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Pediatric TB: What to Expect and When to Expect it

Case History

12/18/2010—A 34 year old Hispanic male was diagnosed with pulmonary tuberculosis based on clinical findings, positive AFB sputum smears and a Nucleic Acid Amplification test (NAAT) positive for *M. tuberculosis*. During the course of the subsequent contact investigation three pediatric contacts were identified aged 11 months, 4 years old and 15 years old. The contacts were the case's children and had been co-habiting with him.

12/22/2010—The children are evaluated for TB disease. The 11 month old and the 4 year old were asymptomatic but the 15 year old complained of cough. The 11 month old and the 4 year old children had tuberculin skin tests (TST) with 0mm induration while the 15 year old patient had a TST with 13 mm induration. All tests were read as negative.

The 15 year old contact was examined radiographically due to cough and the chest radiograph showed right upper lobe abnormalities consistent with cavitory tuberculosis. After cultures were obtained, the adolescent patient was started on a treatment regimen for active pulmonary tuberculosis consisting of rifampin, isoniazid, pyrazinamide, and ethambutol.

The four year old contact was examined clinically and radiographically and the findings were not indicative of active tuberculosis disease. The patient was initiated on daily isoniazid mono-therapy as window prophylaxis.

After clinical and radiographic examination the infant contact was diagnosed with miliary pulmonary tuberculosis along with subcarinal and hilar lymphadenopathy. The patient was admitted for gastric aspirates and underwent a lumbar puncture and cerebrospinal fluid (CSF) findings were not indicative of TB meningitis. The infant was started on isoniazid, rifampin, ethambutol and pyrazinamide.

On 2/24/11 the 4 year old contact was tuberculin skin tested a second time and the results were read as 10 mm (positive). Based on these findings the child was diagnosed with LTBI and treatment was extended to 9 months (including the 2 months already received). He completed treatment in September of 2011.

The adolescent completed 6 months of short course therapy in May of 2011. The infant completed a 9 month treatment regimen. Both children improved clinically and radiographically. The treatment courses of both children were uneventful.

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER

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NATIONAL TB CENTER

A PARTNERSHIP OF UT HEALTH SCIENCE CENTER AND TCID

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Epidemiology



The World Health Organization (WHO) estimated in 2009 there were approximately 1 million cases of pediatric TB globally; given disparities in reporting and diagnostic difficulties in children, this likely represents an underestimate. The majority of these cases are found in the developing world. In countries

with a high TB burden, pediatric TB constitutes 20-40% of the case load, as opposed to low burden settings where it only constitutes 4 - 7% (1, 3).

The global epidemiology of pediatric tuberculosis is difficult to describe accurately. Pediatric TB is significantly under diagnosed. Until recently only AFB smear positive cases were reported under the WHO DOTS strategy (3), however only 5% of children with TB are AFB smear positive and therefore most cases were not counted. Pediatric TB is more challenging to diagnose because children are less likely to be either smear or culture positive and providers must rely on clinical and radiographic findings as well as identification of exposure to adult cases. This challenge is magnified by limited diagnostic resources in many low income countries. These are the same countries which have the highest burden of pediatric TB and often lack the resources to conduct active case finding and good contact investigations.

Both the global TB epidemic and pediatric TB are fueled by many of the same factors. The HIV pandemic, malnutrition and the emergence of drug resistant disease are all factors sustaining pediatric TB globally.

A child's risk for contracting tuberculosis is directly related to the degree of contact and proximity to an active infectious case. The source of infection is usually an adult with cavitory tuberculosis. Children are generally not infectious, unless they have cavitory radiographs, draining skin lesions, or are smear positive. Although older adolescents have been known to transmit infection. Younger children tend to be infected by a household source and as they become older they become increasingly more likely to be infected outside the home, making source case identification more challenging (3). Social factors also play a role in the likelihood of a child being exposed to *Mycobacterium tuberculosis*. Children living in impoverished areas, in poor housing, and crowded urban environments are subject to increased rates of transmission (3).



