The diagnosis of childhood tuberculosis in low/intermediate burden settings

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Estimated TB incidence rates by country, 2007

WHO Global Tuberculosis Control 2009
Germany: TB low-incidence setting

TB incidence in Germany 2007:
Total: 5020; 6.1/100 000
Children: 180; 1.6/100 000

1952: Isoniazid
Diagnosis of Childhood Tuberculosis

Suspicion

Knowledge on
- The local epidemiology of TB
- Risk groups
- Specific aspects of childhood TB
Background of Migration

Estimated TB incidence rates, by country, 2007

Central Europe: 20 - >50% TB cases of foreign origin
Who is at risk?

Infants 43%
Toddlers (1-5 years) 24%
Adolescents (11-15 years) 15%
Adults 5-10%

Children 57-85%

modified from Sharma SK, Lancet Infect Dis 2005
Other risk groups

• Immune-compromised
  – HIV-infected: risk of disease progression 10%/year
  – Rheumatology patients
  – Oncology

• Poor living circumstances (asylums)
  – Homeless
  – Drug users
  – Prisoners
Diagnosis of Childhood Tuberculosis

Suspicion

Infection?

No gold standard ➔
- History
- Targeted Tuberculin Skin Test
- IGRA

Disease?
Contact?
Risk evaluation for TB infection in a low-burden setting

1. Has your child had contact to a person with TB?

2. Was your child or another family member born in a country with a high TB burden? In the last two years, has your child/a family member spent a period of time in a high-burden country?

3. Is your child in contact with adults at high risk of TB? (e.g. drug users, people living in asylums)

4. Is your child HIV-infected/has your child an immune deficiency?
Risk evaluation for TB infection in a low-burden setting

Results from New York:

• 413 children (14%) had at least one risk factor
  23 (5,6%) had positive TST

• 4 (0,16%) of 2507 children without risk factors had positive TST

• Sensitivity: 85,2%, Specificity: 86,0%
• Negative predictive value: 99,6%
• Positive predictive value: 5,4%
• OR: 35,2 (95% Konfidenz-Intervall: 12,1-102,4)

One Question answered with yes ➔ targeted skin testing

Ozuah JAMA 2001
Tuberculin Skin Test (Mendel-Mantoux)

Comprable tuberculins:
- 2 TU RT23 (WHO Reference-tuberculin)
- 5 TU PPD-S (USA)

Cut off values (ATS 2000)
- > 5 mm: Close contacts, immune suppressed
- > 10 mm: children <4, with other medical conditions, from high-burden settings, contact with risk groups
- > 15 mm: children ≥4 without risk factors
Cross-reactivity - BCG

2005

Left upper arm
Cross-Reactivity - NTM

Reported cases of mycobacteriosis due to M. avium complex Sweden 1969-1993

Discontinuation of mass BCG vaccination

Romanus V Smittskyddsinstitutet 1995
TB or NTM?

M. tuberculosis

IGRA

M. avium
Interferon-γ Release Assays

**T SPOT™. TB**
- **ELISPOT**
  - *In vitro* stimulation of PBMCs with ESAT-6 and CFP-10
  - Incubation **16-20 h**
  - **Specific** IFN-γ-producing T-cells
  - Positive: > 5 Spots

**QuantiFERON®-Tb Gold In-Tube**
- **ELISA**
  - *In vitro* stimulation of **whole blood** with ESAT-6, CFP-10 and Tb7.7
  - Incubation **16-20 h**
  - **IFN-γ**
  - Positive: > 0.35 IU/l
## Specificity of ESAT-6 and CFP-10

*orange* = Sensitivity, *red* = Cross-reactivity = false positive, *green* = Specificity

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>ESAT</th>
<th>CFP</th>
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<td><em>M. tuberculosis</em></td>
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<td><em>M. africanum</em></td>
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<td><em>M. bovis</em></td>
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<td><em>M. canetti</em></td>
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<td><em>M. xenopi</em></td>
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IGRA instead of TST

- Adults and children
- Contact investigations
- Evaluation of recent immigrants
- Sequential testing survey programs for infection control (Health Care Workers)

Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis
Recommendations from the National Tuberculosis Controllers Association and CDC

Empfehlungen für die Umgebungsuntersuchungen bei Tuberkulose
Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose

Stepwise testing: IGRA as confirmation of positive TST

- Active TB and LTBI
- Adults and children
But...

