Tuberculosis Update

Eric Bihler

Objectives

- Brief overview of epidemiology and transmission
- Differentiate between latent and active tuberculosis
- Treatment of tuberculosis
- Common side effects of therapy

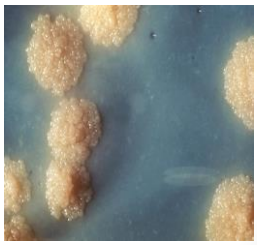
Introduction

- Tuberculosis
  - Multisystem disease
  - Myriad of presentations
  - One third of the world's population is infected with TB
  - 10.4 million active cases worldwide 2016
  - Responsible for 1.7 million deaths worldwide in 2016
  - Has caused disease in humans since 4000 B.C.

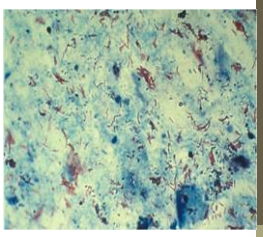
Introduction

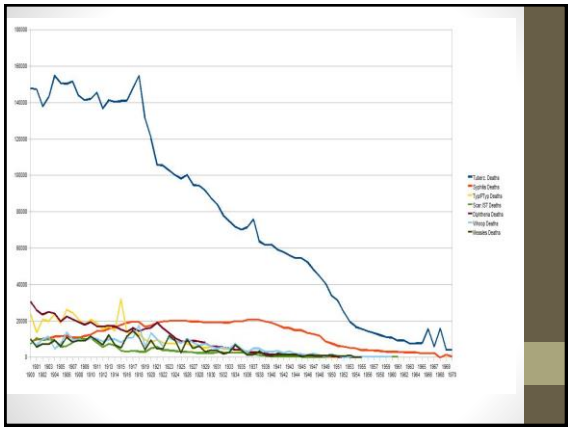
- Mycobacterium tuberculosis complex
  - Mycobacterium tuberculosis
  - Mycobacterium bovis
    - Accounts for less than 2%
    - Spread from cattle
    - Once as common as MTB
    - Largely eliminated with pasteurization
  - Mycobacterium africanium
    - Mainly found in west Africa
    - 25% of cases in Gambia
    - From 2004-13
      - 315 cases (0.4%) in U.S.

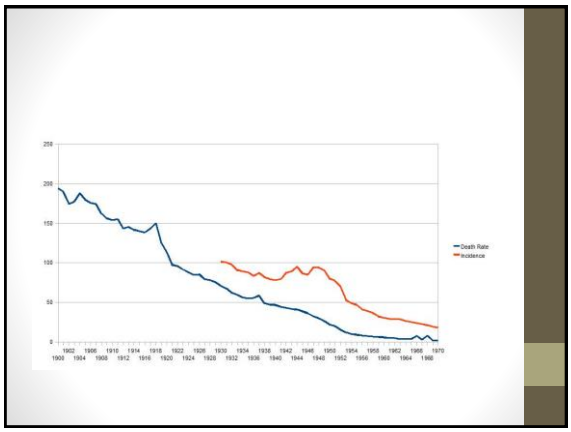
- MTB
  - Large nonmotlie rod shaped bacterium
  - Obligate aerobe
  - Facultative intracellular parasite
  - Slow generation time
    - 15-20 Hrs
    - Can take 4-6 weeks to visualize



- Acid Fast
  - Refers to the ability to resist decolarization by acids
  - High mycolic acid content of cell walls
  - Zeihl-neelsen stain
  - MTB, NTM, Actinomyctes, Nocardia







