Tuberculosis in Children and Adolescents 2012-Part II

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#4. “Have never seen him, didn't know he existed”….Dr. Barry Kreiswirth says you have and you did....or, the DNA doesn't lie....

“Have never seen him, didn't know he existed”....

- 21 month old boy is admitted to the hospital due to severe dehydration brought on by 2 days of vomiting.
- He had fever, was lethargic, and had had no urine output for 12 hours
- Bilious vomiting is noted suggesting intestinal obstruction
  - X-rays and CT scan of the abdomen are done:
Have never seen him, didn’t know he existed”....

- Child undergoes emergency laparotomy and ileostomy
  - 2 ft. of necrotic small intestine is removed
    - Hemorrhage, necrosis, multiple granulomas noted in bowel wall and the mesentery
    - Cultures of gastric drainage grow Mycobacterium Tuberculosis
    - Thrombosis of small vessels
- Months of hospitalization (Acute and rehab)
  - Two additional surgeries
  - NGT placed for feeding
  - Has to re-learn to eat and walk
- Months of outpatient rehab and TB treatment

Have never seen him, didn’t know he existed”....

- Children are usually infected by an adult or adolescent in the immediate household
  - Source case investigation:
    - Paternal grandmother with “chronic lung disease”
    - Diagnosed with smear/culture positive pulmonary TB 8 months previously
    - Did not name grandson or his family in contact investigation maintaining: “Have never seen him, didn’t know he existed....”
  - Dr. Kreiswirth’s opinion:
    - RLFP: Match between grandson and grandmother

The High Cost of Missed Opportunities

- Missed opportunities documented:
  - Failure to find and appropriately manage adult source cases (Case finding)
  - Contact investigation interview failure
  - Delay in evaluation of exposed children
  - Failure to completely evaluate exposed children
  - Failure to prescribe prophylactic INH
  - Failure to complete treatment for LTBI (Adherence)

- Resulted in: 20 cases of TB in children (23 total cases):
  - 3 miliary
  - 1 TBM, 1 GI TB
  - Extended hospitalizations (acute and rehab), CIs, DOT
AAP Recommendations: Targeted TB Testing

• What is Targeted TB Testing?
  – Identifies persons at high risk for TB who would benefit by treatment of LTBI

• Risk of exposure to TB should be assessed at routine healthcare evaluations:
  – Risk Assessment Questionnaire
  – Only children with an increased risk of TB infection or disease (a positive response to a question on the questionnaire) should be considered for tuberculin skin testing

Why Use Risk-Assessment-Based Targeted TB Testing?

• Why not use routine, universal, administratively mandated TB testing? Why not use the TST or IGRA as the screening tool?
  – Daycare
  – Schools
  – Colleges
  – Summer camps

• Answer: Limitations of the TST (Mantoux Skin Test)/igra
  – Universal testing means that large numbers of low risk children will be tested
  – Even if the specificity of the TST approaches 99%, testing of persons in low-prevalence groups would result in mostly false-positives
  – IGRA specificity reduces but does not eliminate all false positives in low risk population

Targeted TB Testing

• Risk assessment:
  – Signs and symptoms consistent with TB disease
  – Contact and source-case investigations
  – >1 risk factor identified on screening risk-assessment questionnaire
    • General pediatric practice
    • School-based healthcare
  – High risk of progression due to underlying conditions

Targeted TB Testing Risk-Assessment Questionnaire

• Has a family member or contact had TB disease?
• Has a family member had a positive TB skin test?
• Was your child born in a high-risk country (i.e. outside US, Canada, Australia, New Zealand, or Western European countries)
• Has your child traveled to a high-risk country and spent >1 week with the resident population?

