PEDIATRIC TUBERCULOSIS
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Presented by:

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Objectives

- Mycobacteriology
- TB epidemiology
- Risk factors to develop TB
- Transmission
- Pregnancy and the newborn
- TB Testing and Diagnosis
- Clinical Manifestations
- Complications and extrapulmonary manifestation
- TB adults vs children
- TB treatment
TB overview: infection and disease

- Primarily spread by respiratory route
  - Largely a lung disease
  - Transmission by skin and gut can also occur
- Person with active disease coughs
  - TB bacilli suspended in very tiny particles
  - Can stay airborne for extended period
- Exposed individual directly inhales the contaminated particles
  - Risk of infection depends on disease burden in the index case, proximity and duration of exposure
  - Household exposure from adult with active disease is strongest source
  - Children are typically less infectious than adults
TB overview: infection and disease

- **Primary TB infection** - acquiring TB directly after exposure to someone with active disease
  - Inhaled TB bacilli penetrate into lungs and settle - "set up shop"

1. Infection is contained in a small area without spread or replication (latent TB infection or LTBI)
   - These individuals are **not infectious to anyone**
   - The TB bacilli are well-contained and cannot be released

2. Infection spreads to nearby lymph nodes and the lung tissue itself → TB pneumonia → primary active TB
   - Risk of spread chiefly depends on age and immune status
   - Very young children <4 yrs, immune compromised eg HIV, cancer, immunosuppressive meds eg steroids
There are five closely related mycobacteria in the Mycobacterium tuberculosis complex: M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti. M. tuberculosis is the most important cause of tuberculosis disease in humans. The tubercle bacilli are non–spore-forming, nonmotile, pleomorphic, weakly Gram-positive curved rods 2–4µm long. They may appear beaded or clumped in stained clinical specimens or culture media.

A hallmark of all mycobacteria is that they are considered to be acid fast bacilli.
TB bacilli

http://www.ihcworld.com/royellis/gallery/zn.htm
What do we mean by acid-fast bacilli (AFB)?

Mycobacteria are rod/bacillus shaped
- Thick lipid cell wall (mycolic acid) that repels standard stains (e.g. gram stains)
- Concentrated dyes are used, then
- Acid decolorization is performed
- Mycobacteria resist the acid and retain color
- “Acid-fast”
Percent of US Pediatric TB Cases by Age Group
1993–2006
N=15,946

Age 10-14: 18.2%
Age < 1: 9.2%
Age 5-9: 23.1%
Age 1-4: 49.5%

TB Epidemiology

CDC data
WHO estimate of TB in children
- 1.3 million annual cases
- 450,000 deaths
- 15% of TB in low-income countries children vs. 6% in United States
Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Developed Countries

- Children exposed to high-risk adults
- Foreign-born persons from high-prevalence countries
- Poor and indigent persons, especially in large cities
- Homeless persons
- Persons who inject drugs
- Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
- Health care workers caring for high-risk patients
RISK FOR PROGRESSION TO TUBERCULOSIS DISEASE ONCE INFECTED

- Infants and children \( \geq 4 \) yr of age, especially those \( <2 \) yr of age
- Adolescents and young adults
- Persons co-infected with HIV
- Persons with skin test conversion in the past 1–2 yr
- Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
Transmission of M. tuberculosis is person to person, usually by airborne mucus droplet. The chance of transmission increases when the patient has an acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Young children with tuberculosis rarely infect other children or adults. However, children and adolescents with adult-type pulmonary tuberculosis can transmit the organism.
Pediatric (<15 yrs) TB Cases by Site of Disease, 1993–2006

Pulmonary 71.1%

Extra pulmonary 21.9%

Both 7.0%

Any extrapulmonary involvement* (totaling 28.9%)
- Lymphatic 18.9%
- Meningeal 3.1%
- Miliary 1.5%
- Bone & Joint 1.5%
- Other 3.9%

All ages US 2008: 80% pulmonary + EP, and 20% EP only

*Any extrapulmonary involvement includes cases that are extrapulmonary with or without pulmonary involvement.
Pregnancy and the Newborn.

- Pulmonary and particularly extrapulmonary tuberculosis other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight and perinatal mortality. Congenital tuberculosis is rare because the most common result of female genital tract tuberculosis is infertility.
Clinical Manifestations and Diagnosis.

