

PEDs Tuberculosis

Background

1. Definition
 - Infection w/ Mycobacterium tuberculosis
2. General information
 - Notifiable disease
 - Mandatory reporting⁶

Pathophysiology

1. Pathology of disease
 - Transmission
 - Inhalation of acid fast Mycobacterium tuberculosis
 - Congenital (hematogenous spread)
 - Granuloma
 - Right lung base (ghon focus)
 - After initial exposure, bacterium can:
 - Progress (infants)
 - Lay dormant without Sx (LTBI)
 - Spread hematogenously to organs
 - Recur years later in the lung (adolescents)
 - Infection chronology
 - 2-6 mos: milliary (disseminated)
 - 4-12 mos: pulmonary/ lymphatic
 - 1-2 yr: skeletal
 - 5 yr: renal
2. Incidence, Prevalence
 - 1/3 of global population has LTBI
 - ~11% of these cases are children <15 years⁸
 - New global cases: 9 million/yr
 - New U.S. cases: 13,000/yr⁴
 - Children: 820/yr⁴
 - More prevalent in immuno-compromised individuals and developing countries
3. Risk factors
 - Travel to high prevalence areas
 - http://www.mass.gov/Eeohhs2/docs/dph/cdc/tb/endemic_country_list.pdf
 - Foreign born individuals
 - 9.5x risk of contracting TB than US born⁴
 - Immunocompromise (untreated HIV)
 - High risk population contact
 - Prisons
 - Health care workers
 - IV drug users
 - Socioeconomically disadvantaged groups
 - Children <4 years at increased risk for disseminated disease
4. Morbidity / mortality

- Mortality low, but difficult to measure⁴
- TB meningitis
 - Mortality 33%
 - Residual neuro deficits in 50%⁴
- Congenital/neonatal TB
 - Mortality 50%⁹

Diagnosics

1. History

- Chronic cough ≥ 3 weeks (pulmonary dz)
- Hemoptysis (cavitary lesions)
- Low grade fever ≥ 2 weeks
- Weight loss
- Failure to thrive

2. Physical Examination

- Pulmonary TB
 - Cough
 - Hemoptysis (cavitary lesions)
- Extrapulmonary TB
 - Lymphadenopathy: 67%⁴
 - Ant. cervical, post. triangle, submandibular, and supraclavicular
 - Meningitis: 13%⁴
 - Subacute onset, communicating hydrocephalus, stroke, incr ICP
 - Pleural TB: 6 %⁴
 - Older children and adolescent
 - Auscultation mimics pneumonia
 - Miliary TB: 5%⁴
 - Pyrexia, hepatomegaly, splenomegaly
 - Skeletal: 4%⁴
 - Spondylitis (thoracic/lumbar), arthritis, osteomyelitis
- Congenital TB:
 - Respiratory distress
 - Fever
 - Hepatomegaly
 - Splenomegaly
 - Poor feeding
 - Lethargy, irritability
 - Low birth weight

3. Diagnostic Testing

- PPD
 - Measure induration (not erythema) 48-72 hours after injection of 0.1 ml PPD
 - Becomes positive 3 wks to 3 mos after infection and stays positive for life
 - False negative
 - Infants, untreated HIV, miliary TB

- False positive
 - Nontuberculous mycobacterium, multiple sequential PPD tests
 - BCG vaccine in past 10 yrs
 - Protects against meningeal and disseminated TB (not pulmonary TB) it is advised to treat a positive PPD in a vaccinated person the same as in a non vaccinated person¹³
 - Sensitivity
 - 60% immunocompetent (culture-confirmed TB)
 - 90% pulmonary TB,
 - 80% extrapulmonary TB
 - 50% miliary or meningeal TB ^{2,7,10,12,13}
 - Chest X-ray
 - 1° Ghon focus
 - Calcification in lower right hilum
 - 2° reactivation
 - Does not typically occur in lung apex as in adults
 - Findings include
 - Infiltrates
 - Nodules
 - Consolidation
 - Cavities
 - Fibrosis
 - Bacteriologic confirmation (30-40% of cases)
 - Gastric aspirates (for swallowed sputum)
 - 3 early AM aspirates before child eats or ambulates
 - Induced sputum culture
 - Must be induced, children often lack tussive force
 - Whole Blood Interferon-Gamma Release Assays (IGRAs)
 - No false positive result from other mycobacteria or past BCG
 - No return visit
 - Like PPD, does not distinguish LTBI and TB dz
4. Diagnostic criteria⁴
- Clinical case definition
 - Must include all:
 - Pos tuberculin skin test or positive IGRA for M. tuberculosis
 - Other s/s of TB:
 - Abnl CXR
 - Abnl chest CT
 - Other chest imaging study or clinical evidence of current dz
 - Tx with ≥ 2 anti-TB medications
 - Completed diagnostic evaluation
 - Laboratory criteria for diagnosis
 - Must incl 1 of the following:
 - Isolation of M. tuberculosis from clinical specimen
 - M. tuberculosis complex found by nucleic acid amplification test (NAAT)

- Evidence of acid-fast bacilli in clinical specimen when culture
 - Has not/ cannot be obtained
 - Falsely negative or contaminated

Differential Diagnosis

1. Key DDx
 - Fever
 - Lymphoma/Leukemia
 - Pertussis
 - Pneumonia
 - Weight Loss
 - Lymphoma/Leukemia
 - Cough
 - Bronchitis
 - Pertussis
 - Pneumonia
 - Empyema
2. Extensive DDx
 - Wegener's granulomatosis
 - PCP
 - Sarcoidosis
 - Cystic Fibrosis