The **MISSION** of the Heartland National TB Center is

to build capacity with our partners. We will share expertise in the treatment and prevention of tuberculosis by: developing and implementing cutting-edge trainings, delivering expert medical consultation, providing technical assistance, and designing innovative educational and consultative products.

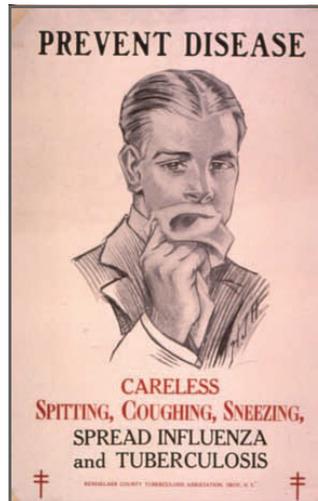
Pathophysiology/Immunology

Children are at increased risk of developing active tuberculosis once infected. They are also at increased risk for disseminated disease and poor outcomes (3). Infants are particularly vulnerable and have notably high morbidity and mortality rates. Young children, especially infants, are at an increased risk of acute hematogenous dissemination and tuberculous meningitis.

Most children and adults infected with TB do not progress to active disease. Progression to active disease is prevented by a successful immune response, associated with a strong T-Helper cell/CD4 lymphocyte response and adequate levels of interferon gamma. The response begins after the inhalation of *Mycobacterium tuberculosis* into the pulmonary alveoli. The tubercle bacilli are then phagocytized by the alveolar macrophages, dendritic cells and interstitial monocytes. During this period the mycobacteria undergo a period of uninhibited growth in the alveolar spaces or within non-activated macrophages. A complex response of cytokines develops, involving interferon gamma, TNF-alpha, interleukin-2 and -12. As a result of this response during the next 4 to 12 weeks an influx of CD4+ and CD8+ lymphocytes and activated macrophages occurs and they surround the tubercle bacilli causing granuloma formation (Ghon focus). This effectively halts replication of the mycobacterium. This stage is known as Latent Tuberculosis Infection (LTBI) and is achieved in 90-95% of healthy individuals. This is not always the case in young children.

The risk of progression from LTBI to active disease is increased in children, especially neonates and infants due to an underdeveloped immune system. The alveolar macrophages, the first level of resistance against tuberculosis, have shown a reduced bactericidal activity and monocyte engagement at the site of infection in infants compared to adults (3). This impairment may allow mycobacteria to overwhelm the innate immune system before the mounting of an antigen specific response can be mounted.

Untreated children with LTBI who are less than a year old have a 30 to 40% chance of progressing to active tuberculosis within two years of infection. This progression is rapid and can occur before the TST can become positive; this is the rationale behind window prophylaxis for preschool aged children. Five to 20% of children aged 1 to 5 and 10 to 20% of children 10 to 15 years old progress to active tuberculosis within 2 years of TB infection. Children between the ages of 5 and 10 years old have a considerably lower risk of developing active tuberculosis; this has been observed in multiple countries, and the physiologic reason behind this is unclear.



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The VISION of Heartland National TB Center is to provide *excellence, expertise, innovation* in training, medical consultation, and product development to reduce the impact of tuberculosis in our region.

Clinical Presentation

Children infected with tuberculosis are generally asymptomatic (7). After the initial infection there are 4 possible outcomes; containment (no disease), primary parenchymal disease, progressive primary disease and reactivation disease. (5)

Primary parenchymal disease is the most common form of TB disease in children(5). Adolescents and infants are more likely to be symptomatic and have physical indications of pulmonary disease, as opposed to 5 – 10 year olds who in many cases present with radiographic manifestations but lack clinical symptoms (5). Radiographically, children may present with segmental pneumonia due to bronchial compression of an airway with distal atelectasis, bulging of fissures, and calcifications (5). The most common radiographic finding in young children identified through active case-finding is intrathoracic lymphadenopathy (5,6).