- The majority of children with tuberculosis infection develop no signs or symptoms at any time and are non-specific. Infection is marked by low-grade fever and mild cough, Hemoptysis (bloody sputum), night sweats and rarely by high fever, cough, malaise, and flu-like symptoms that resolve within a week. About 15% of adult tuberculosis cases are extrapulmonary, and 25–30% of children with tuberculosis have an extrapulmonary presentation.
Poor appetite, weight loss, failure to thrive, intermittent fevers, +/-cough, listlessness, decreased activity, irritability (TB meningitis)
Tuberculin skin test

TB TESTING AND DIAGNOSIS
Purified Protein Derivative (PPD) test

- Aka tuberculin sensitivity test (TST), Mantoux test, TB skin test
  - First described by Robert Koch in 1890
  - Test further developed and refined by Charles Mantoux in 1907
- Purified protein extracts from M TB cultures are injected into skin
- Immune T cells that have been sensitized to TB from prior infection migrate to the injection site
- Release chemicals that produce local inflammation and induration (bumpy reaction)
- After initial infection, it takes 2-10 wks (median 3-4 wks) to develop hypersensitivity to the PPD test.
- At best, PPD is ~90% sensitive, ~90% specific
Once positive, a PPD will always be positive.

It will not go away with treatment, either for LTBI or for active disease.

Don’t bother to recheck it after the patient has been treated.

It is a badge that will always be worn by the patient.

Exceptions: immune compromise that affects the T cells that are supposed to react eg HIV; and young infants, elderly.

This is called anergy-negative PPD test in one who you know/suspect has been infected.

Minimum recommended age for PPD: 3 months.
*How does one determine a positive PPD?*

- It depends on the patient being evaluated
  - Where they were born/coming from,
  - Household or close contact exposure,
  - Immune status
- Subject to the provider’s interpretation, clinical experience and skill
- Either way, you still need a measuring tape!
  - Do not measure redness
  - Measure induration (bumpiness) only
  - Measure perpendicular to forearm plane (short arm of a cross)
- Is it ≥5, 10 or 15 mm?
  - Based on risk of acquiring infection and progression to active disease
<table>
<thead>
<tr>
<th>Categories</th>
<th>Measurement cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Child in close contact with known or suspected contagious TB case</td>
<td>≥5mm</td>
</tr>
<tr>
<td>2. Child suspected to have active TB</td>
<td></td>
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<tr>
<td>- CXR findings <em>consistent</em> with active or previous untreated, non-healed TB</td>
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<tr>
<td>- Clinical evidence of active TB</td>
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<td>3. Child immunosuppressed eg HIV or meds</td>
<td></td>
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<tr>
<td>1. Child at increased risk of disseminated TB</td>
<td>≥10mm</td>
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<td>- &lt;4yrs old, -other medical conditions eg cancer, diabetes, malnutrition</td>
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<tr>
<td>2. Child with increased exposure to active TB</td>
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<tr>
<td>- born in TB-endemic areas</td>
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<td>- <em>lives with people born in TB-endemic areas</em></td>
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<td>- <em>Native American children</em></td>
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<td>- frequently exposed to HIV infected adults, homeless, drug users, incarcerated, migrant workers</td>
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<td>- travel to TB endemic regions</td>
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<tr>
<td>1. Children ≥4 yrs with no identifiable risk factors</td>
<td>≥15mm</td>
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</tbody>
</table>
Variations of +PPD

Correct Measurement

Blisters, granulomas, local necrosis may occur
If the PPD is positive:

- This means your patient is infected with TB
  - BCG or non-TB mycobacteria may cause a “false positive” PPD
  - This effect fades significantly by 2-5 yrs after BCG vaccine—should not even be an issue with adolescents or adults
  - In practice, BCG is not taken into consideration with +PPD. This is the recommendation from TB experts.
- You have to determine if they have active disease
- Perform a CXR: two-view, PA/AP and lateral
- Looking for most common manifestation of active TB
Positive PPD + Negative CXR = Latent TB Infection
Positive PPD + TB-Positive CXR = active TB
Complications and extrapulmonary manifestation

