Pediatric TB and HIV: Deadly Duo in our Most Vulnerable

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Overview

- Epidemiology of Pediatric TB and HIV
  - Global and National Perspectives
- Pediatric TB in HIV-infected
- Pediatric Presentations of TB
- Challenges in Diagnosis
- Pediatric TB Treatment in HIV-infected
- Immune Reconstitution Syndrome (IRIS)
- New Tools: interferon-gamma release assays in children
- Preventing TB disease in Children
- BCG vaccination in HIV-infected

Pediatric TB – Global & National Perspectives

- Global burden
  - 884,000 (11%) of the 8.3 million cases (2000) were in children < age 15
    - Of those, 75% live in the 22 HBCs
  - Low-income countries 15% of TB cases are children
  - South Africa: 40%
  - Co-infection of children with HIV and M.tb → profound impact
- Tanzania
  - 61,022 TB cases reported to WHO (2005)
  - 461/25,264 (2%) new ss+ notifications (2005) were < age 15
  - M:F ratio among children: 1:1.4
  - Of all TB patients tested, 51% HIV-infected

Source: WHO TB Global Report, 2007

Pediatric HIV – Global & National Perspectives

- Global burden
  - 2.3 million (range 1.7-3.5 million)
  - 6% of the estimated 38.6 million cases (33.4-46 million) were in children < age 15 (2005)
    - 2.0 million (87%) live in sub-Saharan Africa
  - 15.2 million orphans (ages 0-17) due to HIV/AIDS worldwide (2005)
    - 12 million orphans live in sub-Saharan Africa (2005)
- Tanzania
  - 1.4 million people living with HIV
  - 110,000 (43,000 – 210,000) or 8% of those are children (2005)
  - 1.1 million orphans (ages 0-17) due to HIV/AIDS (2005)

Source: UNAIDS, 2006

Overview
Pediatric TB in HIV-infected

- Until recently, few published series of TB in HIV-infected children
- Clinical presentation of PTB and EP similar in HIV-infected and HIV-uninfected children
- HIV-infected children are more likely to have
  - Extensive disease
  - EP TB
  - Higher rate of intracranial mass lesions
- Recurrent TB reported in 10% & 17%
  - Caused by recurrence or re-infection with second strain

Transmission of *M. tuberculosis* to Children

- Children are usually infected by an adult or adolescent in the immediate household
- Casual extra-familial contact is much less often the source of infection
- Children rarely infect other children or adults
  - Paucibacillary disease, esp in HIV+
    - Tubercle bacilli are relatively sparse in secretions (smear-negative)
  - Children with pulmonary TB rarely cough
  - Even when cough is present, children lack the tussive force needed to aerosolize bacilli

Pediatric TB Presentations

- Primary TB disease
  - Unilateral lymphadenopathy (70-80%)
  - Typical "primary complex" (~20%)
  - Lobar or segmental opacity (rare)
- Acute disseminated post-primary TB
  - Miliary TB with or without meningitis
- Post-primary pulmonary TB
- Post-primary EP
- PTB:EP TB = ~1:3

Tuberculosis in Adolescents

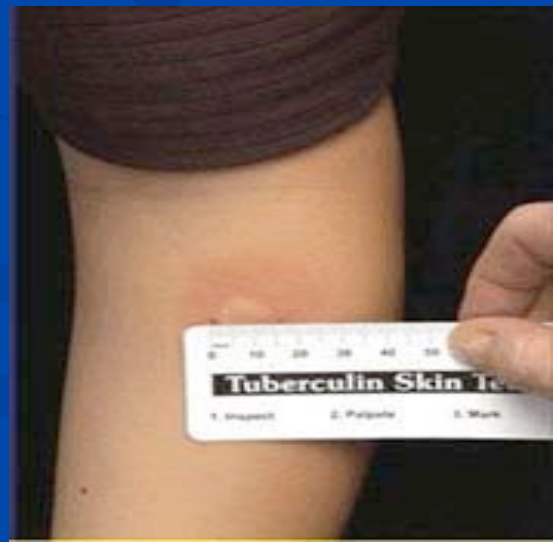
- Adolescents develop tuberculosis in one of two ways:
  - Reactivation of infection acquired during childhood
    - The closer to puberty at the time of infection the greater the risk of progression to TB disease
  - Progression of infection acquired during adolescence to disease:
    - Classic primary disease
    - Progressive primary pulmonary tuberculosis

Reactivation 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

Pediatric TB - Diagnosis

- Difficult in children < age 6-8
- Typically only 10-15% are ssm+
- Scoring systems: lack standardized definitions and ranking of characteristics, rarely validated
- History of contact CRUCIAL
- Respiratory symptoms > 2-3 wks, no response to broad-spectrum antibiotics
- Weight loss or FTT
- Chest radiograph may be suggestive
- Positive TST
  - ≥5mm in HIV-infected