Reactivation disease is most commonly seen in the adolescent population. It is a most common in areas where TB is endemic and HIV co-infected patients. Symptoms include weight loss, productive cough, fever, hemoptysis and night sweats. Radiographic findings may include apical involvement and cavitory disease.

Lymphadenopathy

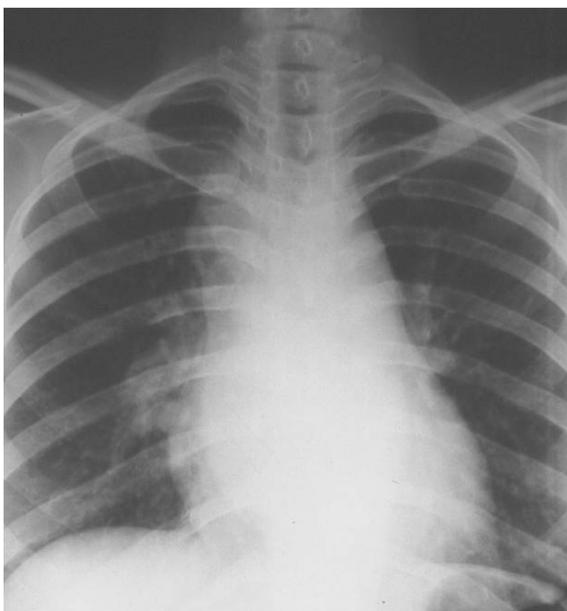


Photo courtesy of Andrea Cruz, MD

Half of children with asymptomatic tuberculosis have intrathoracic lymphadenopathy (5). For TB patient's of all ages, peripheral lymphadenopathy is the most common form of extrapulmonary TB (2), and account for 47 -67% of all pediatric extrapulmonary TB cases (2). Isolated mediastinal or hilar lymphadenopathy is generally asymptomatic and is frequently diagnosed serendipitously during the course of an assessment as part of a contact investigation. Sometimes the intrathoracic lymph nodes may not be radiographically visible, but lymph node compression on an airway segment may result in atelectasis. Another radiographic finding with enlarged intrathoracic nodes is extrinsic compression on the airway, which can sometimes be better visualized when a digital film is inverted in contrast. The most common symptom associated with intrathoracic lymphadenopathy is wheezing that is unresponsive to albuterol or other beta agonists. Subcarinal lymph nodes are most often involved, followed by hilar, anterior mediastinal, precarinal and right paratracheal lymph nodes. If left untreated lymph nodes continually enlarge and develop caseous necrosis. Involved extrathoracic cervical, axillary, and inguinal nodes will be tender to palpation and may develop an erythematous and fluctuant

center. The lymph node may suppurate and develop a chronic draining sinus tract. Subcarinal lymph nodes are at risk for extension into the pericardium.

Pleural Disease

Pleural involvement complicates 2 -38% of TB cases (5). Pleural TB can result either from reactivation disease or primary disease although the mechanism for the pleural effusion is fundamentally different in each circumstance. In the context of pediatric TB, pleural TB is most often associated with adolescents. The vast majority of immunocompetent children with pleural involvement will have a positive tuberculin skin test, cough, chest pain, lethargy, shortness of breath and anorexia.

Central Nervous System (CNS) TB Disease and Meningitis

In the developing world, tuberculosis is the most common cause of subacute meningitis and meningeal involvement is the most common form of CNS TB, followed by tuberculomas (which in TB hyper endemic areas are the most common cause of mass occupying lesions).

