Tuberculosis
Pulmonary Therapeutics
PHMPR 732

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TB in General

• As of 2007, TB is present in 1/3 of the world’s population (~2 billion people)
• 8 million new cases occur worldwide annually
• 2-3 million people died of TB in 2006


TB Morbidity
United States, 2000–2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>16,309</td>
<td>5.8</td>
</tr>
<tr>
<td>2001</td>
<td>15,946</td>
<td>5.6</td>
</tr>
<tr>
<td>2002</td>
<td>15,056</td>
<td>5.2</td>
</tr>
<tr>
<td>2003</td>
<td>14,840</td>
<td>5.1</td>
</tr>
<tr>
<td>2004</td>
<td>14,515</td>
<td>4.9</td>
</tr>
<tr>
<td>2005</td>
<td>14,097</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Cases per 100,000, updated as of March 29, 2006.

Reported TB Cases*
United States, 1982–2005

*Updated as of March 29, 2006
TB Case Rates* by Age Group
United States, 1993–2005

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Cases per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 yrs</td>
<td>6%</td>
</tr>
<tr>
<td>15–24 yrs</td>
<td>11%</td>
</tr>
<tr>
<td>25–44 yrs</td>
<td>34%</td>
</tr>
<tr>
<td>45–64 yrs</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;65 yrs</td>
<td>20%</td>
</tr>
<tr>
<td>Overall</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Updated as of March 29, 2006.

Reported TB Cases by Age Group, United States, 2005

- <15 yrs (6%)
- 15–24 yrs (11%)
- 25–44 yrs (34%)
- 45–64 yrs (29%)
- >65 yrs (20%)

TB Case Rates by Age Group and Sex, United States, 2005

- Men
- Women
- Males
- Females

*Updated as of March 29, 2006.
### Major Factors Contributing to Resurgence of TB in the 1980’s
- Co-infection with HIV
- Decline in public health services
- Immigration
- Homelessness, drug abuse, poverty, crowded housing

### Groups at high risk for exposure
- Foreign-born from a high prevalence country
- Residents of correctional institutions
- Residents of nursing homes
- Homeless persons
- Drug abusers
- Poor health & medically indigent city dwellers
- Health care workers
- Children living with adults in these categories

### Groups at high risk to develop Active Disease
- HIV co-infection
  - ~12-14 million people are co-infected
- Certain medical risk factors (e.g., diabetes)
- Immunosuppressive therapies
- Malnutrition and body weight <10% ideal
- Infants

### Persons at Increased Risk for Drug Resistance
- History of treatment with TB drugs
- Contacts of persons with drug-resistant TB
- Foreign-born persons from high prevalent drug resistant areas
- Smears or cultures remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks
Other Epidemiologic Points of Interest

TB: A disease of big cities
- Cities with populations > 250,000:
  - 18% of the country’s population
  - 42% of the country’s TB cases
- 11% of nation’s counties report 83% of cases
- 7 states account for 63% of cases
  - California, Georgia, Florida, S. Carolina, Texas, Illinois

TB: a disease of immigrants
- Immigrants from 7 countries account for 63% of foreign-born cases:
  - Mexico, Philippines, Viet Nam, S. Korea, Haiti, China, India

Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2005*

*Updated as of March 29, 2006.
Reported TB Cases by Origin and Race/Ethnicity,* United States, 2005

U.S.-born
- American Indian or Alaska Native (6%)
- Asian (3%)
- Black or African-American (24%)
- Hispanic or Latino (40%)
- White (6%)

Foreign-born**
- White (6%)
- Asian (48%)
- Black or African-American (13%)
- Hispanic or Latino (15%)

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.
**American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander accounted for less than 1% of foreign-born cases and are not shown.

Countries of Birth of Foreign-born Persons Reported with TB
United States, 2005

- Mexico (25%)
- Philippines (11%)
- Other Countries (53%)
- Guatemala (2%)
- Haiti (3%)
- China (5%)
- India (5%)
- Viet Nam (5%)

HIV co-infection
- The major factor contributing to resurgence of TB in the 80's
- The strongest risk factor for development of active disease
- Co-infection rate highest in 25 - 44 year olds


*Per 100,000 population.
**Data for 2006 are provisional.