Pediatric TB - Diagnostic Approach

Recommended approach to diagnose TB in children

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. TST
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
6. HIV testing (in high HIV prevalence areas)

WHO, Guidance for NTPs on Management of TB in Children, 2006

Pediatric TB – Diagnostic Tools

- Chest Radiograph
  - Disparity in descriptions of childhood TB identified through active case-finding (e.g., USA) versus passive case-finding
  - Proposed standardized radiologic classification
  - Marais et al (South Africa) showed good correlation between severity of radiographic changes and symptoms
- Gastric Lavage
  - Yield approximately 30-40%
  - Complicated (logistically) to execute
- Sputum Induction (SI) – Zar el al, Lancet, 2005.
  - Compared gastric lavage to SI in 250 children (age 1m-5yrs) in South Africa
    - 62 with positive smear or culture specimen
  - Yield of 1 induced sputum similar to that of 3 gastric lavage samples
  - 14 more cases identified through SI
  - SI procedure well tolerated
  - No difference in microbiological yield between HIV-infected (38% of total) and HIV-uninfected

Special Challenges: Diagnosing Pediatric TB in HIV-infected Children

- Diagnostic challenges even more profound
- HIV-infected children likely to live with HIV-infected adult (ssm-)
- Symptom-based approach:
  - confounded by presence of chronic HIV-related symptoms (e.g., GER, bronchiectasis)
  - Limited by rapid disease progression
- Wt loss and FTT common in both HIV and TB
- CXR interpretation complicated by HIV-related co-morbidities & atypical disease presentation
- TST has poor sensitivity
  - $\leq$50% HIV-infected children with confirmed TB are TST positive, (5mm cutoff) [Schaff el al, Pedi Inf Dis J, 1998]

Treatment of Tuberculosis in Children

- Few major advances in the treatment of childhood TB in recent years.
  - Isoniazid: 5 mg/kg/dose, range 4-6, max. 300)
  - Rifampin: 10 mg/kg/dose, range 8-12, max. 600
  - Pyrazinamide: 25 mg/kg/dose, range 20-30
  - Ethambutol: 20 mg/kg/dose, range 15-25
  - Streptomycin: 15 mg/kg/dose, range 12-18
- Current guidelines emphasize use of intensive short-course therapy with fixed-dose combinations and DOT
- Lower Emb levels in all children
- Lower PZA levels seen in HIV-infected children

Treatment of Tuberculosis in Children – Special Considerations

- Treating Drug-Resistant TB:
  - Child epi link to adult with DR-TB
  - Treatment usually successful and children tolerate drugs
  - 95% cure rate among 38 children in Peru with MDR-TB
- Adherence issues – caretaker education important
- For HIV-infected:
  - Optimal duration TB therapy?
    - Relapses documented (role of cellular immunity), 6 vs. 9 mos
  - Starting ART
    - Optimal timing?
    - Consider age, degree of immune suppression
    - Risk of immune reconstitution
- Co-trimoxazole prophylaxis
  - RCT in Zambia in HIV-infected, >age 2 showed survival benefit [Mermin et al, Lancet, 2004.]
  - Clear and consistent benefit for HIV-infected adults with TB

Pediatric TB in HIV-infected Children - Immune Reconstitution Syndrome (IRIS)

- Initial mos of ART, immune reconstitution can lead to adverse clinical phenomena
  - "Unmasking" of subclinical infections
  - Deterioration of partly treated OIs
- Published reports of IRIS in children rare, anecdotal evidence suggests increase as pediatric ART rolled-out
- Typical onset 1-3 wks after ART start, up to 3-4 months
- Common manifestations: fever, enlarging cervical or thoracic lymph nodes, appearance/worsening of tuberculomas in the brain ± meningitis
- Usually subsides spontaneously, some cases severe
- Treatment: best management unknown
  - Many cases resolve on own
  - Steroids appear beneficial if severe
- No clear consensus on when to start ART – delay 2-8 wks recommended
- Balance risk of IRIS with risk of death from other HIV complications

IFN-Gamma Release Assays – New Diagnostic Tests

- 2 new commercial tests available
  - QuantiFERON TB-Gold: Based on quantification of IFN-gamma produced by primed T-cells in response exposure to antigens ESAT-6 and CFP-10
  - T-SPOT TB (ELISPOT): Based on quantification of number of INF-gamma producing T-cells exposed to ESAT-6 and CFP10
- ESAT-6 and CFP10 (proteins encoded by RD-1, genomic segment unique to M. *tuberculosis*)
- No cross reactivity with M. *bovis* (BCG vaccine) or non-tuberculous mycobacteria (e.g., MAC)
- Obtain whole blood or PBMCs from patient
- Stimulate in vitro with 2 TB specific mycobacterial antigens (ESAT and CFP) and measure interferon-gamma
- Excellent specificity (neg with BCG and NTM) and promising sensitivity
- Does not distinguish latent TB infection from disease

