

# Tuberculosis

# Introduction

- Ethiopia ranks seventh among the world's 22 high-burden tuberculosis (TB) countries.
- WHO's and Global TB Report 2009:
  - 314,267 TB cases in 2007 or 378 cases per 100,000 population.
- Ethiopia's National Tuberculosis and Leprosy Control Program (NTLCP) began to implement DOTS (the internationally recommended strategy for TB control) in two zones in 1991;
  - in 2007, WHO reported that DOTS coverage reached 95 percent of the population.
- However, while treatment is integrated into general health services and DOTS geographical coverage is 95 percent, due to the limited health infrastructure in the country, only approximately 60 to 70 percent of the population has access to DOTS services.

# Introduction

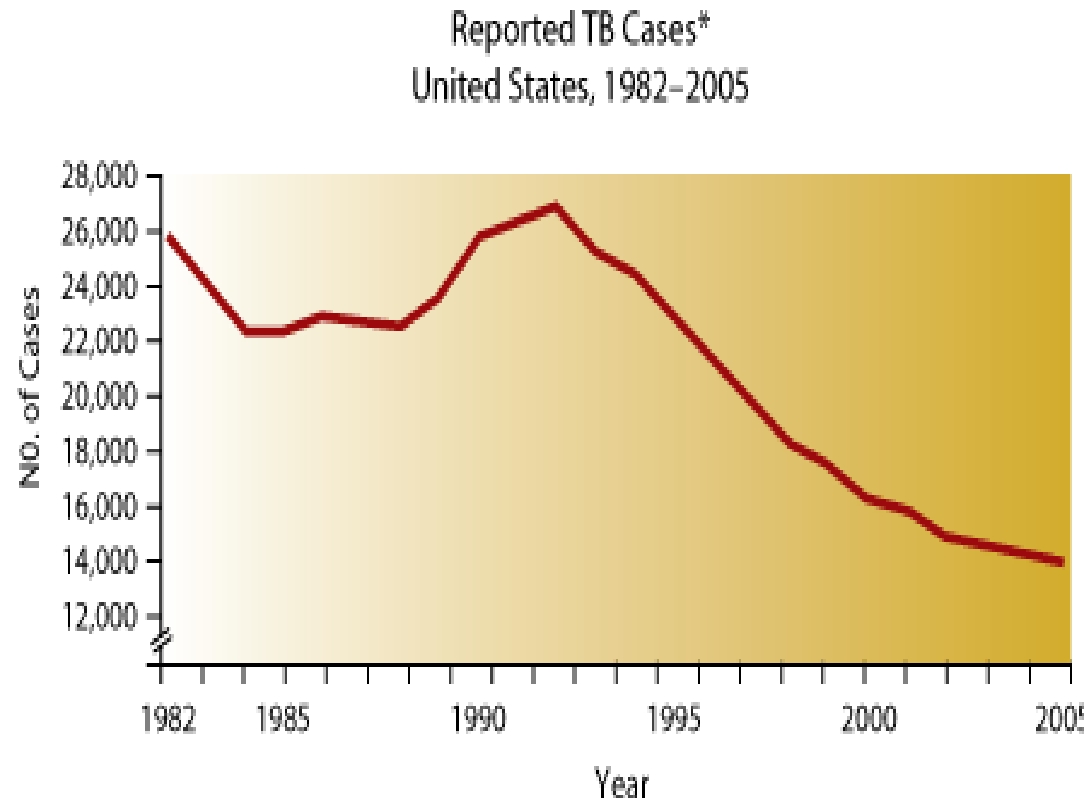
- The number of TB cases is likely to increase as Ethiopia's HIV/AIDS epidemic expands
  - 16 percent of notified TB patients tested for HIV
  - 40 percent are HIV positive.
- The level of MDR TB among new TB cases is estimated at 20 percent
  - 5,979 cases of MDR-TB were reported in 2007.

# Introduction

- TB is a communicable infectious disease caused by ***Mycobacterium tuberculosis***.
- It can cause a silent, latent infection or a progressive, active disease
- One-third of the world's population currently is infected
- M. tuberculosis vs. Mycobacterium bovis
  - drinking milk contaminated with M. bovis (pasteurization)
  - "consumption" (weight loss)
- Left untreated or improperly treated, TB causes progressive tissue destruction and, eventually, death

# EPIDEMIOLOGY

- 2 billion people are infected by *M. tuberculosis*
- 1.5 million people die from active TB each year despite the fact that it is curable.



