lower sensitivity in gastric aspirates than in sputum. The results for all culture methods are rarely obtained before 1 week of incubation [48].

Improvement in the protocol to expedite culture results has been published but not yet implemented. These improvements include a new medium, microaerophilic atmosphere or ascorbic-acid supplement, and autofluorescence detection [49].

Nucleic acid amplification tests

Nucleic acid amplification tests (NAAT) are technologies that vary from in-house assays to fully automated, self-contained kits. Data on their performance in children are limited. These tests are usually expensive [48] and are

mostly intended for use at reference laboratory level only, requiring dedicated infrastructure and experienced staff [7]. The Xpert MTB/Rif test is a cartridge-based fully automated NAAT and is discussed later.

Among the first FDA-approved NAAT was the *M tuberculosis* direct test (Hologic Gen-Probe, San Diego, CA, USA) for detection of MTBC from *N*-acetyl-L-cysteine–NaOH concentrated specimens, either smear-positive or smear-negative. The test marked a successful beginning of the molecular era in the United States for TB diagnosis with high sensitivity and specificity, and remarkably shortened the turnaround time with cost savings [10].

Loop-mediated isothermal amplification

The loop-mediated isothermal amplification (LAMP) assay is a rapid, easy-to-perform technology that has recently been used to develop diagnostic tests for several pathogens such as *Staphylococcus aureus*, foot and-mouth disease virus, and salmonella. Some of these assays can be performed in specimens collected on swabs and are completed within 1 to 2 hours, requiring only a water bath or heat block for reaction. Results of initial studies reporting the performance of LAMP amplification assays of Mtb-specific DNA in clinical specimens, including specimens of patients with extra PTB, have been promising, as opposed to conventional polymerase chain reaction (PCR), in which LAMP is isothermal and eradicates the need for expensive thermocyclers. LAMP assays for TB have reported sensitivity ranging from 88% to 100% and specificity between 94% and 99% in sputum. The most recent prototypes perform better than conventional PCR. The low cost and technology requirements of these assays, their performance in nonsputum specimens, and the potential to develop tests for a large number of pathogens make the technique promising for children [48]. Because of insufficient evidence, this platform has not yet been endorsed by the WHO. FIND (Foundation for Innovative New Diagnostics) has subsequently re-evaluated TB LAMP in multiple country settings in comparison with fluorescent smear microscopy, Xpert MTB/RIF, and culture and plans to submit a dossier of performance characteristics and diagnostic accuracy to WHO for review in 2015 [7].

BlaC-specific fluorogenic probe

The BlaC-specific fluorogenic probe approach uses BlaC, a highly conserved class A β-lactamase enzyme, which is naturally expressed and secreted by the tubercle bacilli. The fluorogenic substrates then enhance the natural fluorescence, facilitating detection, and increasing the specificity of the reaction. The light emitted can be detected by a camera built on a mobile phone. As the probe would not require laboratory infrastructure, it has the potential to be developed as a rapid, low-cost TB diagnostic tool that might be suitable for children [48].

Xpert MTB/RIF

Even though the author of "Xpert MTB/RIF: a game changer for the diagnosis of pulmonary tuberculosis in children?" [50] has concluded that this test will not be a crucial diagnostic tool in high burden countries, the WHO endorsed its use in

children in 2013. Several studies published on its use in the pediatric population have shown promising results be it in gastric lavage [51,52], sputum [53–59], bronchoalveolar lavage specimens [60], or stool in HIV-infected patients [61].

In 2010, WHO endorsed the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real-time PCR to identify MTBC DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than 2 hours. The assay has similar sensitivity, specificity, and accuracy as culture on solid media. A policy update was issued at the end of 2013 to include its use in children.

a. Xpert MTB/RIF should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults and children suspected of having MDR-TB or HIV-associated TB.
b. Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children suspected of having TB.
c. Xpert MTB/RIF may be used as a follow-on test to microscopy in adults and children, where MDR-TB and HIV is of lesser concern, especially in further testing of smear-negative specimens [62].