Studies of T-SPOT Use in Children

- Nicol et al, CID, 2005, Cape Town, South Africa.
  - 70 < age 12, all immunocompetent
  - Sensitivity: 83% among definite TB (10/12)
  - Sensitivity: 72% among probable TB
- Liebescheutz et al, Lancet, 2005, kwaZulu-Natal, South Africa.
  - 293 <age 15, 75/164 HIV-infected
  - Sensitivity: 83% among confirmed/probable TB
  - TST sensitivity at 10mm cutoff: 65%
  - 73% (22/30) among HIV-infected, confirmed/probable TB
- Difficult to evaluate when no gold standard
- Further research to determine:
  - Role in diagnosing TB disease versus latent infection
    - In children, HIV-infected
  - Role in areas where latent infection common

Preventing TB

- WHO guidelines for childhood contact screening and management to prevent TB
- Evaluate children under age 5 and HIV-infected in close contact with ssm+ patient
- Evaulate for active TB disease
  - History, exam, TST, CXR
- If active TB ruled out, but evidence of latent TB infection
  - INH daily therapy for 9 months
- Treatment of LTBI important due to high risk of progression to active disease
- Difficulties in operationalizing, poor adherence

Table 1. Quantification of the risk of infection after tuberculosis (TB) exposure and the risk of progression to active TB in children.

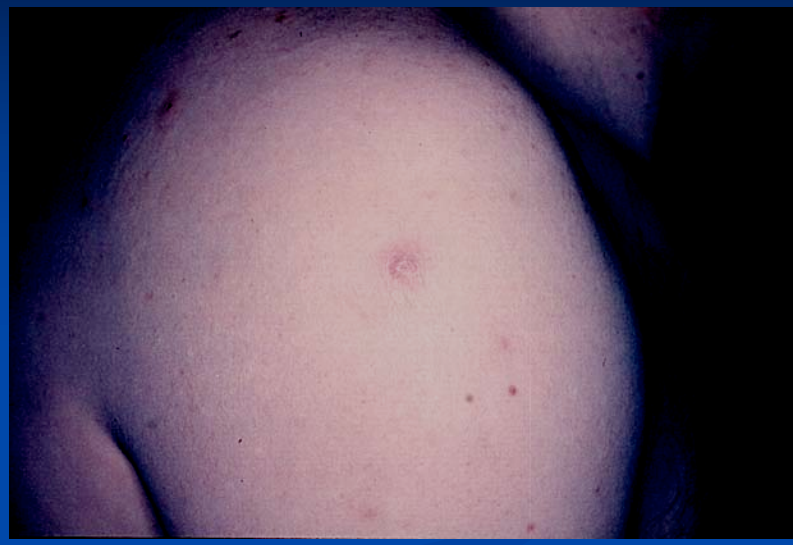
Progression	Risk, %
From TB exposure to infection,[a] by exposure type	
Prolonged household exposure to an index case with sputum smear–positive TB[b]	60–80
Prolonged household exposure to an index case with sputum smear–negative TB[c]	30–40
From TB infection to active disease,[d] by age group and disease type	
<1 year	
None	50
Pulmonary disease	30–40
Disseminated (miliary) disease or TBM	10–20
1 to <2 years	
None	75–80
Pulmonary disease	10–20
Disseminated (miliary) disease or TBM	2–5
2 to <5 years	
None	95
Pulmonary disease	5
Disseminated (miliary) disease or TBM	0.5
5 to <10 years	
None	98
Pulmonary disease	2
Disseminated (miliary) disease or TBM	<0.5
⩾10 years	
None	80–90
Pulmonary disease	10–20
Disseminated (miliary) disease or TBM	<0.5

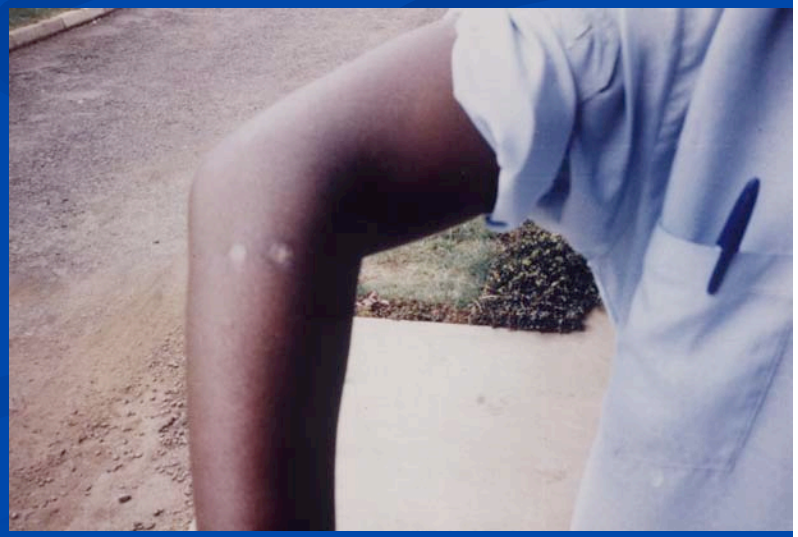
NOTE. TBM, tuberculous meningitis.