\*Updated as of March 29, 2006

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach*, 7th Edition: [Http://www.accesspharmacy.com](http://www.accesspharmacy.com)

# Risk Factors for Infection

- Location
- Close contacts of pulmonary TB patients
  - The more prolonged the contact the greater is the risk, with infection rates as high as 30%.
- limited access to healthcare, live in crowded conditions, or are homeless, histories of alcohol abuse or illicit drug use, hepatitis B or human immunodeficiency virus (HIV)

# Risk Factors for Infection

## Race, Ethnicity, Age, And Gender

- Hispanics, blacks, and Asians:
  - Rates 7.3, 8.3, and 17.9 times higher than whites
- Age:
  - among people 25 to 44 years of age (35%)
  - 45 to 64 years of age (28%) and
  - 65 years of age and older (21%).
- Co-infection with Human Immunodeficiency Virus
  - TB and HIV seem to act synergistically – increased risk vs. progression to active disease

# Risk Factors for Disease

- Once infected:
  - lifetime risk of active TB is **10%**
  - Children younger than 2 years of age and adults older than 65 years of age have
    - **two to five times greater risk**
- The greatest risk for active disease occurs during the first 2 years after infection
- Immune suppression
  - e.g., renal failure, cancer, and immunosuppressive drug treatment: 4 to 16 times greater risk
- **HIV-infected:**
  - **100 times** more likely to develop active TB than normal individuals
  - have an annual risk of active TB of approximately 10%



# ETIOLOGY

- M. tuberculosis
  - a slender bacillus with a waxy outer layer
  - 1 to 4  $\mu\text{m}$  in length
- It doesn't stain with Gram stain
  - Ziehl-Neelsen stain or the fluorochrome stain should be used instead
  - Hence, they are called **acid-fast bacilli (AFB)**.
- **Doubling time** in culturing is very slow (every 20 hr)
  - comparing with gram-positive or negative bacteria which is about every **30 minute**

# Transmission

- Person-to-person
  - coughing or sneezing
    - **Laryngeal** form of TB – can transmit TB even with talking
  - Incidence is 30% for close contacts
  - A person with **cavitary, pulmonary TB and a cough** is considered very infectious and may infect greater than 30% of contacts until that person is treated effectively.
- "Droplet nuclei":
  - Contains one to three organisms , small enough (1-5 mm) to reach the alveolar surface

# Pathogenesis

- T-lymphocyte responses are essential to controlling *M. tuberculosis* infections
- **T-lymphocytes** activate macrophages that, in turn, engulf and kill mycobacteria and also destroy immature macrophages (harbor *M. TB* but are unable to kill the invaders)
  - CD4+ cells are the primary T cells involved
    - B-cells- do not appear to contribute much to the control of TB
- Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and INF- $\gamma$  are important cytokines involved in coordinating the host's cell-mediated response.

# Pathogenesis...

- M. tuberculosis has several ways of evading or resisting the host immune response
- Particularly it can inhibit the fusion of lysosomes to phagosomes inside macrophages
  - This prevents the destructive enzymes found in the lysosomes from getting to the bacilli captured in the phagosomes
  - This inhibition of destructive mechanisms allows time for M. TB to escape into the cytoplasm
  - multiply in the macrophage cytoplasm,
- Lipoarabinomannan, the principal structural polysaccharide of the mycobacterial cell wall, also inhibits the host immune response.
- These survival mechanisms make M. tuberculosis a particularly difficult organism to control.
- Any defects in the host immune system make it likely that M. TB will not be controlled and that active disease will ensue.