Central Nervous System (CNS) TB Disease and Meningitis (continued)

TB meningitis accounts for 9-16% of extrapulmonary TB in children. TB meningitis is an extremely common complication of miliary tuberculosis in children. Up to 50% of children with miliary tuberculosis also develop TB meningitis and the majority of these cases are in children younger than 2 years of age (5). The frequency of CNS TB in infants is the rationale behind performing lumbar punctures in any child in the first year of life in whom pulmonary TB is suspected. Recognition of CNS tuberculosis alters selection of antibiotics, route of administration, duration of therapy, the decision to use corticosteroids, and prognostic conversations with the family.

The clinical course of TB meningitis is divided into three stages. The first stage is the non-specific stage of prodromal symptoms. These symptoms include headache, nausea, and fever. The second stage is distinguished by the development of palsies of the III, VI and VII cranial nerves along with meningeal irritation which is heralded by symptoms such as facial paralysis, otalgia and diplopia. The third stage is characterized by the development of altered mentation and increased intracranial pressure. Unfortunately, most cases of TB meningitis are diagnosed during the 2nd or 3rd stages; these stages are associated with death or negative long term neurological sequelae (5).

The most common radiographic findings in pediatric patients diagnosed with TB meningitis is hydrocephalus which is present in more than 80% of cases. Ninety percent of children with CNS TB also have abnormal chest radiographs; findings may include intrathoracic adenopathy, parenchymal lung disease, or miliary disease. TB meningitis should be considered in any child with lymphocytic meningitis with elevated cerebrospinal fluid protein, particularly if associated with hydrocephalus or basilar enhancement. Tuberculomas are also a common manifestation of CNS TB, though less common than TB meningitis. Tuberculomas and meningitis may be present simultaneously in up to 10 % of cases(5). In contrast to adults, who often have multiple supratentorial tuberculomas, children are more likely to have single and infratentorial tuberculomas. Hilar lymphadenopathy, pulmonary infiltrates and miliary TB are all commonly found in children with TB meningitis.



Photo courtesy of Andrea Cruz, MD

Clinical Presentation: Skeletal TB

1 – 2 % of pediatric TB cases have skeletal involvement. This finding is due to the hematogenous spread of the tubercle bacilli to bone. Immunocompetent patients usually present with singular, axial skeletal lesions as opposed to immunocompromised patients who display multifocal osseous involvement. Most patients with skeletal TB are over ten years of age (5). Patients generally exhibit localized symptoms which include; pain on palpation, diminished range of motion and swelling. The most common manifestations of skeletal TB in pediatric patients are spondylitis, arthritis, and osteomyelitis. Spondylitis accounts for 50% of pediatric skeletal TB cases and the most common location is the thoracolumbar column (Pott's disease). The most common early symptoms of Pott's disease are low grade fever, back pain, irritability, and altered gait. Dactylitis is more common in patients under 5 years of age.

LTBI: Diagnosis

Latent tuberculosis infection (LTBI) is defined as asymptomatic infection with tubercle bacilli. A person with LTBI has no signs, symptoms or radiographic findings consistent with active TB. The United States (US) places an emphasis on diagnosing and treating LTBI as a primary mechanism for controlling and eliminating TB and to identify and treat vulnerable populations such as children who are more likely to progress from latent to active disease(young, malnourished or immunocompromised children) . US public health structures accomplish identification and treatment of children with LTBI through the use of targeted testing, which is defined as the testing of children with risk factors for either acquiring tuberculosis (household contacts) or for progressing from LTBI to active disease (infants). The American Academy of Pediatrics supports use of a 4 question screening history to identify children with risk factors (birth in or residence in a high-prevalence nation, contact with someone with TB or someone with a positive TST); children who are risk-factor positive should be screened by TST or IGRA(7).

LTBI: *Diagnosis (continued)*



Testing for LTBI is done through the use of assays that measure pre-existing *M. tuberculosis* specific immune responses. The Centers for Disease Control and Prevention (CDC) approved methods are the tuberculin skin test (TST) and the interferon gamma release assays (IGRA).

A positive TST usually develops 3 to 12 weeks after infection and approximately 80-90% of infected children will have a positive reaction (2). Younger, malnourished and immunocompromised children are less likely to have a positive reaction.