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2004*

Epidemiologic Variation with Race/Ethnicity

TB Case Rates by Race/Ethnicity* United States, 1993–2005**

Reported TB Cases by Race/Ethnicity* United States, 2005

*Updated as of March 29, 2006.
Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

**Updated as of March 29, 2006.

*All cases are non-Hispanic. In 2005, Asian/Pacific Islander category includes persons who reported race as Asian only and/or Native Hawaiian or Other Pacific Islander only.
"Updated as of March 29, 2006."
TB Case Rates by Age Group and Race/Ethnicity,* United States, 2005

Pathophysiology of TB

Etiology

• *Mycobacterium tuberculosis*

Reservoir & Transmission

• Man is the reservoir
• Transmission by droplet nuclei
  – Formed through coughing
  – Portal of entry is the lower respiratory tract
  – Major site of infection is the lung

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.
Pathogenesis: Primary Infection

- General
  - Phagocytosis by alveolar macrophages
  - Inflammatory exudate
  - Dissemination in lungs and regional lymph nodes
  - Extrapulmonary dissemination
  - Decreased multiplication and dissemination (latent TB infection)

- Immunologic processes
  - Delayed hypersensitivity
    - PPD+ in 2-10 weeks
  - Acquired cellular immunity
    - Macrophage inhibition of multiplication

Pathogenicity: Primary Infection

- Bacterial Populations
  1. Extracellular
     - Largest number
     - Cavitary lesions
     - Fast multiplication, neutral or alkaline pH
  2. Closed caseous lesions
     - Slow multiplication, intermittent growth, neutral pH

Pathophysiology

- Inhalation of Droplet Nuclei
- Transport of Mycobacteria in Blood and Lymph
- Caseous Necrosis & Cavitation
- Infection Containment
- Infection Controlled (no granuloma)
- Granuloma Formation
- Bronchoscopy Spread
- Multiplication within Alveoli & Alveolar Macrophages
- Seeding of Regional Lymph Nodes & Extrapulmonary Sites
- Hypersensitivity Development (3 to 8 weeks)
- Extrapulmonary Disseminated TB

Principles and Practice of Infectious Diseases, 5th Ed. pp 2576-2607.
Pathogenesis: Primary Infection

3. Intracellular (macrophages)
   • Slow multiplication
   • Intermittent growth
   • Neutral pH

Pathogenesis: Reinfection (Secondary)

• Endogenous vs. exogenous
• Localization of initial lesion
  – Necrosis
  – Localization
• Spread by extension
• Miliary TB
  – Spread through blood and lymph to multiple organs

Pathogenesis: Reinfection (Secondary)

• Conditions predisposing to endogenous reinfection
  – Decreased resistance in previous infected individuals

Pathogenesis: Reinfection (Secondary)

<table>
<thead>
<tr>
<th>SITE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>85-90</td>
</tr>
<tr>
<td>Pleural space</td>
<td>3</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>2</td>
</tr>
<tr>
<td>Miliary</td>
<td>1.7</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.2</td>
</tr>
<tr>
<td>CNS</td>
<td>0.65</td>
</tr>
<tr>
<td>Bone</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Symptoms of Pulmonary TB

- Productive, prolonged cough (duration of >3 weeks)
- Chest pain
- Hemoptysis

Systemic Symptoms of TB

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

Evaluation for TB

- Medical history
- Physical examination
- Mantoux tuberculin skin test
- Chest radiograph
- Bacteriologic or histologic exam

Medical History

- Symptoms of disease
- History of TB exposure, infection, or disease
- Past TB treatment
- Demographic risk factors for TB
- Medical conditions that increase risk for TB disease
Diagnosis: Identification of Organism

- Culture (2-8 weeks)
- Smear
- Rapid diagnostic tests
- Susceptibility testing (3-8 weeks)

Cultures

- Use to confirm diagnosis of TB
- Culture all specimens, even if smear negative
- Results in 4 to 14 days when liquid medium systems used