# Primary Infection

- Transmitted by Inhaling airborne particles
- Progression to clinical disease depend on three factors
  - a. the amount inhaled (infecting dose)
  - b. the virulence, and
  - c. the host's immunity (cell mediated)
- Role of macrophages
  - At the alveolar surface, the bacilli that were delivered by the droplet nuclei are ingested by pulmonary macrophages. If these macrophages inhibit or kill the bacilli, infection is aborted. If the macrophages cannot do this, the organisms continue to multiply

# Primary infection....

- Some of the intracellular organisms are transported by the macrophages to regional lymph nodes as well as through blood stream.
- When this intravascular dissemination occurs, M. TB can infect any tissue or organ in the body.
- Most commonly, M. tuberculosis infects the **posterior apical region** of the lungs.
  - This may be so because of the
    - high oxygen content, and
    - a less vigorous immune response in this area

# Primary Infection...

After 3 weeks

- By this time (more than 3 weeks), in most recently infected individuals, macrophages have begun to form **granulomas** to contain the organisms.
- In a typical tuberculous granuloma, activated macrophages accumulate around a caseous lesion and prevent its further extension
  - At this point, the infection is largely under control, and bacillary replication falls off dramatically

# Primary infection....

- Over 1 to 3 months, activated lymphocytes reach an adequate number, and tissue hypersensitivity results.
- In practical terms, this is the reason why tests to diagnose latent TB infection, purified protein derivative (PPD) skin test, and the INF- $\gamma$  release assays, take between 2 and 12 weeks to become positive
- Approximately 90% of infected patients have no further clinical manifestations.
- Most patients show a positive skin test (70%), whereas some also have radiographic evidence of stable granulomas



# Reactivation Disease

- Occurs in 10% (50% within 2 years of infection)
- Site:
  - the apices of the lungs (85% of cases)..most common site
- Organisms within granulomas emerge and begin multiplying extracellularly
  - Hole (cavity) in the lungs....b/c of inflammatory response
- regional necrosis and structural collapse:
  - toxic mixture including cytokines and lysozymes release secondary to the killing of mycobacteria, macrophages, and neutrophils
- Partial healing may result from fibrosis, but these lesions remain unstable and may continue to expand
- If left untreated:
  - hypoxia, respiratory acidosis, and eventually death.

# Extrapulmonary Tuberculosis

- Caseating granulomas at extrapulmonary sites can undergo liquefaction, releasing tubercle bacilli and causing symptomatic disease.
- Extrapulmonary TB without concurrent pulmonary disease is uncommon in normal hosts but more common in HIV-infected patients.
- Challenge in diagnosis
- Lymphatic and pleural diseases are most common forms
  - Followed by Bone, joint, genitourinary, meningeal, and others

# Miliary TB

- Occasionally, a massive inoculum of organisms enters the bloodstream, causing a widely disseminated form of the disease known as miliary TB.
- It is named for the millet seed appearance of the small granulomas seen on chest radiographs, and it can be rapidly fatal.
- Miliary TB is a medical emergency requiring immediate treatment.

# Influence of HIV Infection on Pathogenesis

- HIV infection and TB are synergistic
- A risk factor for disease progression to active TB
- HIV multiplies within these cells and selectively destroys them. In turn, the TB-fighting lymphocytes are depleted.
  - This vicious cycle puts HIV-infected patients at 100 times the risk of active TB compared with HIV-negative people
- As mycobacteria spread throughout the body, HIV replication accelerates in lymphocytes and macrophages. This leads to progression of HIV disease

# CLINICAL PRESENTATION

- The onset of TB may be gradual, the diagnosis may not be considered until a chest radiograph is performed
- **Signs and Symptoms**
  - Patients typically present with weight loss, fatigue, a productive cough, fever, and night sweats
  - Frank hemoptysis at the late course of the disease
- **Physical Examination**
  - Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation

# CLINICAL PRESENTATION

- **Laboratory Tests**

- Moderate elevations in the white blood cell (WBC) count with a lymphocyte predominance

- **Chest Radiograph**

- **Patchy or nodular infiltrates** in the apical areas of the upper lobes or the superior segment of the lower lobes
- Cavitation that may show air-fluid levels as the infection progresses

# Atypical presentations

- HIV-positive patients
- Less likely to have +ve Skin tests; cavitory lesions or fever
- Radiographic findings are minimal or absent

# Skin Testing

- The Mantoux test uses
  - Tuberculin purified protein derivative (PPD))
- 5-tuberculin-unit PPD dose subcutaneously
- It will produce Small, raised, blanched wheal
  - Result: 48 to 72 hours (the "bump")
- The area of induration (the “bump”) is the important end point, not the area of redness