Red Book 2009
**Using the Risk Assessment Questionnaire**

- At first contact with child and every 6 months until age 2 years
- After age 2 years, ask risk assessment questions every year if possible
- Anytime a risk factor is identified, a TST or IGRA should be performed

Red Book 2009

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**BCG Vaccine and Tuberculin Skin Testing**

- History of a BCG is never a contraindication to tuberculin skin testing
- Interpretation of TST results in BCG recipients is the same as for people who have not received the vaccine
- Difficult to distinguish between (+) TSTs caused by infection with *M. tuberculosis* and those caused by BCG
  - Reactivity does not occur in some children after receipt of BCG
  - If BCG does cause a positive TST, the reaction is generally negative by 6 years of age
  - If child is from a high-burden country, (+) PPD is almost always due to LTBI
- Therefore, management of children with a history of BCG and a (+) TST includes:
  - Diagnostic evaluation including a chest radiograph
  - Appropriate treatment

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**Interferon gamma release assays: Use in children**

- Published experience less in children
- Can be used in children ≥5 yrs of age
- May be useful in children who received BCG vaccine
- Do not distinguish between LTBI and TB disease
  - Negative IGRA does not rule out either in child with suspicious findings
- Interpretation of negative IGRA in child with (+) TST is not clear
  - No longitudinal studies to establish negative predictive value

AAP Red Book 2009

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**Evaluation of the Child with a positive TB test (TST, IGRA)**

- Evaluation of all children with a positive TB test should include:
  - A careful history for symptoms of disease
  - Physical examination
  - Chest radiographs (PA & lateral)
  - Household investigation
Treatment of Latent Tuberculosis Infection

- INH 10-15 mg/kg (max., 300 mg) PO daily for 270 doses
  - Efficacy approaches 100%
- Alternative: Twice weekly directly observed (DOT) INH 20-40 mg/kg (max., 900 mg) PO for 72 doses
- Monitor index case isolate sensitivities
- Hepatotoxicity from INH is rare in children:
  - A monthly assessment for clinical evidence of hepatotoxicity should be made: malaise, loss of appetite or weight, nausea, vomiting, abdominal pain, jaundice
  - Routine monitoring of LFTs is not indicated

- Rifampin 10-15 mg/kg/day (max. 600 mg) po daily for 6 months is an alternative
  - INH not tolerated
  - Index patient isolate INH-resistant
- MDR-LTBI: TREAT???? NOT TREAT????
  - Treatment can reduce risk of disease by up to 2/3
  - Regimen based on susceptibilities of index patient isolate
- Child from a country with “a lot of resistance” shouldn’t treat with more than just INH? No.

What about INH-RPT for children?

- Children >12 years of age: Recommended as equal alternative to 9 months of INH
- Children 2-11 years of age: INH for 9 months recommended
  - INH-RPT: Insufficient safety and efficacy data to recommend universal use in this age group
  - INH-RPT: An option if completion of 9H unlikely and likelihood or hazard of TB is great
- Children <2 years of age: INH for 9 months recommended
  - INH-RPT: Not recommended
  - Lack safety and pharmacokinetic data in this age group

How Children with Tuberculosis are Identified

- Presentation with a symptomatic illness
- Discovery of a child with pulmonary tuberculosis during contact investigation of an adult with tuberculosis
  - Few or no symptoms
  - Evaluation: (+) TST and abnormal CXR
  - In some areas of U.S. up to 50% of children with PTB are discovered in this manner
    - Before significant symptoms have developed
Pediatric TB Cases by Site of Disease, 1993–2008

Any extrapulmonary involvement* (totaling 29.1%)
- Lymphatic 18.9%
- Meningeal 3.1%
- Miliary 1.5%
- Bone & Joint 1.5%
- Other 4.1%

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both are counted in mutually exclusive categories

**Pediatric TB Cases by Case Verification Criterion**, 1993–2008
N=17,502

Mycobacteriologic Diagnosis of Tuberculosis

**Adults:** 70-90% have a sputum that is (+) for *M. tuberculosis*

**Children:**
- Tubercle bacilli are relatively few in number
- Sputum generally cannot be obtained from children <10 yrs old
- Gastric aspirates in children with PTB
  - 30-40% sensitive in children
  - 60-70% sensitive in infants
- Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates

Difficulties in the Diagnosis of Tuberculosis in Children

- Children are often asymptomatic or symptoms are nonspecific: Fever, poor appetite, poor weight gain or weight loss
  - Approximately 25-30% of disease is extrapulmonary
  - Meningitis and miliary disease tend to develop soon after infection
    - 70-80% occur in children 0-4 years of age
- Epidemiologic link (The adult source case)
  - Crucial to identify the adult source case for the child
    - Provides strong evidence that the child suspected of having TB disease actually has TB
    - May be the only isolate available for susceptibility testing
Difficulties in the Diagnosis of Tuberculosis in Children