Children suspected of having PTB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

Another benefit was demonstrated in a study that showed that Xpert significantly reduced duration of airborne isolation [63].

A few of Xpert's strengths include simplicity of use, accuracy, rapidity of result, and ability to use on a variety of samples, including lymph node aspirates, cerebrospinal fluid (CSF), and other areas. On the other hand, it is expensive; needs calibration, maintenance, and linkage to a computer and secured premises; needs continuous electrical power supply and air conditioning; cannot differentiate between live and dead Mtb; and thus, cannot be used to monitor treatment success, failure, or relapse [15]. Use of Xpert MTB/RIF was not supported in a study done in malnourished children from a high TB area in Malawi [64].

Difficulty in acquiring sputum samples from children has led researchers to test new blood assays: the T-cell activation marker–tuberculosis, which is a flow cytometric analysis test of the CD27 on circulating Mtb-specific T cells that can discriminate active TB from latent TB [65] and transcriptome signatures [46]. The first study was published in *Lancet* as a proof of concept and the second in *New England Journal of Medicine*. Although these seem to be promising new tests, there is always the challenge of their use in poor countries because of their high cost and technical complexity. Also, more validation studies are needed to confirm their accuracy in diagnosing active TB in children. Both of these tests do not address the issue of resistance, which is becoming a crucial element in giving the right treatment for patients with confirmed active TB.

Urine lipoarabinomannan has shown little value in diagnosing children with tuberculous meningitis [66] or PTB [67].

Imaging

CXR remains an important tool for the diagnosis of PTB in children. The commonest abnormality is due to lymphadenopathy and tends to be asymmetrical. CXR does have limitations, especially as quality of CXR is often poor. The diagnostic accuracy of experienced specialist pediatricians and primary level practitioners in detecting radiographic lymphadenopathy was low [68].

Computed tomography (CT) scan is more sensitive than CXR and can help distinguish between an active and an inactive form of TB. In one study aimed at finding the relationship between high-resolution CT findings and smear positivity, the investigators concluded that cavity, tree-in-bud pattern, and upper lobe nodular infiltration were highly associated with smear positivity in children. Conversely, lymphadenopathy and collapse had significant association with a negative smear [69].

Diagnostic problems are more pronounced in HIV-infected children. HIV-infected children who live with HIV-infected adults are more likely to be exposed to an adult TB index case at home. However, HIV-infected adults often have sputum smear–negative TB, and, therefore, the risk of infection posed by this exposure is often not appreciated. TST is much less sensitive in HIV-infected children than in HIV-uninfected children. Chronic pulmonary symptoms may be related to other HIV-related conditions, such as gastroesophageal reflux and bronchiectasis, thus reducing the specificity of symptom-based diagnostic approaches. Weight loss and failure to thrive are typical characteristics of both TB and HIV infection. Rapid TB disease progression is more likely to occur in HIV-infected children, reducing the sensitivity of diagnostic approaches that focus on persistent, non-remitting symptoms. Interpretation of CXRs is complicated by HIV-related comorbidities, such as bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, pulmonary Kaposi sarcoma, and the atypical presentation of TB in immunocompromised children [17].

EXTRAPULMONARY TUBERCULOSIS

TBM is the most common form of extrapulmonary TB, developing 3 to 6 months after primary infection. TBM is the most severe form of childhood TB [30]. The pathologic abnormality in TBM includes an increase in intracranial pressure, cerebral infarction, and severe hydrocephalus. Infants and young children are more likely to experience a rapid progression to hydrocephalus, seizures, and cerebral edema. In older children, signs and symptoms progress slowly over the course of several weeks, with symptoms of fever, headache, and drowsiness, which then proceed to vomiting, seizures, and then finally, to a comatose state. TST may be nonreactive in 40% of cases. TB therapy should be initiated in any child with basilar meningitis and hydrocephalus or cranial nerve involvement that has no other apparent cause [8,70].

Patients with pericardial TB disease experience cardiac tamponade or severe pericardial constriction that can be fatal in those patients with pericardial TB [71].