IGRAs are the preferred method of testing for LTBI in patients older than four years of age who have been immunized with Bacillus Calmette-Guerin (BCG). This test measures the interferon gamma production from T-lymphocytes with antigens relatively specific to *M. tuberculosis* complex. The specificity of IGRAs is higher in BCG vaccinated patients due to the fact the antigens used in IGRAs are not found in BCG so that there is no cross reactivity between BCG vaccination and IGRA response. Interferon gamma release assays can be used interchangeably with the tuberculin skin test in adults. Limited published studies indicate that IGRAs perform well in children 5 years of age and older. CDC guidelines recommend the testing of children < 5 using the tuberculin skin test. The CDC recommendations allow for the use of an IGRA or a TST without preference in children \geq 5 years of age.

A negative, inconclusive or indeterminate TST or IGRA does not rule out the presence of Latent tuberculosis infection or active disease. Ten to forty percent of children with culture documented TB disease did not initially react to a tuberculin skin test (7).

LTBI: *Treatment*

Prior to initiating treatment for LTBI, diagnostic tests should be performed to unequivocally rule out active TB disease.

In the US LTBI treatment in children is performed frequently via Directly Observed preventative therapy (DOPT). The recommended regimen is a 9 month course of Isoniazid chemotherapy dosed daily or bi-weekly.

Other treatment regimens have been approved by the CDC. These regimens include rifampin for duration of six months if isoniazid resistance or intolerance is an issue. The third regimen approved for the use in pediatric patients is the 12 weekly doses of Isoniazid-Rifapentine regimen. However, the CDC has approved this regimen for use only in children 12 and above.

Children less than 5 years of age are more susceptible to TB disease and more likely to develop lethal forms of tuberculosis. They are considered high priority contacts and undergo a full medical evaluation; including a chest radiograph. If the initial skin test is negative and it has been less than 8 weeks since the child's last exposure latent tuberculosis infection is presumed. Treatment is recommended (window prophylaxis) for LTBI as there is conclusive evidence that LTBI is not present. The child should have a repeat skin test at 8 to 10 weeks post-exposure. If the subsequent skin test is negative the decision to treat may be reconsidered, if the skin test is positive treatment for latent infection should be completed.

TB Disease: *Diagnosis*

The diagnosis of active tuberculosis in children is often challenging. Diagnosis of a young child with LTBI or active tuberculosis is considered a public health sentinel event and is indicative of recent transmission. Epidemiology, clinical history, tuberculin skin testing and chest radiographs are crucial to the diagnosis of pediatric tuberculosis. Identification of the tubercle bacillus by AFB sputum smear and culture is unreliable in the pediatric population compared to adults. Due to fact that AFB smear and cultures are often undependable every effort should be made to locate/diagnose the source case (source of infection) for the

TB Disease: *Diagnosis (continued)*

Active tuberculosis in children is diagnosed on the basis of acid fast staining, microscopic examination and culturing of pleural fluid, bronchial washing, gastric aspirates, cerebrospinal fluid, other bodily fluid or biopsy samples. It is difficult to diagnose active tuberculosis in pediatric patients because children are usually unable to produce sputum; early morning gastric aspirates are frequently helpful. A positive culture for *M. tuberculosis* from any source is diagnostic for active tuberculosis (6).

Nucleic acid amplification tests (NAAT) are another type of test which can aid in the diagnosis of active tuberculosis in pediatric patients. These tests detect specific nucleic acid sequences by hybridization to a complimentary probe. Further study is required before NAATs can be recommended for the diagnosis of pediatric tuberculosis (7). Pediatric patients are generally unable to produce sputum; NAATs have been noted to have decreased sensitivity in gastric aspirate, cerebrospinal fluid and other tissue specimens compared with sputum in adults with TB.