Drug Susceptibility Testing

- Drug susceptibility testing on initial *M. tuberculosis* isolate
- Repeat for patients who
  - Do not respond to therapy
  - Have positive cultures despite 2 months of therapy
- Promptly forward results to the health department
Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB

Targeted Testing for TB

Purpose
- Find persons with LTBI who would benefit from treatment
- Groups that are not high risk for TB should not be tested routinely

Groups That Should Be Tested for LTBI

Persons at higher risk for exposure to or infection with TB
- Close contacts of a person known or suspected to have TB
- Foreign-born persons from areas where TB is common
- Residents and employees of high-risk congregate settings
- Health care workers (HCWs) who serve high-risk clients

Groups That Should Be Tested for LTBI (cont.)

Persons at higher risk for exposure to or infection with TB
- Medically underserved, low-income populations
- High-risk racial or ethnic minority populations
- Children exposed to adults in high-risk categories
- Persons who inject illicit drugs
Groups That Should Be Tested for LTBI (Cont.)
Persons at higher risk for TB disease once infected
- Persons with HIV infection
- Persons recently infected with *M. tuberculosis*
- Persons with certain medical conditions
- Persons who inject illicit drugs
- Persons with a history of inadequately treated TB

Testing for TB Disease and Infection

Routine Skin Testing
- Recommended for:
  - Annual testing for those at high risk
  - Periodic testing for those with no risk factors but living in high prevalence area
- Not indicated for those with no risk factors living in low prevalence areas

Testing Materials
- Old tuberculin
  - Useful for screening large populations
- Purified Protein Derivative (PPD)
  - 1st strength (1 TU)
  - intermediate (5 TU)
  - 2nd strength (250 TU)
Methods of Administration

- Mantoux test
  - 0.1ml intradermally
- Vollmer patch
- Tine test
  - OT

Mantoux Tuberculin Skin Test

- Preferred method of testing for TB infection in adults and children
- Tuberculin skin testing useful for
  - Examining person who is not ill but may be infected
  - Determining how many people in group are infected
  - Examining person who has symptoms of TB

Factors that May Affect the Skin Test Reaction

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>Nontuberculous mycobacteria</td>
</tr>
<tr>
<td></td>
<td>BCG vaccination</td>
</tr>
<tr>
<td>False-negative</td>
<td>Anergy</td>
</tr>
<tr>
<td></td>
<td>Recent TB infection</td>
</tr>
<tr>
<td></td>
<td>Very young age (&lt; 6 months old)</td>
</tr>
<tr>
<td></td>
<td>Live-virus vaccination</td>
</tr>
<tr>
<td></td>
<td>Overwhelming TB disease</td>
</tr>
</tbody>
</table>
### Anergy

- Do not rule out diagnosis based on negative skin test result
- Consider anergy in persons with no reaction if
  - HIV infected
  - Overwhelming TB disease
  - Severe or febrile illness
  - Viral infections
  - Live-virus vaccinations
  - Immunosuppressive therapy.
- Anergy skin testing no longer routinely recommended

### Boosting

- Some people with LTBI may have negative skin test reaction when tested years after infection
- Initial skin test may stimulate (boost) ability to react to tuberculin
- Positive reactions to subsequent tests may be misinterpreted as a new infection

### PPD Interpretation

**General**
- Reactivity occurs 3-6 wk after exposure
- Reactivity lowered by young age, poor nutrition, immunosuppression, viral infection, overwhelming TB, corticosteroid therapy
- False-positive with NTM & BCG vaccination

**PPD Interpretation**

- Read as positive with:
  - ≥5 mm induration
  - ≥10 mm induration
  - ≥15 mm induration

Depending on risk factors and history
Prevention of TB

- Contact Isolation
- Early Diagnosis and Treatment
- BCG vaccine
  - PPD neg. infant or child with continuous exposure
  - Certain health care workers

Chemoprophylaxis

- Decision to treat dependent on:
  - Results of PPD
  - Risk factors
  - History
  - X-ray findings
- Current recommended regimen:
  - INH 5-10 mg/kg/d X 6-9 months
  - Alternative: rifampin (600mg/d) + pyrazinamide (20mg/kg/d) X 2 months
  * Associated with higher rate of hepatotoxicity