# Skin Testing

- “Boost” with a second skin test.
  - Past *M. tuberculosis* infection;
  - past immunization with bacillus Calmett -Guerin (BCG) vaccine or
  - past infection with other mycobacteria may
- Falsely skin-test–negative (20%)
- False-positive (BCG)
  - preventive treatment

# Criteria for Tuberculin Positivity by Risk Group

Reaction 5 mm of Induration	Reaction 10 mm of Induration	Reaction 15 mm
HIV-positive persons	People living in high-prevalence countries	Persons with no risk factors for TB
Recent contacts of TB patients	Injection-drug users	
Fibrotic changes on chest X-Ray consistent with prior TB	Prisons and jails; nursing homes, the elderly; hospitals, homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day of prednisone for 1 mo or more)	Mycobacteriology laboratory personnel	
	Persons with: silicosis; diabetes mellitus; chronic renal failure; some hematologic disorders (e.g., leukemias and lymphomas); other specific malignancies; weight loss of 10% of ideal body weight	
	Children younger than 4 y of age or infants, children, and adolescents exposed to adults at high risk	

# Additional Tests

- **Sputum:** A series of at least three single specimens should be collected in 8- to 24-hour intervals (with at least one specimen obtained in the early morning)
  - although the diagnosis often can be made with two specimens
  - For patients unable to expectorate Induction with aerosolized hypertonic saline
  - Bronchoscopy, or aspiration of gastric fluid via a nasogastric tube,
- samples of draining fluid, biopsies of the infected site, or both
- Blood cultures

# General Approaches to Treatment

- Monotherapy (for latent TB)
- Multiple
  - 2-4 drugs must be used
- Duration of treatment:
  - 6 months
  - multidrug-resistant TB (MDR-TB): 18-24 months
- Careful follow-up is a key
- Asymptomatic latent infection:
  - isoniazid monotherapy
- Active TB
  - Use of Rifampin and isoniazid
  - Ethambutol, streptomycin, and pyrazinamide

# General Approaches to Treatment

- Three subpopulations of mycobacteria:
  - The extracellular, rapidly dividing bacteria, often found within cavities
    - isoniazid, followed by rifampin, streptomycin, and the other drugs)
  - The 2<sup>nd</sup> group resides within caseating granulomas; semidormant state, with occasional bursts of metabolic activity.
    - Pyrazinamide, Rifampin and isoniazid
  - The 3<sup>rd</sup> group resides within macrophages
    - Rifampin, isoniazid, and the quinolones

# Treating Latent Infection

- Prophylaxis, chemoprophylaxis, or preventive treatment (efficacy-60-90%)
- Latent TB infection (LTBI): isoniazid 300 mg daily (5 to 10 mg/kg of body weight for 9 months.
- reduces a person's lifetime risk of active TB from approximately 10% to approximately 1%
- The keys to successful treatment
  - (a) infection by an isoniazid-susceptible isolate,
  - (b) adherence to the 9-month regimen, and
  - (c) no exogenous reinfection.
- Administration: empty stomach, avoid antacids within 2 hrs
- Twice-weekly isoniazid (900 mg in an adult)

# Treating Latent Infection

- **Alternative:** Rifampin 600 mg daily for 4 months
- Combination of pyrazinamide plus rifampin
  - Not recommended b/c of hepatotoxicity
- Pyridoxine (vitamin b6) 10 to 50 mg daily:
  - For pregnant women, alcoholics, and patients with poor diets
- Monthly monitoring: toxicity and conversion to active TB