P.M., 1 year
- No BCG
- Father smear positive TB 03/2006
- TST negative 03 and 10/2006
- INH Prophylaxis 3 months
- TST 07/2007 15 mm, ulcerating
- QFT negative

M.A., 4 years
- No BCG
- Grandfather smear positive TB 06/2007, close contact over 2 weeks
- TST 09/2007 15 mm, ulcerating
- T SPOT negative
- No symptoms, CXR normal
TST remains preferred method for screening for LTBI

TST and IGRAs almost no place in diagnosis of active TB

IGRAs may be used as supplementary test for LTBI for increased specificity

High risk contacts: TST (and IGRA), either positive counts

Low risk groups: stepwise testing

Replacement of TST for Dx of LTBI in persons > 15 years

Contact tracing, serial testing (HCW), before TNF-apha antagonists

More cautious:

Infection:

Disease:
Diagnosis of Childhood Tuberculosis

Suspicion

Infection?
- History
- Targeted Tuberculin Skin Test
- IGRA

No

In case of contact: consider exposure prophylaxis for 3 months and re-evaluate

Yes

Disease?

75% pulmonary TB
25% extrapulmonary TB

Gold standard: Culture

But in children often combination of:
- Symptoms
- Radiologic Findings
- Microscopy/Culture/NAAT
Symptoms

• **Early disease often asymptomatic!**

• **Later:**
  – Persistent cough > 2 weeks
  – Documented loss of weight
  – Reduced playfulness

→ **reasonable accuracy in combination (PPV 83.6%, South Africa)**
  – Organ-specific symptoms
    (Lymphadenopathy, neurologic symptoms, Gibbus etc.)

Marais Pediatrics 2006
Most common - Lymphnode disease
The value of lateral CRXs

Thymus
Additional structures
Bronchogenic spread - Expansile pneumonia
Most specific - Miliary TB
Adult-type disease
CT and MRI

**CT indication**
- Pulmonary TB:
  - Small lymphnodes (value?)
  - Endobronchial involvement
  - Bronchiectasis
  - Early cavities
- Pleural/Pericardial disease
- TB Meningitis:
  - Basal enhancement
  - Hydrocephalus
  - Tuberculomas
  - Focal lesions

**MRI indication**
- Brain/spinal cord involvement
- Chronic Osteomyelitis
  - Early marrow involvement
  - Soft tissue extension
- Spinal TB
  - Cold abscess formation

Lighter Curr Probl Pediatr Adolesc Health Care 2009
CT with Contrast: Ring enhancement
Bacteriology

Culture = gold standard

• Challenge: paucibacillary disease in children
  **But**: Sensitivity ↑ with severity of disease

• Bacteriological prove must be tried
  ➡ Rigorous and **standardized** sample collection
  – 3x Gastric washing/sputum
  – Suspected site of infection
Gastric washing vs. induced Sputum

**Gastric washing**
- Fasting for 8 hours
- Up to 50% yield if performed in a standardized manner
- Stain and culture yield from 3 GW higher than BAL

**Induced sputum**
- Inhalation of 3-5% hypertonic saline
- Possible side effect: bronchospasm
- Yield of one induced sputum equivalent to 3 GW
- Physiotherapy to support sputum production

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1 Pomputius Pediatr Inf Dis J1997
2 Lighter Curr Probl Pediatr Adolesc Health Care 2009
3 Zar Lancet 2005
Drug resistance

Drug susceptibility testing has to be performed on the first positive culture

In the case of negative culture:

• History!!!!

• Drug susceptibility results or regimen of the index case
Diagnosis of Childhood Tuberculosis

Suspicion

Infection?
- History
- Targeted Tuberculin Skin Test
- IGRA

No | Yes
---|---

Disease?
- Symptoms
- Radiologic Findings
- Microscopy/Culture/NAAT
- Drug sensitivity testing

No | Yes
---|---

In case of contact: consider exposure prophylaxis for 3 months and re-evaluate

Prophylactic Chemotherapy | Antituberculosis Chemotherapy
Thank you!
TB cases of foreign origin
WHO European Region 2006

http://www.eurotb.org/