TB Disease: *Treatment*



The treatment of active tuberculosis is comprised of multiple drugs to increase the bactericidal and bacteriostatic effects of the regimen and prevent the development of drug resistance. The treatment of pediatric tuberculosis mirrors the treatment of adult disease. Active pediatric tuberculosis disease is initially treated with a 4 drug regimen that is comprised of rifampin, isoniazid, pyrazinamide and ethambutol. The 4 drug regimen is used for 2 months after which, if the patient's *Mycobacterium tuberculosis* isolate is not drug resistant isoniazid and rifampin treatment is continued for a further 4 months.

Short course therapy (6 months) is generally sufficient for drug susceptible pediatric pulmonary

and extrapulmonary disease. CNS TB, most notably meningitis is an exception to this rule and requires extended therapy.

Most experts would initially institute a 3 drug treatment regimen (INH/Rmp/PZA) if the causative organism is confirmed pan-susceptible or the index case for a small child has drug susceptible TB. Ethambutol is omitted by certain experts due to the possibility of optic neuritis. Ethambutol is rapidly metabolized by children of any age likely resulting in the infrequent visual toxicity. If there is clinical concern for TB disease and drug susceptibility is unknown, clinicians should feel comfortable using ethambutol in children of any age, even in the pre-verbal child in whom visual acuity monitoring may be challenging. Children receiving ethambutol should be continuously monitored for visual acuity throughout the course of treatment (7).

Teaching Points

- Most infections caused by *M. tuberculosis* complex are asymptomatic in children. (This includes LTBI as well as active disease)
- Young children are more likely to develop disseminated disease, due to their underdeveloped immune response. This is especially true in children under 2 years of age. TB meningitis is a frequent complication of active TB disease in infants, and can have a rapid onset and devastating neurologic sequelae.
- A negative or inconclusive IGRA or TST does not rule out the presence of infection or the presence of TB disease.
- Inconclusive IGRAs are more common in young or immunocompromised children.

Teaching Points (continued)

- Children are often unable to produce sputum; a positive culture for *M. tuberculosis* from any source is diagnostic for active tuberculosis (6). However, negative acid fast cultures should never exclude tuberculosis disease in a child if the clinical, radiographic, and/or epidemiologic findings are concerning for TB.
- Diagnosis of a young child with LTBI or active tuberculosis is considered a public health sentinel event and is indicative of recent transmission. Every effort should be made to identify the source case for a pediatric TB patient.
- LTBI therapy should not be initiated unless active TB disease has been ruled out with certainty by history, physical examination, and chest radiography.
- Short course(6 month) therapy is usually sufficient for treatment of susceptible pulmonary tuberculosis and some forms of extrapulmonary disease in children. CNS TB disease requires extended treatment regimens(9-12 months).
- Children receiving a treatment that includes ethambutol should be monitored for visual acuity throughout the course of treatment. Optic neuritis has been associated with ethambutol in children but reports of this are rare in children with adequate renal function. (Ethambutol is rapidly metabolized by children of any age likely resulting in the infrequency of visual side effects reported in children. If there is clinical concern for TB disease, clinicians should feel comfortable using ethambutol in children of any age, even in the pre-verbal child in whom visual acuity monitoring may be challenging.)
- Pediatric TB is usually not infectious but post-pubertal are more likely to have adult type cavitory disease and are more likely to be infectious due to an increased bacterial burden and increased tussive force.