Chemoprophylaxis

- Keys to success:
  - INH susceptible isolate
  - Adherence to INH for entire course of therapy
  - Low risk for exogenous reinfection

Chemoprophylaxis

- Alternate Regimens indicated for:
  - HIV+
  - Contacts of INH-resistant TB
  - Contacts of MDR-TB
  - Those with proven INH-resistant TB
Monitoring Patients

Baseline laboratory testing
- Not routinely indicated with chemoprophylaxis
- Baseline hepatic measurements for
  - Patients whose initial evaluation suggests a liver disorder
  - Patients with HIV infection
  - Pregnant women and those in immediate postpartum period
  - Patients with history of chronic liver disorder

Monitoring Patients

At least monthly, evaluate for
- Adherence to prescribed regimen
- Signs and symptoms of active TB disease
- Signs and symptoms of hepatitis (if receiving isoniazid alone, and at 2, 4, and 8 weeks if receiving RIF and PZA)

Treatment of Reinfection (Active) TB

Basic Principles of Treatment
- Provide safest, most effective therapy in shortest time
- Multiple drugs to which the organisms are susceptible
- Never add single drug to failing regimen
- Ensure adherence to therapy
Adherence

- Nonadherence is a major problem in TB control
- Use case management and directly observed therapy (DOT) to ensure patients complete treatment

Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose of medication
- Consider DOT for all patients
- DOT should be used with all intermittent regimens
- DOT can lead to reductions in relapse and acquired drug resistance
- Use DOT with other measures to promote adherence

Mode of Treatment Administration in Persons Reported with TB United States, 1993–2003*

Completion of TB Therapy United States, 1993–2003*

*Updated as of March 29, 2006.
**Healthy People 2010 target: 90% completed in 1 yr or less.
Note: Persons with initial isolates resistant to rifampin and children under 15 years old with meningitis, bone or joint, or miliary disease excluded.
Treatment of TB for HIV-Negative Persons

- Include four drugs in initial regimen (1st 2 mos)
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB) or streptomycin (SM)
- Adjust regimen when drug susceptibility results are known

• Continuation regimen:
  – Lasts 4 additional months
  – INH
  – RIF

Treatment of TB for HIV-Positive Persons

- Management of HIV-related TB is complex
- Care for HIV-related TB should be provided by or in consultation with experts in management of both HIV and TB

RIF-based regimens generally recommended for persons

- Who have not started antiretroviral therapy
- For whom PIs or NNRTIs are not recommended

Initial treatment phase should consist of

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

RIF may be used with some PIs and NNRTIs
Treatment of TB for HIV-Positive Persons (cont.)

- For patients receiving PIs or NNRTIs, initial treatment phase may consist of
  - Isoniazid (INH)
  - Rifabutin (RFB)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
- An alternative non-rifamycin regimen includes INH, EMB, PZA, and streptomycin (SM)

Extrapulmonary TB

- In most cases, treat with same regimens used for pulmonary TB

Bone and Joint TB, Miliary TB, or TB Meningitis in Children

- Treat for a minimum of 12 months

Pregnant women

- 9-month regimen of INH, RIF, and EMB
- PZA and SM are contraindicated
- PZA not contraindicated in HIV-positive pregnant women

Children

- In most cases, treat with same regimens used for adults

Infants

- Treat as soon as diagnosis suspected

Drug-resistant Tuberculosis
Primary Anti-TB Drug Resistance
United States, 1993–2005*

Primary Isoniazid Resistance in
U.S.-born vs. Foreign-born Persons
United States, 1993–2005*

Primary MDR TB in
U.S.-born vs. Foreign-born Persons, United
States, 1993–2005*

Global Incidence of Multi-drug Resistant TB

*Updated as of March 29, 2006.
Note: Based on initial isolates from persons with no prior history of TB.
MDR TB defined as resistance to at least isoniazid and rifampin.

