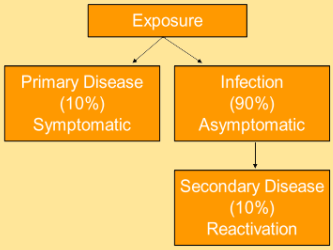
MICROBIOLOGY:
- 20 species, 3 pathogenic to humans
- Most common is M. tuberculosis
- Aerobic, rod-shaped (bacilli)
- Slow growing
- Acid-fast positive

LATENT VS. ACTIVE TB:

LATENT	• Positive reaction to tuberculin skin test AND • Negative bacteriologic studies (if done) AND • No clinical, bacteriological, or radiographic evidence of active TB
ACTIVE TB	• *M. tuberculosis* cultured (if done) OR • Clinical, or CXR evidence of disease AND • Positive PPD test

NATURAL HISTORY OF TB:



CONDITIONS INCREASE RISK OF PROGRESSION TO ACTIVE TB:
- CXR suggestive of previous TB
- HIV infection
- Substance abuse
- Cancer
- Diabetes mellitus, CKD
- Malnutrition
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy

COMMON SITES OF TB DISEASE:
- Lungs
- CNS
- GU system
- Lymphatic system
- Bones & joints
- Disseminated (military TB)

WHAT ARE THE GOALS OF THERAPY?
- Eliminate signs and symptoms
- Prevent transmission to contacts
- Prevent development of resistance (adherence)
- Minimize ADRs
- Increase QOL
- Prevent relapse of TB

ANTITUBERCULOSIS DRUGS:

First line drugs	Second line drugs

• Isoniazid
• Rifampin
  ○ Rifabutin
  ○ Rifapentine
• Pyrazinamide
• Ethambutol
	• Streptomycin
	• Cycloserine
	• p-Aminosalicylic acid
	• Ethionamide
	• Amikacin/kanamycin
	• Capreomycin
	• Levo/moxi - floxacin

RIFABUTIN (RBT):
- Similar activity as RMP but less CYP450 drug interactions (used in HIV-infected or transplant pts due to their meds)
- Hematologic toxicity is more

RIFAPENTINE:
- Once week dosing (5 times longer half-life than RMP)
- Not recommended due to higher rates of failure in HIV pts

PATHOGENESIS:
- Inhale droplet nuclei (1-5 um) which disseminates to the lung
- Ingested by macrophages, T lymphocytes activated & produce more reactive lymphocytes
- Macrophages have begun to form granulomas to contain the organisms, and activated lymphocytes now begin to destroy the MTB-containing macrophages
  - Dissemination is halted and bacteria within granulomas have avoided detection by lysis **(LATENT TB INFECTION** = LTBI)
- If the immune system cannot keep the bacilli under control, the bacilli begin to multiply rapidly **in the lung** and may spread via the bloodstream to seed a variety of organs with high blood flow: lymph nodes, posterior apical regions of the lung, bone, BM, liver, kidney, CNS (**ACTIVE TB DISEASE**)

TRANSMISSION:
- Spread by droplet nuclei
- Expelled when person with infectious TB coughs, sneezes or speaks
- Transmission occurs from person with ACTIVE infectious TB disease (not latent TB infection)

PROBABILITY TB WILL BE TRANSMITTED:
- **Infectiousness of person with TB**
  - Smear positive
  - Cavitary lesion on CXR
- **Closeness of individual**
- Duration of exposure
- Virulence of organism

SYMPTOMS OF TB:
- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easily fatigued
- Cough
- Hemoptysis
- Chest pain
- SOB
- Tachypnea
- Dullness/crackles

DIAGNOSTIC TESTS FOR TB:

CHEST RADIOGRAPH	• Abnormalities often seen in apical segment of upper lobe or superior segments of lower lobe • Central for diagnosis of TB
SMEAR EXAMINATION	• Obtain 3 sputum specimens for smear examination and culture • Results (i.e. **AFB**) should be available within 24 hours • With treatment, bacteria load ↓ within 2 weeks • Some patients may take up to 4 months to clear
CULTURES	• Used to confirm diagnosis of TB • Culture all specimens, even if smear negative • Results in 6-12 weeks • Susceptibility testing on initial isolate
RAPID TESTS - NAAT	• Used to confirm diagnosis of TB • Detects PCR (high sensitivity > 95%) • Results in 24-48 hours • Cannot get susceptibility • Can be used in the field to detect resistance

WHAT ARE THE VIABLE TREATMENT OPTIONS?