Other forms of extrapulmonary TB include superficial lymph node infection (scrofula), osteoarticular, abdominal, gastrointestinal, genitourinary, cutaneous, and congenital disease.

TB of the superficial lymph nodes can be associated with drinking unpasteurized cow's milk or can be caused by extension of primary lesions of the upper lung fields or abdomen leading to involvement of the supraclavicular, anterior cervical, tonsillar, and submandibular nodes. Although spontaneous resolution may occur, untreated lymphadenitis frequently progresses to caseating necrosis and capsular rupture and spreads to adjacent nodes and overlying skin, resulting in a draining sinus tract that may require surgical removal [8].

TB adenitis is most common in the cervical region. Lymph node enlargement is painless and asymmetrical, often multiple, discreet, or matted. Nodes are typically large (>2 × 2 cm; ie, visibly enlarged, not just palpable). Lymph node enlargement is persistent (>1 month) and not responsive to other treatment such as antibiotics. Sinus and discharge may develop. Usual age is 2 to 10 years.

Osteoarticular TB is not uncommon in children. Spinal TB causes destruction of vertebral bodies leading to typical spinal deformity and possibly paralysis. Hips and knees are the other typical site, usually mono-articular with painless effusion.

TB pleural effusion is common and tends to occur in school-aged children. Pleural tap is safe and very useful to differentiate TB from suppurative empyema. Other less common sites for effusion, usually painless, include peritoneal and pericardial spaces, also usually in school-aged children. Ultrasound and tap of effusion for microscopy and protein are very useful [14].

Newborn babies acquire TB from mothers who develop disseminated TB through placenta and into the liver or by aspirating infected amniotic fluid. Early diagnosis and treatment are crucial to prevent rapid disease progression [70].

TREATMENT

Children with TB, even those with drug-resistant disease, usually have an excellent clinical outcome if diagnosed in a timely fashion and treated appropriately [70]. However, it is very difficult to assess the outcome and efficacy of any regimen for treatment of TB in children because they rarely have positive sputum and gastric washings and hence scientific studies are scarce. Treatment should be guided by culture and susceptibilities when available [16].

The effective treatment of TB using current antibiotics faces obstacles that include a lengthy duration of treatment, potential drug toxicity, drug interactions with HIV medications, and increasing rates of drug resistance [24]. Therefore, local TB control programs should take responsibility of ensuring that all persons with suspected TB are identified and evaluated promptly. Unfortunately, when resources are limited, children receive lower priority [8].

Latent infection

After infection with Mtb, children may take up to 3 months to develop an immune response sufficient to produce a positive TST. Children younger

than 5 years of age have a short incubation period and may develop severe disease before developing skin test reactivity. As the result of this risk, children with a negative TST and known or suspected exposure to an adult with contagious TB benefit from INH therapy. TST should be repeated 3 months after the initial exposure. If the second TST is negative, therapy may be discontinued. If skin test conversion occurs, therapy should be continued for the full duration. Although this strategy is considered standard of care in many industrialized countries, resource-poor countries frequently neglect to implement this WHO recommended strategy [8].

Most children with Mtb infection will have LTBI. These children have a reactive TST, normal CXR, no clinical evidence of TB, and presumed infection with low numbers of viable tubercle bacilli that are dormant. The treatment of children with LTBI should be considered a public health priority for numerous reasons: infants and children younger than 5 years of age have been infected recently, risk of progression to active disease is high, risk of developing severe disease is inversely related to age, children with LTBI have more years at risk for the development of active disease later in life, and children with LTBI become adults who may spread disease. Several large clinical trials conducted during the 1950s and 1960s demonstrated the efficacy of INH to reduce the risk of TB developing in children with LTBI. Secondary analysis of 2 large household contact studies suggested that the efficacy of INH treatment of LTBI plateaus at 9 to 10 months of therapy. Other studies demonstrated that a second year of treatment with INH did not result in additional benefit beyond that conferred by the first year of treatment. Treatment of LTBI should be tailored according to host immune factors, drug-susceptibility, tolerance, and compliance. In most cases, treatment may be given daily without observation. If adherence is inadequate, intermittent directly observed therapy (DOT) may be instituted. Treatment of latent MDR-TB should be delivered via DOT [8].

