Tuberculosis in Pregnancy

Background

1. General information
    - Worldwide, 2nd only to HIV in cause of death by a single infectious agent
        - 1/3 of world population infected with TB
    - Unites States
        - 14,093 active cases in 2005
        - 15 million latent cases
    - Pregnant women NOT at increased risk for acquiring disease
    - Pregnant women with active disease should be treated

Pathophysiology

1. Pathology of disease
    - Infection with Mycobacterium tuberculosis
    - Contracted by breathing contaminated droplets or rarely through skin or sexual contacts
    - Bacteria may replicate for weeks in alveoli and macrophages before cellular immunity responds
    - Response may vary from minimal reaction to extreme hypersensitivity
        - With a hypersensitive response, caseous necrosis may occur leading to
            - Decreased cellular replication
            - Unstable granulomas that may allow for reservoirs of TB to exist
            - Possible active TB, which may be spread to other people
    - Once exposed, only 10-20% of people acquire active TB and that is usually acquired within 3 years of exposure
        - Duration and intensity of exposure to TB is directly related to the likelihood of acquiring an active infection
        - HIV infected individuals are more likely to acquire active TB
    - Organism may remain viable in dormant state
        - May be reactivated during a period of immunologic compromise
2. Incidence, prevalence
    - Prevalence: 19-45% of worldwide population infected
    - Incidence: 8 million new cases/year
    - Bronchopulmonary TB most common form: 80% of cases
    - Extra-pulmonary TB accounts <20%
        - Lymphatic involvement
        - Genitourinary disease
        - Osteomyelitis
        - Meningitis
        - Peritonitis
        - Pericarditis
        - Adrenal involvement
        - Miliary dissemination
3. Risk factors
    - Crowded living conditions
    - Immigration from endemic areas
    - Homelessness
    - Alcoholism

- Racial or Ethnic minority status
- Institutionalized
- Malnourished
- Immunosuppression including HIV-infected pts

4. Morbidity / mortality
   - Mortality: 3 million deaths/year

Diagnostics

1. History
   - Similar to nongravid
     - Pulmonary manifestations most common
       - Cough, SOB, pleuritic chest pain, hemoptysis
   - Systemic manifestations
     - Weight loss, fever, malaise, fatigue, night sweats
2. Physical examination
   - Usually nonspecific findings
     - Fever
     - Wasting
     - Ill-appearing
     - Lungs: varies from normal lung sounds to rales
   - Patients with extrapulmonary TB could present with a variety of findings
     - Neurologic: cranial nerve palsies, altered sensorium
     - Lymphadenopathy
     - Swollen joints
3. Diagnostic testing
   - Laboratory evaluation
     - Culture from sputum sample
       - Lowenstein-Jensen or Middlebrook 7H11 media
         - Gold standard
         - Takes 3-8 weeks to grow
     - Acid Fast Stain on sputum smear
       - Less sensitive than culture requiring 10,000 organisms/mL to show up
       - 70% sensitive if 3 different samples are used
       - Results 1 day
     - Polymerase Chain Reaction
       - Intermediate specificity and sensitivity between Acid fast stain and culture
     - **TB skin test**
       - Inject 5 units of Purified Protein Derivative (PPD) into the subcutaneous tissue
       - Read induration at 48-72hr
         - Positive if >15 mm of induration in low risk individuals
         - Differs for certain subgroups
           - Positive if > 5 mm induration:
             - Fibrotic Changes on CXR
             - Recent contact of TB patient
             - Immunosuppressed

- Known or suspected HIV patient
  - Frequently false negative in these patients
- Positive if > 10 mm induration:
  - Recent arrival from area where TB is prevalent
  - Injection drug users
  - People in high-risk living conditions
  - People with certain medical diseases that may prevent full immune response
  - Children under 4 yo
- Same rules of interpretation of PPD skin test apply to pregnant women
- Obtain CXR in all positive patients

- Diagnostic imaging
  - Chest radiograph
    - Findings
      - Patchy or nodular infiltrate in upper lobes
      - Cavity formation
      - Hilar and paratracheal adenopathy
      - Pleural effusion
      - Lower lobe in elderly or late stage HIV
- Other studies
  - CBC, albumin
    - In advanced disease:
      - Normocytic, normochromic anemia
      - Hypoalbuminemia
      - Hypergammaglobulinemia
      - WBC count is usually normal but may be between 10,000 and 15,000 cells/mm3

4. Diagnostic "Criteria"
   - Active tuberculosis
     - Strong presumptive diagnosis with suspicious chest x-ray and symptomatology, especially in patients with risk factors
     - Positive sputum smear confirms diagnosis
     - In absence of findings on CXR, must await culture results
   - Latent Tuberculosis
   - PPD is positive and CXR, AND sputum cultures are negative

Differential Diagnosis

1. Key DDx
   - Pneumonia
   - Pneumonia associated with hilar adenopathy should always suggest primary TB
   - Sarcoidosis
   - Lung cancer
   - Chronic bronchitis
   - Empyema
   - CHF

2. Extensive DDx
    - Other cancers
    - Parasites
    - Malabsorption disorders
    - Inflammatory bowel dz
    - Familial mediterranean fever
    - Meningitis
    - Stroke
    - Rheumatoid arthritis
    - Lupus
    - Herniated disc