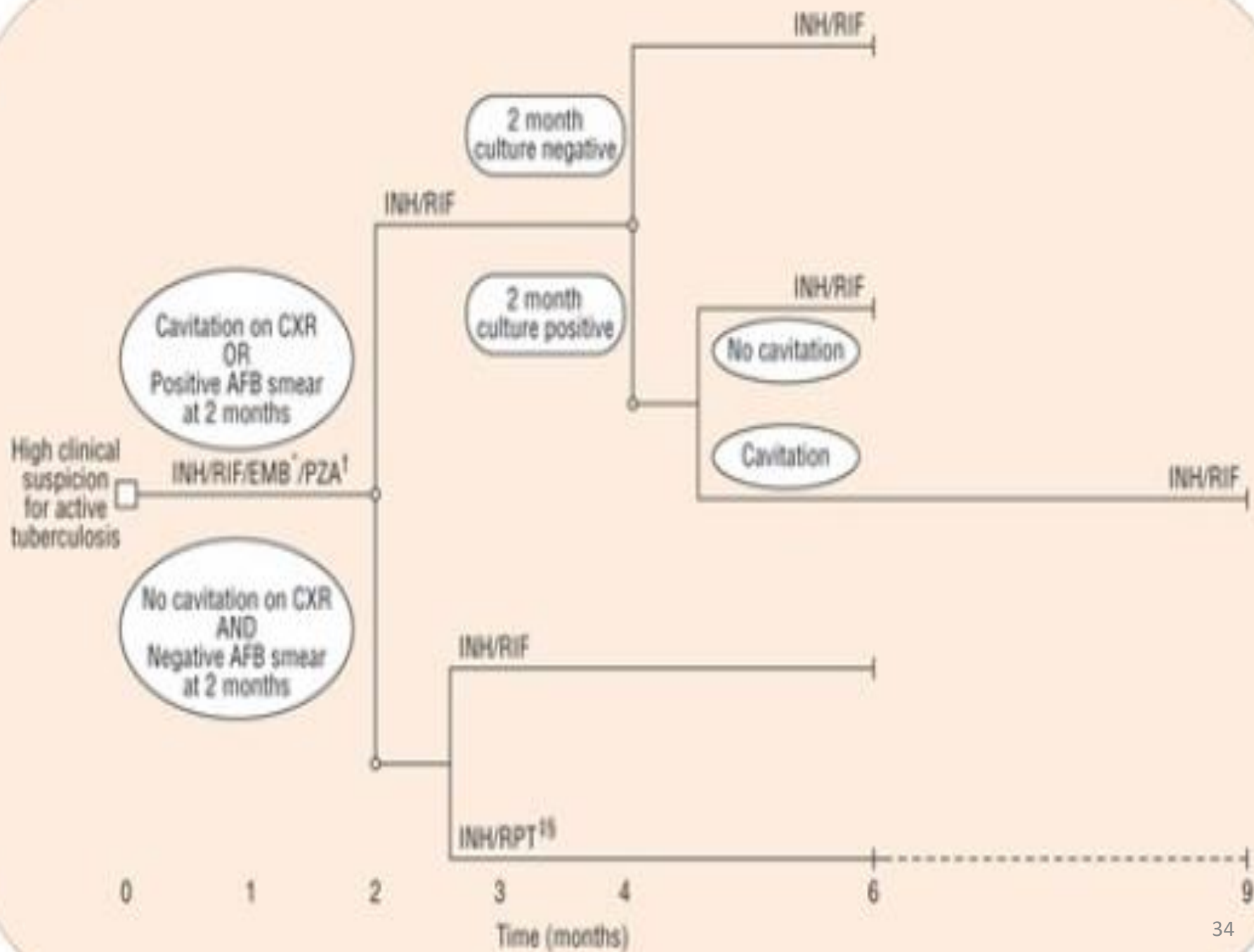
## RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS (TB) INFECTION IN ADULTS

DRUG	INTERVAL AND DURATION	COMMENTS
Isoniazid	Daily for 9 mo	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or nonnucleoside reverse transcriptase inhibitors (NNRTIs)
	Twice weekly for 9 mo	Directly observed therapy (DOT) must be used with twice-weekly dosing
Isoniazid	Daily for 6 mo	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children
	Twice weekly for 6 mo	DOT must be used with twice-weekly dosing
Rifampin	Daily for 4 mo	In isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide



# Treating Active TB

- Isoniazid and rifampin
  - Primary antituberculosis drugs (use together)
- The standard TB treatment regimen
  - isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months,
  - Followed by isoniazid and rifampin for 4 months, for a total of 6 months of treatment.
- If susceptibility to isoniazid, rifampin, and pyrazinamide is shown
  - ethambutol can be stopped at any time.
- Without pyrazinamide, a total of 9 months of isoniazid and rifampin treatment is required.
- Regimens: Daily, five times each week or three times weekly



# Note

- A repeat smear and culture should be performed when 2 months of treatment has been completed.
- If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment.
- If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment).