The diagnosis of LTBI in HIV-infected children is important because of the high risk of disease progression. IPT is recommended for any HIV-infected child with TB risk factors even when the TST is negative and when active TB has been excluded. The beneficial effect of IPT, however, wanes in 2 to 3 years and there is limited protection to future reinfection [17].

The preferred regimen for treatment of LTBI is INH for 9 months or for a longer duration in HIV-infected persons in areas with a high prevalence of TB. DOT with weekly administration of INH and rifapentine for 12 weeks has been shown to be as effective as INH alone in adults without HIV infection in countries with a low burden of TB [72]. The trial is continuing to assess safety and effectiveness in children and HIV-infected persons. HIV patients with a positive TST who are receiving preventive therapy with INH have decreased rates of active TB and death, but protection against TB wanes within a few months after cessation of INH therapy. A trial in Botswana recently showed that 36 months of preventive therapy with INH, as compared with 6 months of therapy, reduced the subsequent rate of TB by 43%. However, compliance with such a long-term regimen may be poor [33].

A phase III randomized noninferiority study comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus INH (900 mg) (combination-therapy group) with 9 months of self-administered daily INH (300 mg) (INH-only group) in subjects at high risk for TB was published. Follow-up was for 33 months. This regimen was as effective as the 9 months INH-alone regimen in preventing TB and had a higher completion rate [72].

The pharmacokinetics of rifapentine was also studied in children and it was found that a higher dose per weight was needed to achieve comparable adult serum concentration of a 900-mg dose [73].

It is very important that before starting preventive therapy that active TB be excluded; this will prevent development of resistance, especially in adolescents and adults, who have a high organism load [17].

Active tuberculosis

Once active TB is diagnosed, effective treatment should be started. Close monitoring for relapse is crucial and its risk factors include cavitation, extensive disease, immunosuppression, and a sputum culture that remains positive at 8 weeks. If any of these risk factors is present, therapy may be extended for up to 9 months [33].

Challenges with current therapy include inconsistent drug quality, the need to ensure that drug administration is directly observed and that other support is provided to patients, treatment interruptions and changes in regimen because of side effects, toxic effects, pharmacokinetic interactions (particularly with antiretroviral therapy in patients with HIV coinfection), and compliance issues owing to the lengthy treatment period. Several trials in progress are adding or substituting fluoroquinolones in an attempt to shorten standard therapy to 4 months (eg, Remox-TB trial). None of these trials have showed noninferiority so far [33,74].

Young children with uncomplicated disease who are from areas with a low prevalence of INH resistance can be treated with 3 drugs (INH, rifampin [RMP], and pyrazinamide) during the 2-month intensive phase of treatment, followed by INH and RMP only during the 4-month continuation phase. Combination therapy is important to prevent emergence of resistant organisms. This regimen is successful with a 95% cure rate and is well-tolerated. 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 INH resistance should receive a fourth drug (ethambutol, which is safe in children of all ages) during the 2-month intensive phase of treatment [8,9].

The 3 main categories of intrathoracic TB in children and appropriate drug regimens are as follows:

1. Sputum smear–negative paucibacillary TB: The success of the standard regimen of 3 drugs (RMP, INH, and pyrazinamide for 2 months) during the intensive treatment phase and of 2 drugs (RMP and INH for 4 months) for the continuation phase is well established, and the risk of acquired drug resistance is low.
2. Sputum smear–positive TB with a high organism load: Older children—especially adolescents—are more prone to sputum smear–positive paucibacillary TB and

may contribute to disease transmission in congregate settings, such as schools. Four drugs (RMP, INH, pyrazinamide, and ethambutol for 2 months) are warranted during the intensive treatment phase because of a higher risk for acquired drug resistance.