- Physical examination may be normal
- TST may be negative (10%)
- Chest radiograph: Any lobe of the lung may be involved
  - Good technique/Experience with children
  - Two views
  - Careful interpretation
Tuberculosis in Adolescents

- Adolescents develop tuberculosis in one of two ways:
  - Reactivation of infection acquired during childhood
    - Chronic pulmonary tuberculosis
    - The closer to puberty at the time of infection the greater the risk of reactivation
  - Progression of infection acquired during adolescence to disease:
    - Classic primary disease
    - Progressive primary pulmonary tuberculosis
    - Chronic pulmonary tuberculosis
• Constitutional symptoms often more prominent than respiratory symptoms
  – Weight loss and fever are very common
  – Cough, chest pain, hemoptysis
  – Drenching night sweats occur several times per week
• Cavitary lesions frequently seen
Another missed opportunity:

Can you die from TB if you are a teenager?

OR

Another example of why LTBI is important

AND

Sometimes you just have to buy ‘em an air conditioner

Case

- 8-year old girl, recently arrived from Haiti was evaluated at the DOH for a 12 mm TST reaction
- There were no symptoms of TB disease and PE was normal
- A chest radiograph was done:
Case

- INH 200 mg po once daily; #30 tabs were dispensed
- There are no notes in the chart until 6 months later when the following is written: “Overdue for medication refill.”
- There were no further notes...until 5 years later.

Hospital Admission

- The pt., now 13-years of age was admitted to an outside hospital with a 3 week history of fever, cough, increasing dyspnea, weakness
  - She had been sent home by the school nurse on 4 occasions over 2 months for the fever and cough and then for weight loss and weakness
  - She was seen on 2 occasions by her PCP and was given antibiotics (azithromycin) And twice in EDs of local hospitals:
    - The last ED visit was 9 days PTA when chest radiographs were done and amoxicillin-clavulanate (Augmentin) was given
    - There was no improvement with antibiotic

Case

- PE: Cachetic, weak appearing female with flat affect and in mild respiratory distress
- T – 103.2°F, HR – 160’, RR – 22’, O₂ sat = 92%
- Wt: 78.7 lbs, UBWt.: 96.7 lbs
- Admitted
- Treatment IV ceftriaxone and oral azithromycin
Case

- **Sputa sent:**
  - Smear: Few AFB; culture (+) MTB; pansensitive
  - Smear: Few AFB; culture (+) MTB
  - Smear: Rare AFB; culture (+) MTB

- **Anti-TB medications started:**
  - INH 300 mg po daily
  - RIF 600 mg po daily
  - PZA 500 mg po, three times a day
  - Emb 400 mg po, twice daily

- Received letter from local pediatric TB doctor and doses were adjusted
- Ensure given tid

Case

- No notes on chart from 7/2-7/7
- Concern with continued fever, a short note appears in the chart:
  - Please arrange social service consult for pt. “noncompliance” with medications, family safety.
  - ? Should we obtain court intervention? Or possible referral to DYFS?
- Health insurance medical director recommend conference call between PCP and a Dr. Lee Richman of TB Center at UMDNJ in Newark

Case

- 7/12: Discharge
  - Remains febrile
  - Came directly to Hudson County Chest Clinic with “TB escort” and brother and sister
  - Cachetic, weak with unsteady gate
  - Continued treatment added supplement, ibuprofen
  - DOT by RN
  - Home visit by CRNP (ped NP)
    - Weak, tires easily, bed ridden, bed-bathroom, bedroom had no windows, home was very warm (no AC)
    - Poor oral intake
    - Tachypneic, tachycardic
Case

- 7/19: Wt 72 lbs
- 7/24: CT scan chest (high resolution)
  - Call from CRNP, pt. very weak, tachypneic, may need admission