- In patients treated for 6 months, having both cavitation and a positive culture at completion of 2 months of therapy, has been associated with rates of relapse of approximately 20% compared with 2% among patients with neither factor

# Management of Treatment Interruptions

Time Point of Interruption	Details of Interruption	Approach
During intensive phase	Lapse is <14 d in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)
	Lapse is $\geq$ 14 d in duration	Restart treatment from the beginning
During continuation phase	Received $\geq$ 80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received $\geq$ 80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 mo in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 mo If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (ie, restart intensive phase, to be followed by continuation phase) <sup>b</sup>
	Received <80% of doses and lapse is $\geq$ 3 mo in duration	Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase)

# Treating Active TB

- Slow responders; those who remain culture-positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and perhaps HIV-positive patients
- Treatment durations become 2 years:
  - isoniazid and rifampin cannot be used,

Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms					
Initial Phase					
	Drugs	Interval and Doses (Minimal Duration)	Drugs	Interval and Doses (Minimal Duration)	Range of Total Doses (Minimal Duration)
1	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)	Isoniazid/rifampin	Seven days per week for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)	182–130 (26 wk)
			Isoniazid/rifampin	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)
			Isoniazid/rifapenti ne	Once weekly for 18 doses (18 wk)	74–58 (26 wk)
2	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 days/wk for 10 doses (2 wk) <sup>e</sup> then twice weekly for 12 doses (6 wk)	Isoniazid/rifampin	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)
			Isoniazid/rifapenti ne	Once weekly for 18 doses (18 wk)	44–40 (26 wk)

Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms					
Initial Phase					
	Drugs	Interval and Doses (Minimal Duration)	Drugs	Interval and Doses <sup>c,d</sup> (Minimal Duration)	Range of Total Doses (Minimal Duration)
3	Isoniazid, rifampin, pyrazinamide, ethambutol	Three times weekly for 24 doses (8 wk)	Isoniazid/rifampin	Three times weekly for 54 doses (18 wk)	78 (26 wk)
4	Isoniazid, rifampin, ethambutol	Seven days per week for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk) <sup>c</sup>	Isoniazid/rifampin	Seven days per week for 217 doses (31 wk) or 5 days/wk for 155 doses (31 wk) <sup>e</sup>	273–195 (39 wk)
			Isoniazid/rifampin	Twice weekly for 62 doses (31 wk)	118–102 (39 wk) <sup>f</sup>



# Drug resistance should be suspected

Patients who

- Have received prior therapy for TB
- Are homeless, institutionalized, intravenous drug abusers, or infected with HIV
- Still have acid-fast bacilli-positive sputum smears after 1 to 2 months of therapy
- Still have positive cultures after 2 to 4 months of therapy
- Fail treatment or relapse after treatment
- Patients known to be exposed to MDR-TB cases

# Drug resistance

- Assumption:
  - Multidrug-resistant TB until proved otherwise.
- Empirical therapy with four or more drugs may be needed for acutely ill patients
- **Extensively** drug-resistant TB "XDR-TB" :  
Resistant to isoniazid, rifampin, a fluoroquinolone and one second-line injectable drug (amikacin, capreomycin, or kanamycin)

# Tuberculous Meningitis and Extrapulmonary Disease

- 9 to 12 months instead of 6 months
- CNS Penetration
  - Isoniazid, pyrazinamide, ethionamide, and cycloserine penetrate easily
  - Rifampin, ethambutol, and streptomycin.. variable
- Quinolones: Levofloxacin is preferred
- Extrapulmonary TB of the soft tissues can be treated with conventional regimens
- TB of the bone is treated for 9 months

