Tuberculosis Updates for Clinicians
San Antonio, Texas
November 13, 2008

Diagnosing Tuberculosis in Pediatric Patients
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November 13, 2008

Childhood Tuberculosis
Kim Connelly Smith
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OUTLINE

• Differences of disease in children and adults
• Diagnostic challenges of pediatric TB
• Radiographic findings
• New diagnostic tests & research
• Clinical Cases

Percent Risk of Disease by Age

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Risk of Active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 1 year*</td>
<td>43%</td>
</tr>
<tr>
<td>1 – 5 years*</td>
<td>24%</td>
</tr>
<tr>
<td>6 – 10 years*</td>
<td>2%</td>
</tr>
<tr>
<td>11 – 15 years*</td>
<td>16%</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>5 10% lifetime risk</td>
</tr>
<tr>
<td>HIV Infected Adults+</td>
<td>30-50% lifetime</td>
</tr>
</tbody>
</table>

*Miller, Tuberculosis in Children
Little Brown, Boston, 1963

WHO, 2004

**Note:** The term “Tuberculosis” is now more commonly referred to as “Tuberculosis” in public health literature. The term “TB” is still commonly used in medical contexts.

Image: Billboard promoting awareness of tuberculosis, emphasizing its curability and preventability. The message reads, “If you are not infected or have a cough, get a medical examination.”
### Risk of Progression to TB Disease by Age

<table>
<thead>
<tr>
<th>Age @ primary infection</th>
<th>Risk of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth - 12 months</td>
<td>Disease 50%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Dis 30-40%</td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM 10-20%</td>
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<tr>
<td>1-2 years</td>
<td>Disease 20-25%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Dis 75%</td>
</tr>
<tr>
<td></td>
<td>Miliary of TBM 2.5%</td>
</tr>
</tbody>
</table>

Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402

### Differences In Adult and Pediatric TB
**Reactivation Disease**

- Occurs years after primary infection
- Typical of adult disease
- Occasionally seen in teens
- Often cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious

**Primary Disease**

- Typical of childhood TB
- Usually not cavitary
- Most common x-ray: pulmonary infiltrate with or without hilar adenopathy
- Low numbers of organisms
  - AFB smears negative in 95% of cases
  - Culture negative in 60% of cases
- Not contagious in children < 12 yrs
- Often asymptomatic (50%)
Radiographic Findings

- Primary TB has variable and often non-specific appearance on imaging
- Lymphadenopathy a key finding
- Sometimes advanced imaging helps when radiographs are suggestive or confusing
Adult TB Disease

- 85% Pulmonary
- 15% Extrapulmonary

Adult Extrapulmonary TB Disease (15%)

- 25% Lymphatic
- 23% Pleural
- 16% GU
- 13% Other
- 10% Bone/Joint
- 9% Miliary
- 4% Meningeal

CDC
Pediatric TB Disease

- Pulmonary: 75%
- Extrapulmonary: 25%

Extrapulmonary TB Disease in Children (25%)

- Lymphatic: 6%
- Bone/Joint: 5%
- Miliary: 14%
- Pleural: 67%
- Meningeal: 14%
- Other: 5%

CDC
Lymphadenopathy Case

Clinical Case
Cervical Lymphadenopathy

- 8 yr old with cervical lymphadenopathy
- **History:**
  - LAN for 3 months
  - PMHx: Healthy
  - BCG vaccine at birth
  - TB skin test 15 mm
- **Physical Exam:**
  - 3 cm anterior cervical LAN
  - 1.5 cm supraclavicular lymphadenopathy
- **CXR:**
  - Hilar LAN, no infiltrates
- Is this TB disease?
- What else could it be?
Hilar & Cervical Lymphadenopathy

**Differential Dx**
- Tuberculosis
- Non TB mycobacteria (NTM)
- Lymphoma/Leukemia
- HIV
- Other causes

**Diagnostic tests**
- Biopsy (FNA or surgical for culture and path)
- Interferon \( \gamma \) Blood test for TB infection

**Results**

- **Fine needle aspirate of node:**
  - Pathology: lymphoma, no TB by culture or microscopy

- **Interferon \( \gamma \) Blood test for TB**
  - Positive
  - Diagnostic for latent TB infection or disease

- **Diagnoses:**
  - LTBI
  - AND
  - Lymphoma

- **Treatment:**
  - Chemotherapy for lymphoma AND
  - INH daily for 9 months for LTBI
  - continued treatment during immunosuppression
Diagnosis for TB in Children

- **Gold Standard** – Positive TB Culture
  
  OR, Clinical Diagnosis:

- Abnormal CXR, laboratory, or physical examination consistent with TB **AND**

  1 or more of the following:
  
  - Positive tuberculin skin test
  - Contagious adult source case identified
  - Clinical course consistent with TB disease
  - Improvement on TB therapy