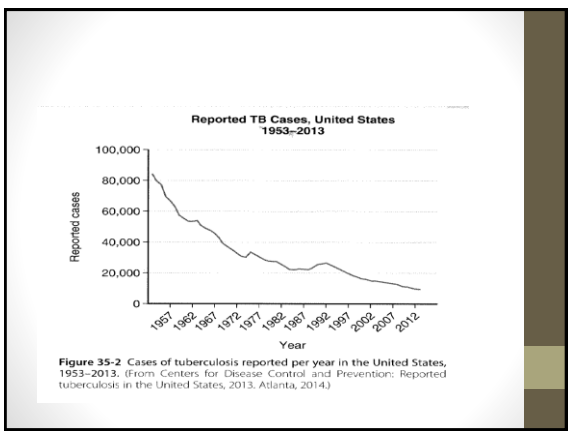
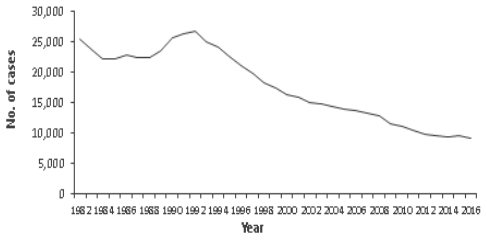


Figure 35-2 Cases of tuberculosis reported per year in the United States, 1953–2013. (From Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 2013. Atlanta, 2014.)

Reported Tuberculosis (TB) Cases United States, 1982–2016*



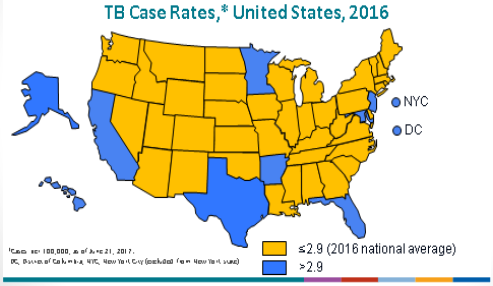
* As of June 21, 2017.

TB Morbidity United States, 2011–2016

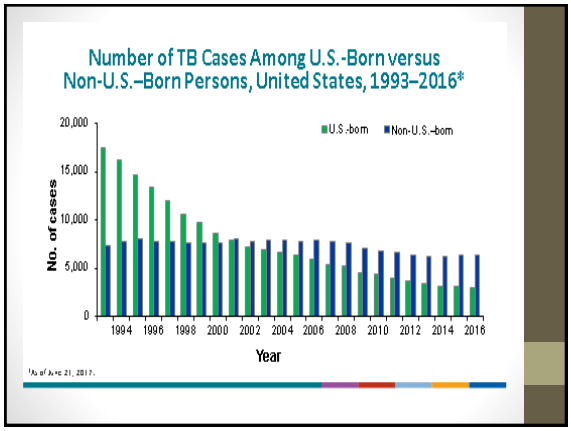
Year	No.	Rate*
2011	10,509	3.4
2012	9,940	3.2
2013	9,561	3.0
2014	9,398	3.0
2015	9,547	3.0
2016	9,272	2.9

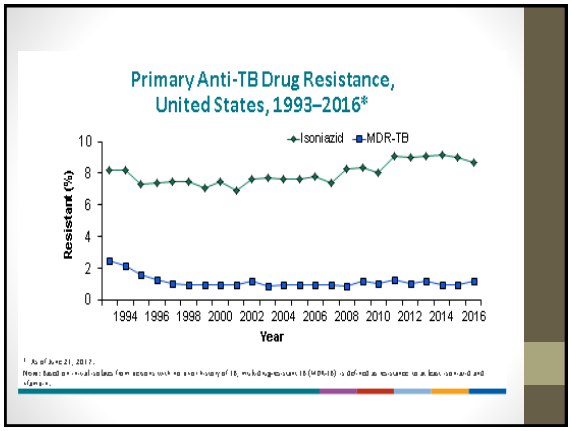
* Cases per 100,000 population, as of June 21, 2017.