Case

- Hospitalized 7/24-8/17: TB, weaker, hypoxia, cachexia; wt down to 66 lbs
- RR - 40’ O₂ sat 90%
- Continued TB meds; oxygen
- NGT placed for continuous nutritional supplementation
- Gradually regained strength and began to walk
- Discharge: 8/17 RR – 20’ on 1L oxygen; Wt 76 lbs
  - TB meds and supplement
  - AC purchased and placed in home

Case

- 8/23: Wt. 88 lbs; RR = 18’ O₂ sat 97% on RA
- 9/20: Wt. 97 lbs; RR = 18”
- 11/1: Wt. 99 lbs
- 12/13: Wt 102 lbs

What happens to adolescents who survive the healthcare system and TB? Some become all-state volleyball players (actually many!), All-American college softball players, summa cum laude college graduates in IT, physicians
Treatment of Tuberculosis in Children and Adolescents

- If INH resistance rate >4% or if other risk for resistance include four drugs in initial regimen:
  - Isoniazid (10 mg/kg/day, range 10-20, max. 300)
  - Rifampin (15 mg/kg/day, range 10-20, max. 600)
  - Pyrazinamide (20-30 mg/kg/day)
  - Ethambutol (15-25 mg/kg/day)

- Treatment complicated by child unfriendly preparations of the medications
- Directly observed therapy (DOT)
- Monitor LFTs – Depends on severity of disease
- Follow susceptibility studies of Mtbc isolate (Index and/or child isolate)
  - Important to be familiar with resistance patterns in the community

Difficulties in Treatment

- Lack of symptoms initially
- Lack of observable improvement
- Lack of culture “proof”
- Education of the caregiver
- Multiple caregivers
- Chronic dosing
- Language/cultural differences
- Child unfriendly dosing forms
- Communication with the child

Negotiating a Plan for DOT

- Establish plan for DOT while patient is in the hospital or at first out-patient visit
  - Assess child/family
  - Coordinate necessary resources/services
  - Individual treatment regimens:
    - Time/food/place/who
    - Daily vs. intermittent
    - Involve outreach worker/school nurse
  - Plan should be discussed with child and family
  - Renegotiate if non-adherence occurs

Assessing Adherence Barriers

- Parents: Adherence can be influenced by:
  - Parenting skills
  - Motivation
  - Personal health beliefs, stigma
  - Other competing life circumstances

- In children and adolescents adherence can be influenced by:
  - Developmental level
  - Behavioral characteristics
**School-Based DOT**

- School nurse can administer DOT in school
- Clinician will provide regimen for nurse to follow
- School nurse can give feedback to clinician on frequency of dosing that works well for child (medication must be given only once a day, but can vary the amount of times per week as per physician order)
- School nurse can also provide feedback on child’s medical condition

**TB Clinic: Non-TB Diagnoses among Immigrant Children**

- Bacterial pneumonia: S. aureus, S. pneumoniae
- Sinusitis
- Brain tumor, lymphoma
- Psychoses-schizophrenia
- Cystic fibrosis
- Diabetes mellitus
- Glomerulonephritis
- Lead poisoning: By chest radiograph
- Scoliosis
- Scabies: Entire families
- Tinea corporis

*Aguiia H. Tortoriello S. Personal Communication 2010*

**Indications for Isolation of the Hospitalized Child with Pulmonary Tuberculosis**

- Most children with tuberculosis are not contagious and require only standard precautions
- Exceptions are:
  - Potential adult source case not yet identified
  - Cavitary disease
  - Laryngeal involvement
  - Extensive pulmonary disease
  - (+) sputum AFB smears
  - Suspected congenital tuberculosis
  - Productive cough

**Summary**

- Reported cases of tuberculosis in the U.S.:
  - More than 2/3 occur in nonwhite racial and ethnic groups
  - More than 50% occur in foreign born persons
  - Among children case rates are highest in infants and postpubertal adolescents
- Children are usually:
  - Infected by adult or adolescent household contacts
  - Not infectious (contagious)
- Contact investigations and targeted TB testing are mainstays of TB control in the U.S.
  - Evaluation of TB-exposed child: PA, CXR, window prophylaxis
  - Risk assessment questionnaires are the most effective screening tool to detect children at risk for LTBI
- TB diagnosis in young children requires a high index of suspicion
- DOT is key to successful treatment