TB in Pediatrics
Amin Ostovar, MD, FAAP
March 13, 2015

TB for Pulmonologist
March 13, 2015
Phoenix, AZ

Amin Ostovar, MD, FAAP has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Disclosures:

- I have NO relevant financial interests to disclose.
- I receive my annual influenza vaccine for free through my employer.
- I am the PI in two clinical trials sponsored by Cubist and sub-I in another trials sponsored by Cerexa.

Mycobacteria

- Aerobic, nonspore-forming, nonmotile
- Slightly curved, 1-10 µm
- Acid fastness
- \textit{M. tuberculosis} complex: \textit{M. tuberculosis}, \textit{M. bovis}, \textit{M. africanum}, \textit{M. canetti}, \textit{M. micr}oti (rodents), \textit{M. pinnipedi} (aquatic mammals), \textit{M. capral} (animals in Europe)
TB: Immunology

- Clinical spectrum: asymptomatic to disseminated
- Progressive pulmonary TB versus TB pleuritis
- T lymphocytes and macrophages
- Tumor necrosis factor
- PMNs and NK cells, B cells

TB: Epidemiology

- Transmission: person to person, direct contact with body fluids and fomites
- Sputum as the marker for contagiousness
- Children versus adolescents
- Decision to discontinue isolation
Mycobacterium tuberculosis Infection

- One-third of the world's population
- Total risk of acquisition for children in the US < 1%
- Less than 1% of children in public schools are infected

Mycobacterium tuberculosis Disease

- 8-10 million develop TB disease annually
- 1.3 million in children younger than 15
- Epidemiology follows epidemiology in adults
Reported TB Cases
United States, 1982–2013*

*Updated as of June 11, 2014.

M. tuberculosis Disease

- Risk of exposure currently confined to well-developed groups
- Disease of racial or ethnic minorities
- 58% foreign-born (Mexico, Philippines, India, Vietnam, China and Guatemala)
- 18% detected in 5 years
TB Case Rates by Race/Ethnicity,*
United States, 2003–2013**

*All races are non-Hispanic.
**Updated as of June 11, 2014.

Number of TB Cases in
U.S.-born vs. Foreign-born Persons,
United States, 1993–2013*

*Updated as of June 11, 2014.
TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2013*

*Updated as of June 11, 2014.

Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2013

*Foreign-born TB patients for whom information on length of residence in the U.S. prior to diagnosis is unknown or missing.
M. tuberculosis Disease

- Residence in jails, prisons, homeless shelters, illicit IV drug use and socioeconomic disadvantage in urban areas
- Age and sex: infection, development of disease
- 60% in <5 years, those >14 higher risk of disease
- Age affects site of infection

- 8 states (AZ, CA, FL, GA, IL, NY, TX and WA) 61% of the cases in children <5
- Higher among foreign-born, ethnic and racial minorities
- Most infected at home, but outbreaks occur
TB in immunocompromised children

- Profoundly affected by HIV epidemic
- AIDS defining condition
- Adults with HIV (sputum +/-)
- Directly related to rates of HIV infection in adults

TB in immunocompromised children

- Usually under-diagnosed
- IRIS
- Malignancies, high dose corticosteroids, anti-TNF
Clinical Manifestations

- Intrathoracic disease: Pulmonary, pleural, cardiac
- Extrapulmonary disease

TB: Pulmonary disease

- Silent pulmonary disease: initiation to hypersensitivity
- Primary pulmonary complex
- Segmental lesion
- Progressive primary TB
- Reactivation of TB
TB: Pleural and Cardiac disease

- Hypersensitivity
- Pleural TB
- Pericarditis

Extrathoracic Disease: Lymphohematogenous Disease

- Dissemination
- Blood stream infection
- Miliary Disease
Lymphatic Disease

- Scrofula: the most common extrapulmonary TB (67%)
- *M. bovis; M. tuberculosis*
- Differentiation from NTM

CNS Disease

- Reactivation of caseous lesion versus uncontrolled dissemination
- Inflammation, obstruction and infarction
- Extremely rare <4 months, common 6 m-4 years
- Rapid or slow progression (three stages)
- Prognosis dependent on the stage
- Clinical suspicion in a child with basilar meningitis
CNS Disease

- Diagnosis: CSF findings, imaging findings
- Tuberculoma: common in <10 years, single, infra-tentorial, basilar near the cerebellum
- Paradoxical tuberculoma

Osteoarticular Infection

- Lymohematogenous or contiguous
- Weight bearing bones
- Pott disease
- TB dactylitis
Abdominal and GI Disease

- Lymphohematogenous spread or swallowing the bacilli
- Jejunum, ileum and appendix
- Peritonitis (generalized versus localized)

Genitourinary Disease

- Renal TB (rare in children)
- Genital TB
- Fallopian tubes, epididymitis
- IVF
Cutaneous Disease

- Primary infection, hematogenous spread or hypersensitivity/ EN
- Scrofuloderma
- Papulonecrotic tuberculids (face, trunk, upper thighs) apple-jelly center
- Verruosa cutis

Congenital TB

- Rare
- Hematogenous, aspiration or ingestion of amniotic fluid
- Delayed symptoms
- Diagnosis: examination of different body fluids
Diagnosis
Tuberculin Skin Test

- TST?