Therapeutics

1. Overview
 - Respiratory isolation
 - Establish case source
 - Report to local public health authorities
 - Standard of care: Directly Observed Therapy (DOT)
 - Completion rate of therapy rises from 50% to 100%³
2. Tx protocol
 - TB exposure
 - <4 yo or immuno-compromised:
 - Start INH pending results of PPD testing
 - D/c treatment if PPD is negative
 - >4 years of age and immuno-competent: place PPD
 - LTBI (positive PPD without symptoms)
 - INH for 9 months (SOR:B), or
 - INH and Rifampin for 3 months (SOR:A)
 - Randomized controlled trials, but not yet on CDC recommendations¹¹
 - TB disease: Combined treatment with
 - INH 6 months
 - Side effects: hepatotoxicity, abdominal pain, dark urine, pale stools
 - Rifampin 6 months
 - Side effects: reddish orange body fluids, hepatotoxicity

- Pyrazinamide 2 months
 - Side effects: gout, rash
- Ethambutol 6 mos if case source not susceptible to all 3 other drugs
 - Side effect: optic neuritis
- Disseminated TB, persistent positive sputum cultures, cavitory lesions, or HIV positive:
 - Treat 9-12 mos
- Drug resistant TB:
 - Treat 12-18 mos
- If Tx interrupted for ≥ 14 d, restart course from the beginning
- Always add ≥ 1 drug if resistance occurs to current regimen
- No age cut off for Tx of LTBI or TB disorder

Follow-Up

1. Return to office
 - Monthly f/u to check adherence to Tx, wt gain and milestones
 - Pulmonary dz
 - CXR 1-2 mos after beginning Tx
2. Refer to specialist
 - Multi-drug resistant TB (MDR-TB)
3. Admit to hospital:
 - Respiratory collapse/organ failure

Prognosis

1. LTBI \rightarrow TB dz
 - >3 yo: 5-10% progress within in 1-2 years
 - <3 yo: 30-40%⁴
2. LTBI Tx 100% effective if "excellent" adherence⁴
3. TB dz has cure rate 95-100% with good adherence to Tx⁴
4. Clinical cure 100% of children with LTBI if adherence to Tx

Prevention

1. Chemoprophylaxis of exposed or LTBI children (see therapeutics section)
2. Respiratory Isolation of confirmed cases of TB disease
3. Treatment of source cases
4. BCG vaccine only approved in the U.S for HIV negative, PPD negative children continually exposed to MDR-TB who cannot be removed from that setting or receive chemo prophylaxis

References

1. Advisory Council for the Elimination of Tuberculosis (ACET) *The Role of BCG Vaccine in the Prevention and Control of Tuberculosis in the United States A Joint Statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices*. CDC Morbidity Mortality Weekly Report April 26, 1996 / 45(RR-4);1-18
2. American Academy of Pediatrics. *Tuberculosis*. In: Red Book: 2009 Report of the Committee on Infectious Diseases, 28th ed, Pickering, LK (Ed), American Academy of Pediatrics, Elk Grove Village, IL 2009. p. 680.

3. Campos-Outcalt D, *Tuberculosis, Old Problems, New Concerns*. The Journal of Family Practice. October 2003. Vol 52, No 10 pg 792-798.
4. Cruz AT, Starke JR, *Pediatric Tuberculosis*. Pediatrics in Review. 2010, 31; 13-26.
5. CDC. (2009, June) *CDC Tuberculosis Surveillance Data Training: Report of Verified Case of Tuberculosis (RVCT) Instruction Manual*. Atlanta, GA: U.S. Department of Health and Human Services, CDC. (Appendix A - Tuberculosis Case Definition for Public Health Surveillance) Available at: <ftp://ftp.cdc.gov/pub/Software/TIMS/2009%20RVCT%20Documentation/RVCT%20Training%20Materials/RVCT%20Instruction%20Manual.pdf>
6. Centers for Disease Control and Prevention. [Summary of notifiable diseases—United States, 2007]. Published July 9, 2009 for MMWR 2007;56(No. 53):[1-3]. Available at: <http://www.cdc.gov/mmwr/PDF/wk/mm5653.pdf>
7. Hatherill, M, Hawkrigde, T, Zar, HJ, et al. *Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis?*. Arch Dis Child 2009; 94:195.
8. Nelson, LJ, Wells, CD. *Global epidemiology of childhood tuberculosis*. International Journal of Tuberculosis Lung Disease 2004; 8: 636.
9. Starke, JR. *Tuberculosis in childhood and pregnancy*: In: Friedman LN, editor. Tuberculosis: current concepts and treatment. 2nd ed. Boca Raton: CRC Press; 2000.
10. Steiner, P, Rao, M, Victoria, MS, et al. *Persistently negative tuberculin reactions: their presence among children with culture positive for Mycobacterium tuberculosis (tuberculin-negative tuberculosis)*. Am J Dis Child 1980; 134:747.
11. Safranek S, Sharma U. *What is the recommended approach to asymptomatic patients who develop a reactive PPD?* February 2006. The Journal of Family Practice, Vol 55, No 2 pg 163-165.
12. van den Bos, F, Terken, M, Ypma, L, et al. *Tuberculous meningitis and miliary tuberculosis in young children*. Trop Med Int Health 2004; 9:309.
13. van der Weert, EM, Hartgers, NM, Schaaf, HS, et al. *Comparison of diagnostic criteria of tuberculous meningitis in human immunodeficiency virus-infected and uninfected children*. Pediatr Infect Dis J 2006; 25:65.

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