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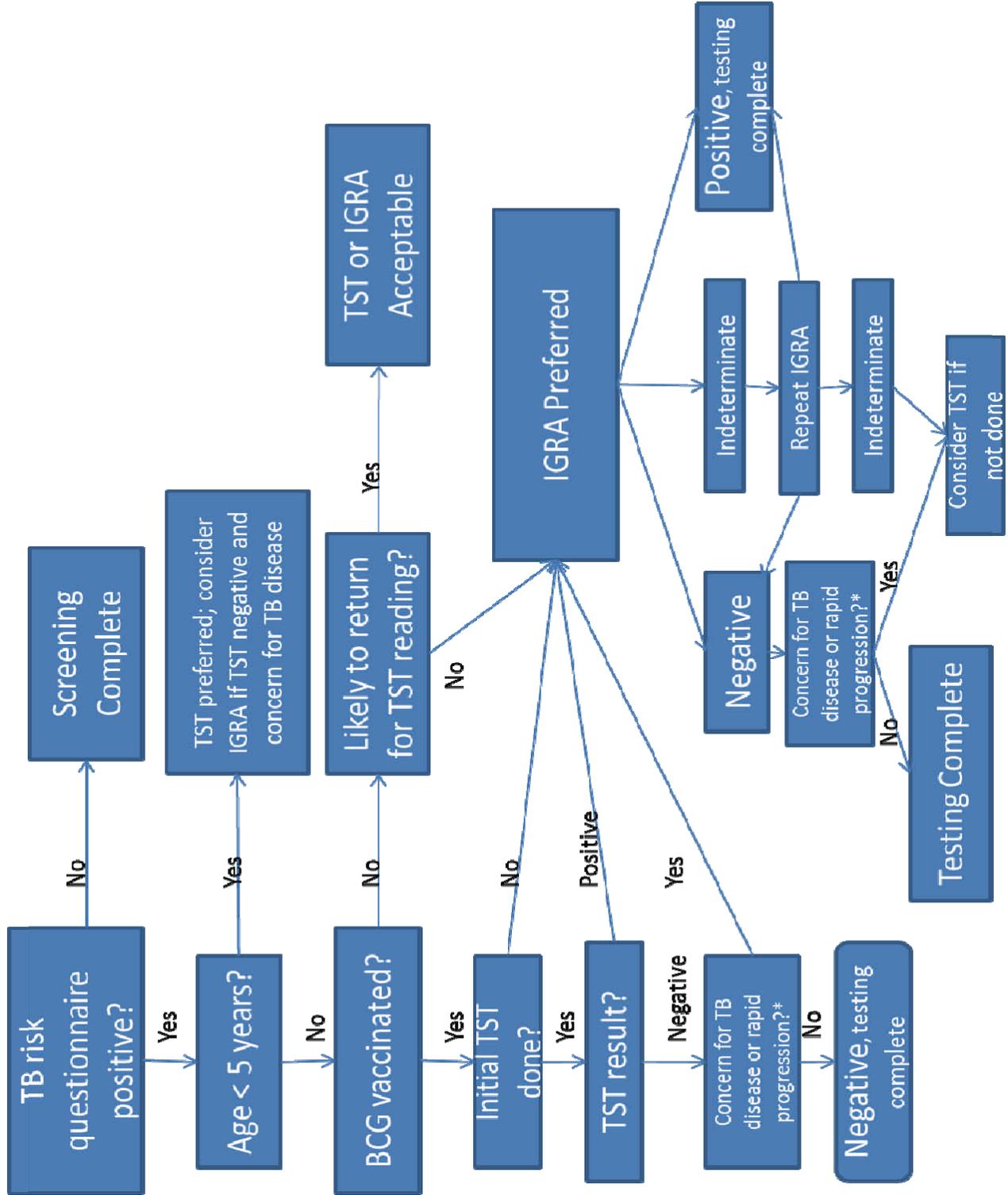
Written and Reviewed by the following:

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Algorithm for TB Testing in Children
 Produced by Kim C. Smith, MD, MPH
 University of Texas Houston Medical School

Algorithm for TB Testing in Children



*Either positive TST or IGRA considered significant if clinical suspicion of TB disease or risk for rapid progression

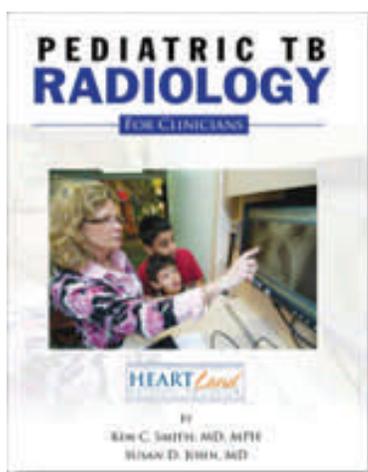
Introducing...