Factors That Cause Decreased Response to Tuberculin Skin Test:

- Host-Related Factors: Infections: viral (rubella, rubeola, varicella, influenza), bacterial (typhoid fever, brucellosis, leprosy, pertussis, overwhelming tuberculosis), fungal (blastomycosis), vaccines – live viral, chronic renal failure, malnutrition Diseases affecting lymphoid organs (leukemia, lymphoma, HIV) Certain drugs (corticosteroids, antineoplastic agents) Age (newborn infants and elderly) Stress (surgery, burns, mental illness)

- Tuberculin-Related Factors: improper storage (exposure to light or heat), improper dilution, chemical denaturation, contamination, adsorption to glass or plastic

- Administration-Related Factors: injection of too little antigen, delayed administration after loading syringe, injections physically too close together or given SQ

- Reading-Related Factors, inexperienced reader, conscious or unconscious bias, error in recording

False positive TST results

- Prior NTM infections

- BCG

- Losing reactivity: newborns versus older children

- In general, in the U.S., the TST result is interpreted similarly for persons with and without a history of vaccination
TST: interpretation

- Positive Interpretation of Mantoux Tuberculin Test According to Diameter of Induration and Risk Category:
  - Induration $\geq 5$ mm in Diameter: contact with infectious case, abnormal chest radiograph, HIV, or other immunosuppression
  - Induration $\geq 10$ mm in Diameter: foreign-born individual from high-prevalence country, frequently exposed to high-risk adults, user of illicit intravenous drug(s), other medical risk factor(s), healthcare worker, member of locally identified high-risk population, age $\leq 4$ years
  - Induration $\geq 15$ mm in Diameter: regardless of age or risk factors

Interferon-\(\gamma\) release Assays (IGRAs)

- QFT (2001)
- QFT-GIT (2007)
- Early Secretory Antigenic Target-6 (ESAT-6) and Culture Filtrate Protein 10 (CFP-10) and TB 7.7 peptide antigens
- T-spot TB (Oxford Immunotec)(2008)
Laboratory Diagnosis

- Acid-fast staining, culture: slow, expensive and insensitive
- Drug susceptibility, genotyping, spoligotyping, restriction fragment-length polymorphism
- Insertion sequence IS6110

TB, Culture

- The most important diagnostic method
- Positivity from early morning gastric aspirates <40%
- From bronchoscopy 13-62%
- Inducing sputum with warm saline and albuterol
- Löwenstein–Jensen and Middlebrook solid media
- Radiometric techniques using liquid media
Nucleic Acid Amplification Methodology

- Numerous assays
- IS6110
- Sensitivity and specificity in adults >90%, in children in comparison with clinical diagnosis, sensitivity 25% to 83%, and specificity from 80% to 100%

Principles of Antimycobacterial Approach

- Combination of mycobacteriocidal and static drugs
- Success depends on number, activity, primary or secondary resistance and site (cavity, closed caseous space, within macrophages)
- Cavity $10^9$ versus caseous lesion $10^6$ Resistance for INH: $10^6$ to $10^7$, RIF: $10^6$
- MDR versus XDR
Therapy, Regimens:

- One cidal with one static for 18-24 months, relapse rate of 5-10% INH+RIF for 9 months, relapse rate <3%, triple for 6 months
- Treatment with daily INH+RIF for 1 month, followed by twice weekly for 8 months; study from Brazil
- Several studies with multiple drugs for 6 months
- Intermittent therapy safe and effective
- >95% cure, >99% for significant improvement after two years

Suspected INH, RIF susceptible TB

- AAP and ATS: RIPE
- Daily administration for the first 2 weeks to 2 months
- Subsequently intermittent dosing under DOT
Treatment of Children with HIV

- Adults for 9 months or 6 months after clearing the sputum
- Children: RIPE for 9 months
- IRIS

Extrapulmonary TB

- Adult data
- In general 6 months
- Bone and joint infections 9-12 months
- AAP recommends 9-12 months for meningitis with at least INH+RIF+PZA
- Corticosteroids: meningitis, CNS inflammatory mass, airway compromise
Management of MDR and XDR TB

• Resistance rate is increasing
• Adult data
• Second line drugs well-tolerated

Bacillus Calmette-Guerin Vaccine

• Prevents 50% of primary infections and 60-80% of serious infections
References:

- Centers for Disease Control and Prevention: Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings. MMWR Recomm Rep. 54 (RR-17):1-141 2005
References