## Evidence-Based Guidelines for the Treatment of Extrapulmonary Tuberculosis and Adjunctive Use of Corticosteroids

SITE	LENGTH OF THERAPY (MO)	CORTICOSTEROIDS
Lymph node	6	Not recommended
Bone and joint	6–9	Not recommended
Pleural disease	6	Not recommended
<b>Pericarditis</b>	<b>6</b>	<b>Strongly recommended</b>
<b>CNS tuberculosis including meningitis</b>	<b>9–12</b>	<b>Strongly recommended</b>
Disseminated disease	6	Not recommended
Genitourinary	6	Not recommended
Peritoneal	6	Not recommended

# Children

- TB in children may be treated with regimens similar to those used in adults
- Pediatric doses of isoniazid and rifampin on a per-kilogram basis are higher than those used in adults

# Pregnancy

- Women with TB should be cautioned against becoming pregnant because the disease poses a risk to the fetus and to the mother.
- **Isoniazid, rifampin, and ethambutol** for 9 months is the preferred regimen.
- INH and ETM are relatively safe during pregnancy
- B vitamins should be supplemented
  - ⊕ Rifampin (limb reduction and CNS lesions)
  - ⊕ Streptomycin (hearing loss)
  - ⊕ Ethionamide (premature delivery and congenital deformities)
  - ⊕ quinolones (permanent damage to cartilage)
- LTBI in pregnancy ..treatment can be delayed

# Renal Failure

- For nearly all patients, isoniazid and rifampin do not require dose modification in renal failure. They are eliminated primarily by the liver
- Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly

# Dosing Recommendations for Adult Patients with Reduced Renal Function and for Adult Patients Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min or for Patients Receiving Hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week
Ethambutol	Yes	15–25 mg/kg per dose three times per week
Levofloxacin	Yes	750–1,000 mg per dose three times per week
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week
Ethionamide	No change	250–500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week
Amikacin	Yes	12–15 mg/kg per dose two or three times per week



# ISONIAZID

- Activity:
  - M. tuberculosis
- Resistant:
  - Most nontuberculous mycobacteria (M. avium)
- Administration: Oral (empty stomach)
- Metabolism:
  - *N*-acetyltransferase 2
  - Antimycobacterial activity

# ISONIAZID

- Genetics:
  - Presence or lack of *N*-acetyltransferase 2
- Fast acetylators: Half-life < 2 hours.
  - 50% of whites and blacks
  - 80% to 90% of Asians and Eskimos
- Slow acetylators: Half-life: 3 to 4 hours
  - Risk of neurotoxicity
  - Risk of hepatotoxicity

# ISONIAZID

- Adverse Effect:
  - Serum transaminases (12% to 15%)
  - 8 to 12 weeks of therapy; Overt hepatotoxicity (1%)
- Risk factors for hepatotoxicity:
  - age, preexisting liver disease, excessive alcohol intake, pregnancy
- Peripheral neuropathy: seizures and coma (overdose)
- Risk factors:
  - Patients with pyridoxine deficiency, such as pregnant women, alcoholics, children, and the malnourished, are at increased risk.
- Drug Interactions:
  - Isoniazid may inhibit the metabolism of phenytoin, carbamazepine, primidone, and warfarin

# Rifampin

- Introduced in 1970s
- Allowed for true short-course treatment of TB
  - 6 to 9 months vs. 18 months or longer
- Need to protect susceptibility to rifampin
- Bactericidal activity against *M. tuberculosis*
  - *M. bovis* and *M. kansasii*
- Rifampin also is active against a broad array of other bacteria.

# Rifampin

- Usually is given orally (empty stomach), but it also can be given as a 30-minute intravenous infusion.
- Metabolism: 25-desacetyl rifampin
  - antimycobacterial activity
- Cleared in the bile
- Dose: 600 mg daily or intermittently
- Concentration-dependent killing

# Rifampin

- Elevations in hepatic enzymes: 10% to 15%
- Overt hepatotoxicity: < 1%
- More frequent adverse effects:
  - Rash, fever, and gastrointestinal distress
- Allergic reactions: Intermittent rifampin doses 900 mg or more twice weekly
  - Flu-like syndrome with development of fever, chills, headache, arthralgias, and, rarely, hypotension and shock
  - Alternatively, hemolytic anemia or acute renal failure may occur, requiring permanent discontinuation.