Marais et al, JID, 2007.

Bacille Calmette-Guerin (BCG) Vaccine

- Live-attenuated vaccine
- first used in 1921
- Administered to 100 million children each year
- Immunization at birth worldwide in countries with high TB prevalence
- Variable protection in different setting
- Important protection against disseminated TB in young HIV-uninfected (< age2)





HIV-infected Child and BCG Vaccination

- In HIV-infected newborns
  - Uncertain protection
  - Considerable risk of disseminated BCG disease
- WHO advises BCG for all HIV-exposed, asymptomatic infants in TB endemic areas
- Monitor development of BCG disease
- Reports of disease increasing
- Studies from South Africa reported 25 children with BCG disease
  - Most local disease at vaccination site
  - 6/17 HIV-infected with disseminated disease
  - Estimated risk of disseminated BCG disease in HIV-infected children: 110-417/100,000

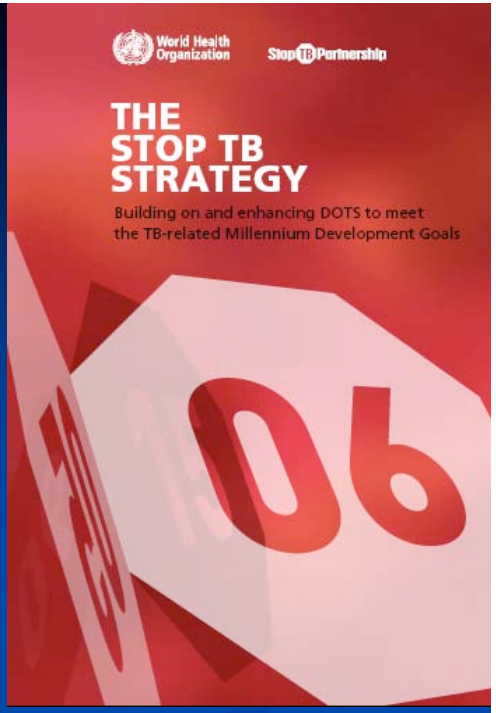
Childhood Tuberculosis: Decreasing Morbidity & Mortality

Heymann et al. Pediatrics 2000; 106:el

Semi-Markov Model – 10 Years

INTERVENTION	EFFECT ON CHILDHOOD CASES
5% increase for adults in therapy	0.05% decline
Improved efficacy of therapy for adults	0.003% decline
5% increase for children in therapy	25% decline in cases 16% decline in deaths

Putting Pediatric TB/HIV on the Global Agenda



New Stop TB Strategy, 2006

1. Pursue high-quality DOTS expansion and enhancement

- Political commitment with increased and sustained financing
- Case detection through quality-assured bacteriology
- Standardized treatment with supervision and patient support
- An effective drug supply and management system
- Monitoring and evaluation system, and impact measurement

2. Address TB/HIV, MDR-TB and other challenges

- Implement collaborative TB/HIV activities
- Prevent and control multidrug-resistant TB
- Address prisoners, refugees and other high-risk groups and special situations

3. Contribute to health system strengthening

- Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
- Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
- Adapt innovations from other fields

4. Engage all care providers

- Public-Public, and Public-Private Mix (PPM) approaches
- International Standards for Tuberculosis Care (ISTC)

5. Empower people with TB, and communities

- Advocacy, communication and social mobilization
- Community participation in TB care
- Patients' Charter for Tuberculosis Care

6. Enable and promote research

- Programme-based operational research
- Research to develop new diagnostics, drugs and vaccines

Summary

- TB diagnosis in children is difficult; in HIV-infected children even more difficult
  - Largely presumptive diagnosis
- TB treatment of children similar to adult treatment
  - Higher dose of Emb; 6 mos (?optimal duration)
- Optimal time to start ART?
  - IRIS does occur in children
- Further studies of IGRAs in children needed
- Use of BCG in HIV-infected newborns being monitored

"The time has come for the hidden epidemic of childhood TB to emerge from the shadow of adult TB and be seen as a neglected child health problem of considerable proportions…"

Donald, Int J Tuberc Lung Dis, 2004; 8:627