Work Up for TB Disease In Children

Hospitalization Standard if Source Not Known

- **Gastric aspirates**
  
  - 3 early morning specimens
  - Sample of overnight swallowed pulmonary secretions from stomach

- **Induced sputum**
  
  - May be worthwhile in children >4 yrs

- **Bronchoalveolar lavage (BAL)**
  
  - Requires anesthesia, day surgery procedure
  - Single specimen with similar yield to 3 GA’s
  - Consider if pt needs bronch for other reasons

- **When to get CT scans**

- **When to biopsy lymph nodes**
AFB smears and Cultures in Children and Infants

- **AFB smear usually negative**
  - In 95% of patients <12 yrs of age

- **Low yield on TB culture**
  - Only 40% positive in children 1-12 yrs of age with pulmonary TB

- **Infants with pulmonary TB**
  - 60-70% cultures positive
  - Sometimes AFB smear positive
  - Adult source case important

Expected Clinical Course for TB Disease in Children

- **Pulmonary**
  - CXR takes months to improve

- **Hilar lymphadenopathy**
  - May take year or more to regress on x-ray

- **Lymphadenitis**
  - Gets worse before improvement

- **Meningitis**
  - Inflammation increases initially with treatment
  - Steroids important for 1st month
  - Hospitalization for 1st month recommended
Interferon-γ Release Assays (IGRA) 
Blood test for TB

- **MTB specific antigens:**
  - Genes in region of difference (RD1) on MTB genome
  - Culture filtrate protein 10 (CFP 10)
  - Early secretory antigen target 6 (ESAT-6)
- **Stimulate T-Cell production of IFN-γ**
- **Diagnosis LTBI &/or disease**
- **Does not cross react with BGC vaccine or most other mycobacteria**
- **Requires:**
  - single medical visit
  - blood collection
  - laboratory equipment and personnel
- **Results in 24 hrs**
- **Little published data in children**

Commercial IGRA Tests

**QuantaFERON-TB Gold or In Tube**
Company: Cellestis, Australia
FDA approved for adults

- **Method:**
  - Whole blood
  - IFN-γ measured by ELISA reader

**T-Spot TB or ELISPOT**
Company: Oxford Immunotec, United Kingdom
FDA approved for adults

- **Method:**
  - T-cells separated
  - Spots counted manually or by reader
**Meta-analysis of 58 IGRA Studies**

- **Sensitivity*** similar
  - IGRA’s & TST 70-88%
- IGRA’s show excellent **Specificity**+
  - IGRA tests 92-97%
  - TST (due to BCG & NTM cross reaction) 66%
- **Pediatric** data insufficient
  - TB diagnosis more difficult in children
    - No Gold standard for LTBI
    - Not enough published data

*Sensitivity in pts with active TB, Cx = Gold standard
+Specificity in healthy low risk patients without TB

Sensitivity of TST vs ELISPOT
693 Children Exposed to Active TB in Gambia

TST positive 32.5%
ELISPOT positive 32.3%
83% agreement Between tests


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Recent Pediatric Published Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Tests</th>
<th>Population</th>
<th>Results</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detjen 2007</td>
<td>Germany</td>
<td>T-Spot.TB, Qft-IT, TST</td>
<td>73 Children 4mos-15yrs 28 culture +</td>
<td>Sens 93% Spec 98-100% PPV 96-100%</td>
<td>3 false neg IGRA's in Cx+, TST+</td>
</tr>
<tr>
<td>Ferrara 2006</td>
<td>Italy</td>
<td>T-Spot.TB, Qft-Gold TST</td>
<td>96 Children (6% &lt; 5yrs) 393 total pts 24 disease 11 culture +</td>
<td>More T-Spot + in contacts &amp; dz 32% indet Qft-Gold in &lt;5yr (7/22 children)</td>
<td>3 false NEG IGRA's in Cx+ TST-patients</td>
</tr>
<tr>
<td>Connell 2008</td>
<td>Australia</td>
<td>T-Spot.TB, Qft-IT TST</td>
<td>96 Children 6mos-19yrs 9 clinical TB</td>
<td>Contacts: +TST&gt;5 +IGRA 42-45% Disease: +Qft-IT +T-Spot 8/9 9/9</td>
<td>Contacts: +Tst/-IGRA 1 pts Of 7 TST&gt;15, 3 no BCG hx</td>
</tr>
</tbody>
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Texas Pediatric T-SPOT.TB Study
Compared TST, T-SPOT and Clinical Dx

- Total children: 212
- Excluded: 9
  - Lab error: 2
  - Missing clinical data: 7
- LTBI: 126
- TB disease: 32
  - 19 culture positive
- Negative controls: 87
- Discordance (TST and T-SPOT.TB): 64%
  - More TST positive among BCG vaccinated