TB Case Rates,* United States, 2016



* Cases per 100,000, as of June 21, 2017.
DC, District of Columbia; NYC, New York City (included in New York state)





- Allegheny county 2017
  - Active cases 15
    - 1.5 cases per 100,000
  - LTBI
    - 327 evaluated

- Tuberculosis is an airborne disease
- Microscopic droplets created by coughing, sneezing, singing
- Evaporate into the droplet nuclei (1to3 micron)
- Capable of reaching the alveolus
- Can remain suspended in air for hours

- One cough produces approx. 500 droplets
- Average patient produces 75,000 droplets per day
- Drops to 25 droplets per day after 2 weeks of therapy

Factors associated with transmission

- Source case
  - Smear status
    - 4 – 5X more infectious
  - Presence of cavities
    - Can produce up to 100mL of sputum per day
    - 10^7 to 10^9 number of organisms
  - Presence of cough
  - Procedures inducing aerosols
    - Bronchoscopy
    - Intubation
  - Laryngeal TB
    - Produce 60 afb per/hr
    - As infective as a child with measles
- Average source case infects 10 people per year

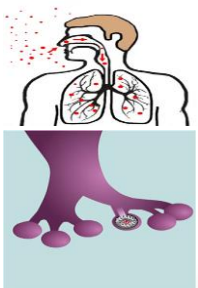
Factors associated with transmission

- Environmental factors
  - Under normal temperature and humidity indoors
    - Viable droplets
      - 60-70% at 3hs
      - 48-56% at 6 hrs.
      - 28-32% at 9 hrs.
        - Ventilation, filtration, uv light
          - effective at dispersing/killing droplet
        - Naval ships
    - Household contacts
      - Approx. 50% infected
    - Casual contacts
      - 15% infected

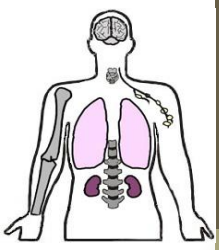
Factors associated with transmission

- Host
  - Variable rates of infection after exposure
  - Suggests variable rates host susceptibility
    - Prospective study of nursing school students
      - Prechemotherapy time
      - After 2 years despite sig exposure
        - Only 30% ppd +
      - However after 3 years
        - 100% PPD +
          - Resistance to infection quantitative not absolute
          - Overcome by sig exposure

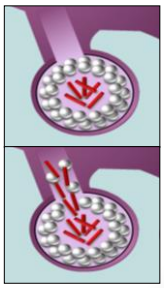
- Droplet nuclei enter the lungs and travel to the alveolus
- Once in the alveolus mycobacterium multiple

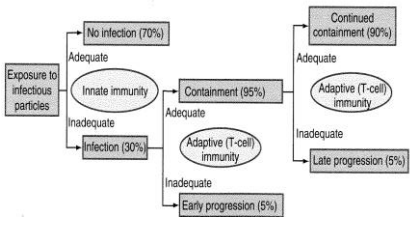


- While replicating within the alveolus
- A small number of organisms may enter the blood stream
  - Brain
  - Lymph nodes
  - Spine
  - Bones
  - Larynx
  - Kidneys



- Within 2-8 weeks macrophages engulph and surround tuberculi
- Granuloma formation
- **LTBI established**
- if the immune system can not contain the tuberculi
- Tuberculi multiply and spread through out the body
- **Tuberculosis disease**





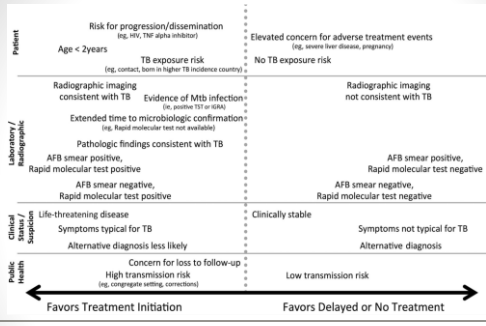
LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

Treatment of active Tuberculosis

- Primary goals
  - Eradicating infection
  - Preventing development of drug resistance
  - Preventing relapse of disease
- Reportable disease- engagement of health department
  - Assure completion of therapy
  - Minimize risk of secondary resistance, treatment failure and relapse

- **Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis**
- Payam Nahid Susan E. Dorman Narges Alipanah Pennan M. Barry Jan L. BrozekAdithya Cattamanchi Lelia H. Chaisson Richard E. Chaisson Charles L. DaleyMalgosia Grzemska ... Show more
- Author Notes
- *Clinical Infectious Diseases*, Volume 63, Issue 7, 1 October 2016, Pages e147–e195,https://doi.org/10.1093/cid/ciw376



From: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Clin Infect Dis. 2016;63(7):e147-e195. doi:10.1093/cid/ciw376

- PICO Question 1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? (Case management is defined as patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, and incentives/enablers).
- Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis (conditional recommendation; very low certainty in the evidence).