INITIAL	• Multiple drugs (INH, RMP, PZA, EMB) used for 2 months ○ Two best agents are INH and RIF • Need drugs which are rapidly bactericidal • Ensures quick sputum conversion

CONTINUATION	• Normally use 2 drugs (INH/RMP) for another 4-7 months
	  ○ Total duration = 6-9 months
	• In patients with risk factors for relapse, continuous phase should be prolonged from 4 to 7 months (=9 months total therapy)
	  ○ Extensive disease and/or cavities on CXR in first 2 m of txt
	  ○ Culture positive after 2 months of txt
	  ○ Having a cavity on CXR at end of treatment

SECOND LINE	• Used if there is ADRs or resistance to first line agents

TREATMENT REGIMENS:

	INITIAL PHASE (2 months)	CONTINUATION PHASE
Standard	INH RMP PZA EMB* daily or 5 days/week	INH RMP for 4 months daily or 3 times/week
Elderly > 65 or other risk factor for hepatotoxicity	INH RMP EMB * daily or 5 days/week	INH RMP for 7 months daily or 3 times/week

* EMB can be stopped as soon as the DST results are available if pan sensitive

DOSING:

	INH	RMP	PZA	EMB
Daily dosing	5 mg/kg (max 300 mg)	10 mg/kg (max 600 mg)	20-25 mg/kg (max 2 g)	15-20 mg/kg (max 1.6 g)
3 x / week	10 mg /kg (max 600 mg)		30-40 mg/kg (max 4 g)	25-40 mg/kg (max 2.4 g)

TOXICITIES OF ANTI-TB MEDICATIONS:

	Common ADRs	Uncommon but important ADRs	Probability* of hepatitis	Probability* of rash
INH	Rash, hepatitis, neuropathy	CNS toxicity, anemia	2	3
RMP	Drug interactions, rash	Hepatitis, flu-like illness, neutropenia, thrombocytopenia	3	1
PZA	Hepatitis, rash, arthralgia	Gout	1	2
EMB	Eye toxicity	Rash	4	4

* ranked from 1 = most likely, 4 = least likely

MONITORING PARAMETERS:

EFFICACY	• Resolution of signs and symptoms • Physical exam parameters • Diagnostic parameters (AFB, culture, CXR)
TOXICITY	• Baseline, 1, 2, 4, 6 months for lab work ○ CBC, SCr, AST or ALT, visual acuity, rash, peripheral neuropathy

LATENT TUBERCULOSIS INFECTION:

DIAGNOSTIC TESTS:

TUBERCULIN SKIN TEST	• Inject intradermally 0.1 mL of 5TU PPD tuberculin • Produce wheal 6 mm to 10 mm in diameter • Read in 48-72 hours • Read the induration, not the redness around	
FACTORS THAT AFFECT SKIN TEST	**BCG vaccine**	• Past vaccine given in high endemic areas • Not really protective, efficacy 0-80% • Will lead to a (+) PPD result • Assume pts with PPD are infected regardless of BCG vaccine
	Infection with other mycobacteria	• PPD can't distinguish from other types of mycobacteria
	Anergy	• Pts who have a dysfunctional immune system → would not react to skin test • HIV pts, elderly, critically ill, malnourished, immunosuppressed
INTEFERON GAMMA RELEASE ASSAY (IGRA)	• Detects patients who have been <u>infected</u> (exposed), but doesn't determine if they have <u>active disease</u> • Blood test and not skin testing • High sensitivity and specificity • Expensive, need a lab • Ex// Quantiferon Gold or T-SPOT	

GOALS OF THERAPY:

- Start LTBI treatment, based on the TST and risk interpreter
- Prevent reactivation of disease
- Prevent ADR from treatment

VIABLE TREATMENT OPTIONS:

- INH 300 mg/day x 9 months (RCT, level I evidence)
  - RCT actually done with 12 months of INH
  - Subgroup analysis shows no difference in efficacy between 12 months and 9 months = hence 9 month regimen
  - 80% compliance → 93% protection, 60-68% compliance → 49% protection
- RMP daily x 4 months (Level II evidence, RCT ongoing vs. INH)
  - Seems to be well tolerated
- INH 900 mg + RPT 900 mg once weekly x 3 months under DOT
  - Better efficacy due to higher completion rates with the once weekly regimen
  - Post-marketing reports of hypersensitivity rxns with RPT