3. Disseminated/miliary TB occurs predominantly in very young (with an immature immune system) or immunocompromised children. It is frequently associated with tuberculous meningitis, and it is important to consider the CSF penetration of drugs used in the treatment of these children [17].

Poorer response to treatment and higher mortality are seen among HIV-infected children with TB. Possible reasons include higher incidence of coinfections with other pathogens, poorer absorption and low levels of anti-TB drugs, presence of underlying chronic lung disease resulting in poor penetration of drugs into fibrotic or bronchiectatic areas, poor adherence to treatment because of chronic illness or the death of the parent responsible for the child's treatment, and advanced immunosuppression and severe malnutrition [17].

In children with HIV and severe immunosuppression, WHO recommends starting HIV therapy after 2 to 8 weeks of TB treatment to prevent immune reconstitution inflammatory syndrome [30].

Although therapeutic trials have not been completed in children with extrapulmonary TB, duration of therapy depends on the site of infection and is generally extended for miliary TB and TBM [8].

Adjunctive therapy

Pyridoxine (25–50 mg/d) is recommended for infants, children, and adolescents treated with INH who have nutritional deficiencies, symptomatic HIV infection, or diets low in milk or meat products, and for breast-feeding infants. The administration of corticosteroids is beneficial in the management of children when the host inflammatory reaction contributes significantly to tissue damage or impaired function. The administration of corticosteroids decreases mortality and morbidity in patients with TBM by reducing vasculitis, inflammation, and intracranial pressure. The administration of corticosteroids may reduce significantly compression of the tracheobronchial tree caused by hilar lymphadenopathy and alveolar-capillary block, pleural effusion, and pericardial effusion associated with miliary disease. Prednisone (1–2 mg/kg/d for 4–6 weeks) usually is used [71,75,76].

A systemic review and meta-analysis on the effectiveness of steroids in all forms of TB was published in *Lancet*. The investigator's conclusion was that steroids reduced mortality in all forms of TB, including PTB. The results of this review are to be interpreted with caution because most of the cases were in patients with TBM and pericardial disease [71,77].

Monitoring for adverse effects

Among children, rates of adverse reactions secondary to antituberculous medication are low. INH and RMP treatment are associated infrequently with elevated levels of serum alanine aminotransferase that generally are less than 3 times the normal values, are not predictive of hepatotoxicity, and are not

indications for discontinuing treatment. Education of caregivers relative to potential adverse events and clinical symptoms necessitating medical evaluation and discontinuation of medication is preferable to routine laboratory screening [8].

Monitoring response

Because of the lack of culture positivity in the pediatric population, monitoring of treatment response is mostly done by measuring weight gain, monitoring for persistent fever, and checking radiological findings. The role of IGRA in monitoring response to anti-TB therapy seems promising, but requires further evaluation. The TST is unsuitable for monitoring response to anti-TB treatment because of the boosting effect through repeated injections [78].

ALTERNATIVE TREATMENTS

In children, the primary tuberculous lymph node complex is directly or indirectly the predominant etiologic factor for surgical intervention. The predominant role of thoracic surgery in children following tuberculous infection lies in relieving airway obstruction to restore lung function and to prevent future irreversible lung damage. Later pulmonary resections during childhood are required for both the sequelae of airway obstruction and the chronic secondary PTB infection [79].

Acute or chronic obstruction of the major airways was the indication for 38% (64/168) of the procedures done for childhood TB during a 15-year review. Surgical decompression of tuberculous lymph nodes causing extraluminal compression made up 56% of these 64 procedures [79].

Collapse therapy in the form of artificial pneumothorax or pneumoperitoneum was used in the past. Some of the indications for this form of therapy were primary cavitation, caseating tuberculous pneumonia, not responding to conservative treatment, lesions involving a whole lung, pleural thickening after effusion, and causing gross interference with the function of the affected lung [80].

Ibuprofen was studied in mice infected with TB. No other treatment was given. Animals treated with ibuprofen had a statistically significant decrease in the size and number of lung lesions, decrease in the bacillary load, and improvement in survival, compared with findings for untreated animals. Because ibuprofen is already known to be safe in children, it might be an attractive adjunctive therapy that will not need a long development process [81].