Table 4. Possible Components of a Multifaceted, Patient-Centered Treatment Strategy

Enablers	Incentives
Interventions to assist the patient in completing therapy [130]	Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient [130]
Transportation vouchers [30]	Food stamps or snacks and meals [30]
Convenient clinic hours and locations [30]	Restaurant and grocery store coupons [30]
Clinic personnel who speak the languages of the populations served [428]	Assistance in finding or provision of housing [429]
Reminder systems and follow-up of missed appointments [28]	Clothing or other personal products [30]
Social service assistance (referrals for substance abuse treatment and counseling, housing, and other services) [429]	Books [428]
Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of directly observed therapy, follow-up on missed appointments, monthly monitoring, transportation, sputum collection, social service assistance, and educational reinforcement) [428]	Stipends [30]
Integration of care for tuberculosis with care for other conditions [429]	Patient contract [30]

- PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?
- Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis (conditional recommendation; low certainty in the evidence).

Table 5. Examples of Priority Situations for the Use of Directly Observed Therapy

Patients With the Following Conditions/Circumstances [17, 130, 137, 139, 430, 431]:
• Positive sputum smears
• Delayed culture conversion (sputum obtained at/after completion of intensive-phase therapy is culture-positive)
• Treatment failure
• Relapse
• Drug resistance
• Homelessness
• Current or prior substance abuse
• Use of intermittent dosing
• HIV infection
• Previous nonadherence to therapy
• Children and adolescents
• Mental, emotional or physical disability (ie, cognitive deficits such as dementia; neurological deficits; medically fragile patients; or patients with blindness or severe loss of vision)
• Resident at correctional or long-term care facility
• Previous treatment for active or latent tuberculosis

Abbreviation: HIV, human immunodeficiency virus.

- PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?
- Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis (strong recommendation; moderate certainty in the evidence).
- Recommendation 3b: Use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not HIV infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (conditional recommendation; low certainty in the evidence).

- PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?
- Recommendation 4a: We recommend the use of daily or thrice-weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis *(strong recommendation; moderate certainty in the evidence)*.
- Recommendation 4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of thrice-weekly instead of twice-weekly therapy *(conditional recommendation; low certainty in the evidence)*. This recommendation allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior

- Recommendation 4c: We recommend against use of once-weekly therapy with INH 900 mg and rifapentine 600 mg in the continuation phase *(strong recommendation; high certainty in the evidence)*. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus rifapentine 600 mg may be considered for use only in HIV-uninfected persons without cavitation on chest radiography.

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

Extending Duration of Therapy

- Either Cavitation or Positive Cx after 2 months of therapy
  - Plus/or
    - > 10% below ideal body weight
    - Smoking
    - Diabetes
    - HIV
    - Other immunosuppresion
    - Extensive disease on CXR

- USPH Study 22
  - Cavitation and positive 2mon Cx
    - Relapse rate 21%
  - Either cavitation or pos 2 mon Cx
    - Relapse 5-6%
  - Neither
    - 2% relapse
- Silacotuberculsis
  - Extended tx to 8 months
  - Relapse 22 to 7 %

Table 6. Management of Treatment Interruptions[a]

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 ≥14 d in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥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)[b]
	Received <80% of doses and lapse is ≥3 mo in duration	Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase)

- Culture negative TB (clinical TB)
  - Based on
    - Symptoms
    - CXR
    - Positive test for LTBI
    - Epidemiologic exposure
  - Accounts for 15-20% of active cases
  - If clinical or radiographic improvement cont. TX for total 4 months
  - If no change- alternative diagnosis
    - LTBI treated