1. PLEURAL EFFUSION.
2. PERICARDIAL DISEASE.
3. LYMPHOHEMATOGENOUS (DISSEMINATED) DISEASE.
4. UPPER RESPIRATORY TRACT DISEASE.
5. LYMPH NODE DISEASE.
6. CENTRAL NERVOUS SYSTEM DISEASE.
7. CUTANEOUS DISEASE.
8. BONE AND JOINT DISEASE.
9. ABDOMINAL AND GASTROINTESTINAL DISEASE.
10. GENITOURINARY DISEASE.
TB: adults vs children

- Compared to adults, children:
  - Tend to develop primary active TB more often after initial infection (0-4yrs)
  - Are more likely to have extrapulmonary disease, especially TB meningitis (0-4yrs)
  - Are more likely to have disseminated TB infection
  - Are less contagious
    - Paucibacillary disease (fewer organisms)
    - Cannot cough/spread infection as well
  - Are more difficult to diagnose
    - May not show typical symptoms
    - May have TB disease in unexpected places
  - Have less FDA-approved treatment meds and formulation options
TB: adults vs children

- A child suspected of having active TB may not yield any positive cultures/smears
- Need the adult contact’s culture results for drug sensitivities and to determine treatment regimen for the child
- A thorough contact investigation is critical in the evaluation, management, and prevention of TB infection in the child.
TB treatment

- Tubercle bacilli can be killed only during replication. The major biologic determinant of the success of antituberculosis chemotherapy is the size of the bacillary population within the host.
TB treatment: LTBI

• Bacilli are well-contained in the lung...forever?
  – Risk of secondary active TB (from this “personal” collection of TB) increases as one gets older
  – Cancer diagnosis, steroids, immune suppressive drugs for autoimmune disease, HIV
  – Aka reactivation TB
• Need to eliminate this small collection to avoid future reactivation
  – People with LTBI are latent reservoirs of TB bugs
  – Of Public Health importance
• Treatment with 1 drug (INH) for 9 months: TB is a slow-growing bug
• No need for any isolation: LTBI is not contagious
• Young children or compliance issues: may get DOT (directly observed therapy) for LTBI
TB Treatment: active disease

- **RIPE drugs-firstline:**
  1. Rifampin (RIF),
  2. Isoniazid (INH),
  3. Pyrazinamide (PZA),
  4. Ethambutol/Ethionamide (ETH)

- Typically 6 month tx:
  - all 4 drugs x 2 months, then INH/RIF x 4 months

- TB meningitis and disseminated TB: 9-12mo
  - 4 drugs x 2mo, then 2 drugs x 7-10 mo.

- MDR and XDR TB:
  - 4-6 drugs for 18-24 months

- HIV coinfection:
  - ≥3 drugs for ≥9 months recommended

- No differences in adult vs child treatment regimens

- DOT critical for all patients on treatment, to ensure consistency and completion
  - May not be feasible in remote areas/understaffed
All 4 standard drugs are taken orally

- Dosing for children is weight-based

INH and RIF are the backbone of treatment

INH comes in syrup form, but due to sugar type (sorbitol), osmotic diarrhea is likely

Hepatitis is biggest concern with TB drugs: adults >> children
Side effects of TB medication

- **Rifampicin:** reddish-orange discoloration of body fluids, such as saliva, tears, urine and perspiration. Elevated liver enzymes

- **INH:** Neuropathy and elevated liver enzymes

- **Pyrazinamine:** elevated liver enzymes and vertigo

- **Ethambutol:** optic neuritis

- **Streptomycin:** ototoxicity and kidney damage
Prevention of TB Disease

- The key method of preventing tuberculosis (TB) is prompt identification and treatment of patients with TB. Other strategies include patient education, treatment of latent infection, and vaccination.

- Patient education
  - Thoroughly educate patients regarding compliance to therapy, adverse effects of medications, and follow-up care.
TB and BCG Vaccination

- Efficacy for adult pulmonary TB 0-80% in randomized clinical trials
- Best efficacy against serious childhood disease
  - 64% protection against TB meningitis
  - 78% protection effect against disseminated TB
- BCG important for young children, inadequate as single strategy
References

- Nelson textbook of pediatric infectious diseases
- Red Book 2009. Tuberculosis
- Pediatric TB: an online presentation.
  - [http://www.nationaltbcenter.edu/pediatric_tb/presentation.cfm](http://www.nationaltbcenter.edu/pediatric_tb/presentation.cfm)