Experiments are also being conducted in mice to test the usefulness of host-directed therapies. Therapeutic small molecules that could inhibit Th2 cells and Tregs, Suplatast tosylate, have been shown to disrupt production of IL-4 and other Th2-type cytokines without impeding IFN-γ production. During progression of TB, Mtb elicits Th2 and Treg cell responses in susceptible hosts, which facilitates disease progression by antagonizing host protective immune responses [82]. Another study established proof of concept for host-directed treatment strategies that manipulate the host eicosanoid network. IL-1 confers

host resistance through the induction of eicosanoids that limit excessive type I IFN production and foster bacterial containment. Host-directed immunotherapy with clinically approved drugs that augment prostaglandin E2 levels in these settings prevented acute mortality of Mtb-infected mice [83].

MULTIDRUG-RESISTANT TUBERCULOSIS

Drug-resistant TB is a serious and growing problem and encompasses MDR-TB and XDR-TB. MDR-TB strains are resistant to INH and RMP, whereas XDR-TB is also resistant to fluoroquinolones and at least one of the second-line injectable drugs (amikacin, kanamycin, and capreomycin) [84]. XDR strains were first reported in 2006 [62].

Despite progress in the detection of MDR-TB cases, a major diagnostic gap remains: 55% of reported TB patients estimated to have MDR-TB were not detected in 2013 [7]. The WHO estimates that 3.7% of new cases and 20% of previously TB treated cases, or greater than 500,000 TB cases each year, are due to MDR strains [11]. Nearly half a million cases of MDR TB are diagnosed worldwide every year and a third of patients with this disease will die because of failure of diagnosis or unavailability of appropriate treatment. Drug resistance beyond XDR-TB is increasingly being reported. In certain settings, patients were infected with TB strains that required all available drugs [62,85]. Rates of MDR-TB and XDR-TB are increasing in southern Africa and the former Soviet Union with immigration leading to an increase in resistant strains in developed countries.

Epidemiologic studies on the prevalence of resistant TB in children are scarce. As in susceptible TB cases, the paucibacillary nature of the disease in the pediatric population makes the diagnosis and reporting of MDR/XDR incidence difficult [86–89]. A high index of suspicion is required in pediatric patients especially if there is a known resistant TB contact, and if the child shows no response to or deteriorates after the TB regimen is prescribed [30].

Resistance might occur because of any of the following: alterations of the binding site of drug-target molecules; loss of enzymes activating drug molecules; permeability changes to the drug, including efflux; and production of drug-inactivating enzymes, such as β-lactamase [90].

Resistance may be primary or acquired. In the case of primary drug resistance, the patient acquires a resistant strain and may transmit it to others. Poor infection control practices lead to the spread of resistant TB strains. On the other hand, acquired drug resistance results from inadequate treatment that leads to the selection of resistant strains. One example that leads to resistance is the stepwise addition of drugs or early discontinuation of proper therapy [33,62,89,90]. Drug-resistant strains of Mtb arise from spontaneous chromosomal mutations at a predictable low frequency. Outbreaks of highly fatal drug-resistant infection have been documented in several settings, especially those in which the prevalence of HIV infection is high [33]. In children, primary resistance is more common than acquired resistance, but the latter occurs mostly in children infected with HIV [30,89].

It is important to detect drug resistance and start proper treatment as early as possible to prevent spread of resistant strains. However, lack of appropriate tools is a major obstacle in achieving this goal [33]. Culture and drug susceptibility testing (DST) methods require prolonged lengths of time to confirm mycobacterial growth and detect drug resistance, during which period patients may be inappropriately treated, drug-resistant strains may continue to spread, and amplification of resistance may occur. Early and rapid diagnosis of TB and drug resistance will therefore have obvious benefits for patient and public health, including better prognosis, increased survival, prevention of acquisition of further drug resistance, and reduced spread of drug-resistant strains to vulnerable populations.