Sam Caballero, M.A. joined the staff as **Director of Education and Training** in May 2012. Sam has an associate's degree in training & development, a bachelor's in urban studies and a master's in management. Sam comes to Heartland with experience in the areas of adult learning, workshop design and development, and learning management. His (20 years) experience in training, course creation, facilitation and project coordination is drawn from a variety of backgrounds including the Air Force, City of San Antonio's Code Compliance Department, Burger King, and Chevron Oil Company. Sam is also a proud member of the Air Force Reserves at Joint Base San Antonio – Lackland where he was awarded Master Instructor for the Air

Education and Training Command. He is a member of the American Society of Training & Development and is fluent in English and Spanish.

Highlighting....



Pediatric TB Radiology for Clinicians By **Kim C. Smith, MD, MPH** and **Susan D. John, MD**

This book shows and describes examples of radiographic abnormalities common in pediatric tuberculosis, emphasizing pulmonary, lymphatic, and meningeal disease. The utility of CT scan and MRI in pediatric TB are also discussed. Radiographs and case studies are used as illustrations throughout the book.

TB LINKS

TB Education and Training Network

<http://www.cdc.gov/tb/education/Tbetn/default.htm>

Find TB Resources

www.findtbresources.org

Tuberculosis Epidemiologic Studies Consortium (TBESC)

<http://www.cdc.gov/tb/topic/research/TBESC/default.htm>

Regional Training and Medical Consultation Centers' TB Training and Education Products – (Joint RTMCC Products Page)

<https://sntc.medicine.ufl.edu/rtmccproducts.aspx>

Program Collaboration and Service Integration (PCSI)

<http://www.cdc.gov/nchhstp/programintegration/Default.htm>

If your organization has any additional links for TB resources you would like published, please send them to Alysia.gibbons@uthct.edu

2012 HNTC Training Calendar

Date	Course	Location
September 18–20	TB-ETN	Atlanta, Georgia
October 4, 11, 25	Introduction to TB Nurse Case Management	ONLINE COURSE
October 19	Interferon Gamma Release Assays	McKinney, Texas
October 23-24	Four Corners TB/HIV Conference	Durango, Colorado
November 7–9	TB Nurse Case Management / TST Practicum	San Antonio, Texas
December 5–7	TB Intensive	San Antonio, Texas

The calendar will be updated in every newsletter as well as on the website to show trainings that have been confirmed

Please visit our website: <http://www.heartlandntbc.org/training.asp> to find detailed information concerning registration and participation. Proposed topics are subject to change; check website for the latest updates.

Products from the Heartland National TB Center are available for download at <http://www.heartlandntbc.org/products.asp>

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New TB Patient Teaching Checklist from the Minnesota Department of Health

The Minnesota Department of Health (MDH) TB Prevention and Control Program posted a new document titled "Tuberculosis Patient Teaching Checklist." This Microsoft Word template includes teaching points and links to patient education sheets and is modifiable for local public health nurses who work with patients with active TB. The checklist was developed by MDH in collaboration with local public health nurses in Minnesota. MDH has other TB patient fact sheets in the following 15 languages: Amharic, Arabic, Bosnian/Serbian/Croatian, French, Hmong, Karen, Khmer, Lao, Nepali, Oromo, Russian, Somali, Spanish, Tibetan, and Vietnamese. To view and download, go to <http://www.health.state.mn.us/divs/idepc/diseases/tb/patchecklist.doc>

Questions? Please contact Ann Sittig, Nurse Consultant at MDH, at Ann.sittig@state.mn.us or 651-201-5549.

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