Texas Pediatric T-SPOT.TB Study
Cases with Culture + MTB | Controls No Exp Risk, -TST <10 | Contacts with +TST > 5mm, no BCG
---|---|---
Total number 152 (table) | 19 | 88 | 45
Percent T Spot+ | 89%* Sensitivity | 6% | 91%
Percent T Spot - | 11% | 94% “Specificity” | 9%
Percent TST + | 84%# Sensitivity | NA | All
Percent TST - | 16% | All | NA

*17/19 T-SPOT.TB positive
#16/19 TST positive
**T-SPOT.TB Texas Study**

**Special Pedi Cases**

- Positive T-SPOT in 3 patients with false - TST, disseminated MTB, culture + disease
  - 15 month old with TB meningitis
  - 6 yr old with Miliary & Renal, immunosuppressed
  - 15 yr old with generalized LAN

- Ruled out TB disease in immunosuppressed
  - Bone marrow transplant pt with cavitary pneumonia, TST -, BCG hx, T SPOT -, routine culture grew strep with quick resolution of pneumonia on antibiotics, AFB & final cx -

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**T-SPOT.TB**

**Specificity in Children**

- Highly specific (98-100% in recent studies)\(^1,2\)
  - Much better than TST
- May confirm/diagnose/or rule out LTBI especially in BCG vaccinated and NTM infected patients

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(1) Detjen, et al, CID 2007 1;45(3):322-8
(2) Connell, et al, PLoS ONE 2008 3(7); e2624
IGRA Sensitivity in Children

- Highly sensitive (93-100% in recent studies\(^1,2\))
- False negatives lower than TST
  - Max sensitivity with TST & IGRA’s
  - May be important in highest risk populations such as young child contacts and immunosuppressed
  - Consider using TST or IGRA’s if either positive in high risk for increased sensitivity
  - Unknown: What is the negative predictive value of IGRA’s in TST positive high risk contact?

(1) Detjen, et al, CID 2007 1;45(3):322-8
(2) Connell, et al, PLoS ONE 2008 3(7); e2624

Pediatric TB Case

- 12 month old boy with:
  - 10 days fever (102-105)
  - 4 days of vomiting and irritability
  - Chronic OM with PE tubes since 9 mos of age, no ear discharge at presentation
  - Admitted to hospital for vomiting & treated with IV cephalosporin
Case Presentation, Cont

- Transferred to Medical Center for mastoiditis
  - Routine culture of middle ear negative at 2 days
- Lumbar puncture and CSF on day 2
  - WBC 360, dif 25 P, 67 L, 8 M
  - Protein 210 (normal 15–45)
  - Routine Cx negative at 2 days
- Tuberculin skin test 0 mm
- CXR – normal initially then miliary pattern
- No risk, travel or known exposure to TB
- Brain MRI
  - Multiple enhancing nodules
  - Enhancement of brain stem and basal ganglion
  - Right otomastoiditis
**Outcome**

- **TB treatment** started for suspected TB meningitis
  - INH, Rifampin (12 months), PZA, EMB & Steroids
- Mother with + TST, normal CXR, no source case identified
- **Middle ear fluid and CSF later grew MTB**
  - Grew > 1 month after presentation
  - Pansusceptible
- Complications & outcome:
  - Hydrocephalous & VP shunt
  - Very mild hemiparesis
  - Cognitively: pos learning disability but doing well
- Note: from research study
  - Interferon γ blood test positive for TB

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**Tuberculosis Meningitis**

- Higher risk in infants
- Gradual onset over days or 1-2 weeks compared to bacterial meningitis
- Cerebral Spinal Fluid (CSF)
  - Normal to moderately high WBC (20’s 100’s), lymphocytic predominance
  - Very high protein, usually >100-300
- MRI
  - Brain stem & basal ganglion enhancement
  - Sometimes no findings on MRI
Tuberculosis Meningitis, cont

Possible complications
- Hydrocephalus
- Stroke/infarcts
- Cognitive impairment
- Normal outcome possible if treated in early stages (50% normal in my experience)

Treatment
- 4 TB meds until susceptibilities known
- Total treatment for 12 months
- Steroids (1-2 months) to decrease inflammation and scar formation
- Symptoms often get worse before better, many treat in hospital for first month

Summary
Challenges of TB in Children
- More difficult diagnosis
- Nonspecific signs and symptoms
- Fewer mycobacteria
- Fewer positive bacteriologic tests
- Increases risk of progression to active disease
- Higher risk of extrapulmonary and TB meningitis
THANKS

- Heartland National TB Center
- Research collaborators:
  - Drs. Jeffrey Starke & Edward Graviss, Baylor College of Medicine, Houston, TX
- Research funding:
  - Oxford Immunotec, Inc, UK