- Relapse
  - Pt whose Cx become negative during therapy
  - After therapy completed
    - Develop clinical and radiographic signs of disease
    - Positive cx
  - Most relapses occur w/I one year of completion
  - Cavitation
  - + cx at the end of initial phase (2 months)
  - Increased risk of acquired drug resistance
    - Particularly if not receiving DOT

- Treatment Failure
  - Positive cx at 4 months in pt who are taking meds
  - Never add a single drug
  - Usually 3 new meds

- Fluoroquinolones
  - Hoped to shorten course from 6 to 4 months
  - 3 phase III trials
    - Moxifloxacin
    - Gatifloxacin
      - Some studies showed faster culture conversion
      - Unacceptably high relapse rates
  - Pending further data
    - Should only be used in patients with intolerance or resistance to first line medications

Treatment monitoring

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐		
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐		
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐		
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐		
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐		
Creatinine[9]	☐	☐	☐	☐	☐	☐	☐	☐		
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

Treatment monitoring

- Hepatotoxicity
  - INF, RIF, PZA
  - Asymptomatic increase in liver enzymes occurs in 20% of pts "adaptation"
    - Not an indication to stop TX
    - Resolve spontaneously
  - RIF
    - Elevated ALP/Bili
  - Stop TX
    - Liver enzymes elevated 3X ULN with Sx
    - Liver enzymes 5X ULN without Sx

- Hepatotoxicity
  - Age likely a factor
    - > 35 22-33%
    - < 35 8-17%
  - CDC surveillance for severe hepatitis 2004-2008
    - INH LTBI Tx
    - 17 pts
    - 5 transplants 5 deaths
    - 15 adults age ranged from 19-64
    - Symptom onset 1-7 months after starting
    - **80% continued taking INH for more than one week after symptom onset**

- Hepatotoxicity
  - Optimal approach to restart meds uncertain
  - In cases where Tx can not be stopped
    - 3 new drugs
      - Aminoglycoside, EMB, quinolone
  - Once LFT's 2-3 ULN
    - Resume RIF + EMB
    - Add INH after one week
    - If INH RIF tolerated and liver injury severe rechalange with PZA not recommended
      - Extend treatment

- Ocular toxicity
  - EMB
    - Optic neuritis
      - Blurry vision
      - Loss of color discrimination
    - Treatment – discontinue drug
- Rash
  - Possible with any drug
  - Minor rashes can be treated symptomatically with antihistamines
  - Petechial rash
    - RIF hypersensitivity reaction
      - Check CBC
      - If thrombocytopenia present D/C rifampin
- Drug fever

- Isoniazid/INH
  - Bactericidal
  - Usual dose 300mg
  - Toxicity
    - Hepatitis
    - Neuropathy
      - Pyridoxine
  - Interactions
    - Increases
      - Anticonvulsants
      - Warfarin
      - Theophylline
    - Decreases
      - Azole antifungals
  - Absorption inhibited by aluminum
    - Avoid antacids

- Rifampin/RIF
  - Bactericidal
  - Usual dose 600mg 10mg/Kg
  - Hepatotoxicity
    - Less common than INH
  - Excreted as orange/red compound in bodily fluids
    - Contact lenses
  - Flu like syndrome
  - Hypersensitivity reaction
  - Leukopenia, thrombocytopenia

- Rifampin
  - Very potent inducer of p450
    - Warfarin
    - Birth control
    - Glucocorticoids
    - Azole
    - Methadone
    - Quinidine
    - Theophylline
    - Verapamil
    - Sulfonylureas
    - Digoxin
    - Beta blockers
    - Clarithromycin
    - Protease inhibitors
    - The list goes on

- Pyrazinamide/PZA
  - Bactericidal for MTB at acidic pH (intracellular)
  - 25-30 mg/Kg
  - Hepatotoxicity
  - Hyperuricemia
    - gout

- Ethambutol/EMB
  - Bacteriostatic
  - 15-25 mg/Kg
  - Optic neuritis

- Thank You