Drug resistance should be considered in children from areas with a high prevalence of drug-resistant TB and in those who have had documented contact with a person with drug-resistant disease, with someone who died during treatment of TB or who is not adhering to therapy, or with someone who is undergoing re-treatment of TB [9].

Treatment must be based on DST for first- and second-line drugs; however, in most cases, DST is not performed. In addition, second-line drug tests are not reliable [11]. Second-line drugs have limited efficacy and toxicity. After thorough diagnostic testing, if Xpert MTB/RIF and culture results are negative, children with active TB who are close contacts of patients with MDR-TB can be started on MDR regimens [62].

The first evidence that mutations in Kat G encoding catalase-peroxidase were associated with INH resistance was reported in 1992. This evidence led to increased efforts in advancing molecular assays to detect drug resistance. These tests are not 100% sensitive and therefore culture-based susceptibility still plays an integral role in confirming the molecular assays [10].

The current standard for first-line DST is an automated liquid culture system, which requires 4 to 13 days for results [33]. Molecular methods used to detect drug resistance include Cepheid GeneXpert MTB/RIF with 2-hour testing time and detecting resistance to rifampicin [10]. Ninety-five percent of all rifampicin-resistant strains have mutations localized to the 81-bp core region of the bacterial RNA polymerase β subunit (*rpoB*) gene, which encodes the active site of the enzyme and therefore molecular detection is reliable [15]. Line probes detect resistance within 6 to 7 hours, pyrosequencing within 5 to 6 hours, and Sanger sequencing within 1 to 2 days. The latter 3 detect resistance to INH, RMP, ethambutol, fluoroquinolones, amikacin, capreomycin, and kanamycin [10]. With molecular DST's excellent turnaround time, management of TB patients has improved. One should realize though that mutations do not always confer resistance, and therefore, a sequence-based method is recommended whenever available [10,91,92].

Benefit of prophylactic treatment of asymptomatic children exposed to MDR-TB has not been well studied and is not yet endorsed by the WHO [7,34,89].

There is a paucity of studies on the treatment of MDR/XDR-TB in children. Case-by-case management is needed with involvement of a childhood TB

expert. Every child should be evaluated with history taking, physical examination, CXR, TST, sputum testing (with Xpert MTB/RIF if available or sputum smear microscopy, culture, and DST), and HIV testing [62]. Cure and probable cure rates in children are 80% to 90% compared with successful treatment in adults of 48% to 62% [86,89,93]. In these studies, it was not possible to judge the optimal treatment duration. It is recommended that children be given drugs based on the index case strain's susceptibility profile, especially in those where bacteriologic confirmation is not possible or delayed [89]. "A second-line injectable drug, a fluoroquinolone and at least two other drugs to which the index case strain or the strain isolated from the child is sensitive by DST should be included in the initial drug regimen. Pyrazinamide should be added to these four drugs for the whole course of treatment but should not be counted among the active drugs, providing that DST suggests susceptibility of the causative Mtb strain to pyrazinamide. Parenteral treatment with the second-line injectable drugs (SLID) should be continued for at least 4–6 months, or sometimes longer, depending on disease severity. When treatment with the SLID is discontinued, treatment should be continued orally with at least three active drugs, not counting pyrazinamide. The optimal duration of MDR/XDR-TB treatment in children is unclear and may be very variable from case to case. Depending on the extent of the disease, the DST pattern of the causative bacteria and the immune status of the child, a total duration of treatment between 12 and 18 months following culture conversion could be reasonable and treatment may have to be prolonged in some cases to avoid the risk of relapse. Finally, the decision on the exact number of drugs and length of therapy also depend on extent and site of disease, penetration of the chosen drugs and treatment response" [30,89]. It is important not to add a single drug to a failing regimen and to use daily treatment regimen with DOT whenever possible. Advice about side effects and importance of adherence should be discussed at every visit [84]. In addition to providing a proper drug regimen, the pediatrician should provide psychosocial support and assess for child and caretakers' risk factors that might lead to nonadherence. Pain management, hearing tests, and nutritional support are also important [94].