# Rifampin

- Drug Interactions:
  - Enzyme inducer (PI)
- HIV patients:
  - Rifabutin instead of rifampin
- Oral contraceptives:
  - Clearance of the hormones
- Urine and other secretions:
  - orange-red or contact lenses.

# Rifabutin

- A long-acting rifamycin that can be used once weekly
- Indications:
  - Disseminated *M. avium* infection in AIDS patients
  - *M. tuberculosis*
- Resistant issues with Rifampin vs. Rifabutin
- Enzyme inducing potential: 85% as potent



# PYRAZINAMIDE

- Benefit of adding pyrazinamide to the first 2 months of treatment with isoniazid and rifampin
- Dose – depends on weight
  - 1 g daily (40-55kg); 1.5 g (56-75kg); 2g (76-90kg)
- Toxicities:
  - Gastrointestinal distress, arthralgia
  - Elevations serum uric acid concentrations vs. true gout.
- Hepatotoxicity: Dose-related

# ETHAMBUTOL

- Ethambutol vs. *p*-aminosalicylic acid (1960s)
- The fourth TB drug
- Dose:
  - 800 mg (40-55kg)
  - 1.2 g (56-75kg)
  - 1.6 g (76-90kg)
- Discontinue Ethambutol during TB therapy:
  - organism susceptible to isoniazid, rifampin, and pyrazinamide

# ETHAMBUTOL

- Bacteriostatic
  - Active against most mycobacteria (*M. tuberculosis* and *M. avium*)
- Use with antacids
- Retrobulbar neuritis:
  - change in visual acuity, the inability to see the color green, or both.
  - Monthly monitoring (Snellen wall charts)
  - Ishihara red-green color discrimination cards
- Dose in renal failure: three times per week

# Second-Line Antituberculosis Drugs

## Streptomycin

- Efficacy
  - Rif > INH > Eth > Cyclo > PZA
- IM vs. Intravenous infusions
  - 100 ml of dextrose 5% water or normal saline over 30 minutes
- Nephrotoxicity, ototoxicity
  - vestibular and cochlear
- Renally Cleared by glomerular filtration
- Dose:
  - 1 gm IM daily (15 mg/kg) or 750 mg dialy

# Second-Line Antituberculosis Drugs

## P-Aminosalicylic Acid

- Gastrointestinal disturbances
  - Diarrhea
  - Opioid
- Hypersensitivity
- Hepatitis
- Goiter (with or without myxedema)

# Second-Line Antituberculosis Drugs

## Cycloserine

- MDR-TB.
- Empty stomach
- Clearance
- Dose-related CNS toxicity
  - Lethargy, confusion, or unusual behavior, seizures
- Use of Pyridoxine 50 mg daily

# Second-Line Antituberculosis Drugs

## Ethionamide

- Prothionamide
  - the *n*-propyl derivative of ethionamide,
- Dose:
  - Gradual increment of 250-mg (1 g/d in divided doses)
- A light snack or prior to bedtime
- Goiter, with or without hypothyroidism
- Gynecomastia, alopecia, impotence, menorrhagia, photodermatitis, and acne
- Diabetes

# CLOFAZIMINE

- Doses of 100 to 200 mg daily in advanced cases of MDR-TB or MAC,
- Half-life that is weeks long
- Gastrointestinal distress and skin discoloration
- Severe gastrointestinal pain (clofazimine crystals)



# Other Drugs

- **QUINOLONES**
  - MDR-TB (Moxifloxacin)
- **B-lactam And -Lactamase Inhibitor Combinations**
  - Role
  - Cefoxitin
  - Combinations of B-lactam with -lactamase inhibitors

# Bacille Calmette-Guérin (BCG) Vaccine

- The BCG vaccine is an attenuated, hybridized strain of *M. bovis*.
- Developed in 1921 and is used as a prophylactic vaccine against TB.
- Administration of BCG vaccine is compulsory in many developing countries
- Sensitization of T lymphocytes and cross-immunity, as well as cutaneous hypersensitivity

# Bacille Calmette-Guérin (BCG) Vaccine

- A positive tuberculin skin test.
- Tuberculous meningitis and miliary TB is
  - 52% to 100%
  - Pulmonary TB is 2% to 80%
- Efficacy against *M. tuberculosis*
- Pregnant