Therapeutics

1. Acute treatment
    - All pts with suspicion for active pulmonary TB should be admitted in respiratory isolation with negative airflow
    - Obtain 3 morning sputum samples for acid-fast staining and culture and sensitivities
    - If no sputum, consider bronchoalveolar lavage
    - If extrapulmonary site is suspected, consider checking
        - Urine, pleural fluid, peritoneal fluid, bone marrow, CSF
    - Medication regimens
        - Drug resistant strains of TB are relatively common, necessitating multi-drug treatment regimens
            - 8% of TB isolates are resistant to INH
            - 1.3% of TB isolates are resistant to INH and RMP
        - TB Medications
            - Isoniazid (INH)
            - Rifampin (RMP)
            - Pyrazinamide (PZA)
            - Ethambutol (EMB)
            - Streptomycin (STM)
        - Toxicity monitoring
            - Prior to treatment all patients need baseline AST, ALT, alkaline phosphatase, platelets and creatinine
            - Patients on EMB should have visual acuity check and red-green color discrimination
            - Patients on INH should receive Vitamin B6 throughout treatment
            - Serial LFTs every 1-2 months ONLY if
                - Baseline LFT's are abnormal
                - Patient is postpartum
                - Patient is at increased risk of hepatotoxicity (alcoholic, hepatitis, etc.)
                - INH and/or RMP should be discontinued and an alternative regimen sought if liver transaminase levels are 3 times above the upper limit of normal in symptomatic patients or 5 times above the upper limit of normal in asymptomatic patients
        - **Uncomplicated, pulmonary TB**
            - Several regimens are advocated by the CDC, the most common:

- INH + RMP + PZA + either EMB or STM
  - Best if can maintain all 4 drugs for first 2 months of therapy
  - All 4 drugs until sensitivities are determined, then may drop EMB and/or PZA
  - Strict adherence to regimen is required
  - If strain is RMP-resistant, will require 18-24 months of therapy
- Alternative regimens may be used as recommended by the CDC
- Directly observed therapy
  - All dosages given by health care officials to non adherent patients
  - No evidence that this method of treatment delivery is more effective than self-treatment
  - Some health departments do this for all patients
  - May need only 3 doses/week

▪ **Pregnant patients**
- Treatment should not be deferred during pregnancy
- Risk of disease progression outweighs risk of fetal toxicity
- The recommended drugs are a level C pregnancy recommendation – fetal effects are unknown but there is no current evidence to suggest teratogenicity from these drugs
- Regimens
- INH + EMB + RMP for 9 months
- Do NOT use STM nor PZA
- Added caution with respect to INH-induced hepatotoxicity is indicated due to increased risk of liver problems in perinatal period
  - As in non-pregnant patients, INH and/or RMP should be discontinued and an alternative regimen sought if liver transaminase levels are 3 times above the upper limit of normal in symptomatic patients or 5 times above the upper limit of normal in asymptomatic patients

▪ **Nursing patients**
- May use standard treatment regimens because drugs do not cause toxicity to nursing infant

▪ **Latent TB**
- Positive PPD but
  - NO CXR findings
  - NO symptoms
  - NO positive culture
- Treatment is controversial but is generally done in the U.S.
  - Most beneficial in recently converted (defined as increase of induration on PPD of 10 mm or more in the last 2 years)
  - May consider waiting to reassess patient in 2 months and if still PPD positive without other findings, may begin treatment then
  - Standard regimen: INH for 9 months

- Pregnant patients
  - If latent TB as defined above, may safely wait 2 months to see if progresses to active infection
  - If still pregnant after 2 months and there is no progression, may consider to continue watchful waiting because the risk of treatment side effects may outweigh benefits
  - Treat if recently converted (defined as increase of induration on PPD of 10 mm or more in the last 2 years) or HIV positive
  - Begin treatment after delivery

2. Further management (24 hrs)
   - May consider corticosteroids (prednisone) in patients with severe constitutional symptoms or poor oxygenation
   - Less common manifestations
     - Lymphadenitis (Scrofula)
     - Renal
       - Sterile pyuria with hematuria
     - Meningitis
     - Peritonitis
     - Pericarditis
     - TB pleuritis
     - Cavitation of renal parenchyma
     - Bone & joint infection
       - Monoarthritis of knee w/ gradual pain & stiffness
       - Osteomyelitis of thoraco-lumbar spine (Potts' disease)
3. Long-term management
   - Follow pts until completion of medication regimen AND 2 consecutive sputum cultures are negative
   - Pts do not need to be followed long term once cured

Follow-Up

1. Return to office
   - Time frame for return visit
     - Most patients may be treated outpatient
     - Return to office every 1-2 months for evaluation of medication side effects and adherence
   - Recommendations for earlier follow-up
     - If pt does not have improvement of symptoms in 2-3 weeks
     - If pt experiences other symptoms or feelings of illness
       - These may be medication side effects and should be evaluated
2. Refer to infectious disease specialist
   - If sensitivities reveal a drug-resistant strain or unacceptable side effects occur
3. Admit to hospital
   - Respiratory compromise
   - Wasting
   - Unable to adhere to medication regimen
   - May put community at risk

Prognosis

1. With adherence to medication regimens, cure is possible and prognosis is excellent
2. Cure is more challenging in those few people with multi-drug resistant strains of TB
3. Without Tx, 80% of people with active TB die within 2 yrs

Prevention

1. BCG
    - Live, attenuated vaccine
    - Decreases incidence of TB in children by 60-80%
    - Effective in high-prevalence areas of the world
    - Not used in the U.S.
    - Causes positive PPD skin test in about 20% of people vaccinated

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