There are limited data on the safety of second-line drugs in TB, but their use with intense monitoring might be warranted in life-threatening situations. Children who have received treatment of drug-resistant TB have generally tolerated the second-line drugs well. The benefit of fluoroquinolones in treating drug-resistant TB in children has been shown to outweigh any risk.

In addition, ethionamide, para-aminosalicylic acid, and cycloserine have been used effectively in children and are well tolerated. Linezolid for XDR-TB has been studied in children with little adverse effects documented. When it occurred, peripheral neuropathy, previously reported to be irreversible, resolved in all children [86].

In general, anti-TB drugs should be dosed according to body-weight dosing. Expert opinion is that all drugs, including fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except

ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with drug-resistant TB, because it is more difficult to monitor optic neuritis in children.

Many new TB drugs are being tested in phase 2 trials. Most of these studies, however, are conducted in the adult population [18]. Thankfully, Delamanid, a new nitro-dihydro-imidazooxazole derivative active against Mtb, is the first new drug to enter phase I/II trials in children with MDR-TB (expected completion is in 2017), and bedaquiline, a diarylquinoline (recommended for adult patients), will soon follow [7,86]. Table 3 lists the 5 different groups of TB medications.

VACCINES

The TB vaccine BCG was first developed in 1921 and remains the only licensed TB vaccine to date. It is well tolerated with an 80-year safety record with 100 million doses administered every year [4]. This vaccine protects young children against severe forms of the disease (eg, TBM) and disseminated TB. It has variable efficacy against PTB. It is not recommended in HIV-infected infants because of a high risk of disseminated BCG disease and the possible acceleration of HIV disease [16,33]. In practice, this has had little effect in HIV-endemic countries, where the HIV status of the baby is rarely established at birth, which is the usual time of BCG vaccination. The BCG is administered in infants at birth in most regions where TB is endemic. Its efficacy for preventing TB is around 50% and ranges from 0% to 80% worldwide [30]. The BCG is not routinely used in the United States, but can be given to adults planning to travel to endemic areas. In light of MDR-TB and XDR-TB becoming more prevalent, there is an urgent need for a more effective vaccine for children [16]. More than 30 vaccines are being studied [33]. Unfortunately, the lack of reliable correlates of protective immunity remains a major obstacle for predicting vaccine efficacy in all TB vaccine trials in adults and children [30]. The WHO advises that all asymptomatic HIV-exposed infants in

Table 3
Different tuberculosis therapy groups

Group name	Anti-TB medications
1. Oral agents	INH, Rifampicin, Ethambutol, Pyrazinamide, Rifabutin, Rifapentine
2. Intravenous or injectable medications	Streptomycin, Kanamycin, Amikacin, Capreomycin
3. Quinolones	Levofloxacin, Moxifloxacin, Gatifloxacin
4. Second-line medications	Ethionamide, Cycloserine, Para-aminosalicylic acid, Terizidone, Prothionamide
5. New anti-TB medications	Bedaquiline, Delamanid, Linezolid, Clofazimine, Amoxicillin-clavulonic acid, Imipenem-cilastatin, Meropenem, Clarithromycin, Thioacetazone, high-dose isoniazid

TB-endemic areas receive BCG vaccination as well as careful monitoring for the development of BCG-related disease [33].

Factors leading to the large variability of BCG's efficacy include strain-specific immunogenicity, technique of vaccine administration age at vaccination, genetic differences between populations, host nutritional factors, host coinfection by parasites, exposure to environmental mycobacteria, and genetic variation in Mtb strains. The longevity of protection is not very clear. A meta-analysis of recent data suggests protection could persist for 50 to 60 years. Additional protection by revaccination with BCG has not been shown [30].

Early in 2013, the long-awaited outcome of the efficacy trial of the first TB vaccine candidate for almost a century, MVA85A, was released. Safety data were encouraging; however, efficacy data were highly disappointing. Because MVA85A induced a large spectrum of IFN-γ responses without protection, these findings emphasize the urgent need for more appropriate biomarkers to determine, and ideally predict, vaccine efficacy [20].

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