Zignol et al. JID 2006;194:479
Treatment Regimens for TB Resistant Only to INH

**HIV-Negative Persons**
- Carefully supervise and manage treatment to avoid development of MDR TB
- Discontinue INH and continue RIF, PZA, and EMB or SM for the entire 6 months
- Or, treat with RIF and EMB for 12 months

**HIV-Positive Persons**
- Regimen should consist of a rifamycin, PZA, and EMB

Multidrug-Resistant TB (MDR TB)
- Presents difficult treatment problems
- Treatment must be individualized
- Clinicians unfamiliar with treatment of MDR TB should seek expert consultation
- Always use DOT to ensure adherence
- A good resource: www.nationaltbcenter.edu

Extensively Drug Resistant TB (XDR-TB)
- Defined as disease caused by bacterial resistant to at least isoniazid and rifampin (MDR) plus risistance to any fluoroquinolone and at least 1 second-line drug

Role of Steroids in TB
- TB meningitis
- TB pericarditis
- Pulmonary TB
- Dosage

Monitoring for Adverse Reactions

- Baseline measurements
- Monitor patients at least monthly
- Monitoring for adverse reactions must be individualized
- Instruct patients to immediately report adverse reactions

Monitoring Response to Treatment

- Monitor patients bacteriologically monthly until cultures convert to negative
- After 3 months of therapy, if cultures are positive or symptoms do not resolve, reevaluate for:
  - Potential drug-resistant disease
  - Nonadherence to drug regimen
- If cultures do not convert to negative despite 3 months of therapy, consider initiating DOT

Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin
- Rifapentine

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin
- Capreomycin
- Levofloxacin
- Moxifloxacin

*Not approved by the U.S. Food and Drug Administration for use in the treatment of TB*

Common Adverse Reactions to Drug Treatment (1)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergy</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changed color vision</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, or Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal LFT results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellowish skin or eyes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark urine</td>
</tr>
</tbody>
</table>
Common Adverse Reactions to Drug Treatment (2)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal intolerance</td>
<td>Upset stomach, vomiting, lack of appetite</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>Joint aches</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Gout (rare)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ear damage</td>
<td>Balance problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ringing in the ears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal kidney function test results</td>
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Common Adverse Reactions to Drug Treatment (3)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td>Thrombocytopenia</td>
<td>Easy bruising</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td>Slow blood clotting</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Gastrointestinal intolerance</td>
<td>Upset stomach</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Drug interactions</td>
<td>Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
</tr>
</tbody>
</table>

Drug Interactions

- Relatively few drug interactions substantially change concentrations of antituberculosis drugs
- Antituberculosis drugs sometimes change concentrations of other drugs
  - Rifamycins can decrease serum concentrations of many drugs, (e.g., most of the HIV-1 protease inhibitors), to subtherapeutic levels
  - Isoniazid increases concentrations of some drugs (e.g., phenytoin) to toxic levels

For more information about TB, visit the CDC website:

http://cdc.gov/nchstp/tb
### CASE STUDY – TUBERCULOSIS

MKR, a 55 year old white male who recently moved here from New York City, is seen in the ER with a complaint of “coughing up blood”. He stated that he had a chronic cough for the last 3 months, productive of small amounts of clear sputum. He lived in a homeless shelter in NYC for the last 2 months before moving to South Carolina. He denies previous history of hemoptysis or chest pain. Other pertinent history includes a blood test positive for HIV two years ago and exposure to an active case of tuberculosis three years ago. He was neither skin tested nor treated at that time. Other symptoms elicited at this time were night sweats and afternoon fevers.

Chest x-ray performed on this admission revealed bilateral apical cavitary lesions. Admission vital signs included T = 98.7°F, pulse = 102 bpm, respiratory rate = 35 bpm, BP = 120/75 mm Hg, height 5’5”, weight 110 lbs.

### STUDY QUESTIONS:

1. What evidence exists to support this diagnosis?
2. What other diagnostic tests would be helpful in confirming the diagnosis and planning drug therapy?
3. What risk factors does this patient have for a.) exposure to TB, and b.) development of active disease?
4. What initial drug therapy would you recommend for this patient and how would you monitor therapy?
5. Several days into hospitalization, the patient reveals that he has been living with his brother since moving to Charleston. What action, if any, should be taken with the brother?