Tuberculosis: The Distillation

EPIDEMIOLOGY

The *M. tb* complex consists of four organisms, only one of which is pathogenic in developed countries
Humans are the sole natural reservoir
TMX is via fine aerosols (droplet nuclei)
Affects 33% of the world population
- 30 million with active disease
- Incidence: 9 million/yr
- Mortality: 2 million per year

15 million infected in US
- Mostly in immigrants from endemic countries, minorities, residents of congregate settings, DM, HIV

Risk Groups: extremes of age (infants, elderly), immunocompromise (HIV)

MICROBIOLOGY

The organism is an acid-fast bacillus (AFB).
- Cells are waxy, lipophilic, impermeable to the Gram stain, and aggregated
- Retain carbol fuschin after elution with acid alcohol (Ziehl-Neelsen)

Facultative intracellular pathogen, obligate aerobe
- Inhibits phagolysosome fusion
- Grows slowly in high-oxygen environment
- Resistant to desiccation and disinfectants

Virulence: NO EXOTOXINS OR ENDOTOXINS
- Intracellular replication (in macrophages)
- The cell wall constituents are mycolic acids (>60%), sulfolipids, and LAM. These disrupt lysosomal fusion. LAM is pyogenic and results in cachexia.
- Cord Factor: a surface glycolipid allowing *M. tb* to form fibrillar structures

PATHOGENESIS

PRIMARY TB (not equivalent to ACTIVE DISEASE)

Inhalation → seeding in lower airway → uptake by alveolar macrophages → replication time ~ 24 hrs → motile macrophages circulate to hilar lymph nodes (initiate CMI) → silent bacteremia → replication at primary and metastatic foci to > 10^3 organisms → DTH → granulomas → fibrosis and calcification → sterilization of secondary sites → residual organisms in lung apices → large granuloma with central caseating necrosis (Ghon complex) → **latent disease**

AMI is inoperative

LATENT TB INFECTION (LTBI)

CMI response required for positive skin test conversion requires > 3 wks.
Untreated: 10% lifetime risk of active disease. Highest risk (> 50% incidence) in first two years.

ACTIVE DISEASE

Focal: meningitis, pleural effusion, pulmonary lesions
Disseminated: military TB
Reactivation occurs in the lung apices
Clinical Presentation: cough (may have hemoptysis), weight loss, fever + chills, night sweats
    Constituional symptoms due to IL-1 and TNF-α
Thus, we classify infection as **active** if it is symptomatic
Extrapulmonary TB: site preferentially affects are: bones, hoints, pleura, lymphatics, GU, CNS, GI
Truly disseminated TB (**military**) metastasizes via **hematogenous spread**
    Various tissues are seeded with small nodules. High mortality if untreated.

DIAGNOSIS of ACTIVE TB

Staining

    Ziehl-Neelsen and Fluorochrome
    Detection threshold is $5 \times 10^3 – 10^4$. Only 50 – 80% of patients are sputum +ve.
    Presume +ve sputum is **active TB:** required to report

Nucleic Acid Amplification

    Only for respiratory samples
    Test is done with +ve sputum smear AND symptomatic patients
    Rapid return
    Low sensitivity in smear –ve patients (even with clinical symptoms)

Culture

    Requires lower organism burden (10 bacilli/mL) for detection
    Due to slow growth, requires 8 wks. of incubation with increased CO2

BUT there are newer culture technologies

    BACTEC can detect growth via carbon isotope production within 2 wks.
    SEPTICHEK
    MGIT: senses oxygen consumption

Drug Susceptibility

    Requires > 5 wks to determine profile

DIAGNOSIS of LATENT TB

Detect latent TB
Detect active TB (without classic clinical presentation)
Test: population at high risk of exposure + active disease with primary infection

RISK GROUPS for INFECTION

Close contacts
Immigrants from endemic countries
Residents of congregate settings
Healthcare workers
Infants and children with exposure to adults in risk category

Ethnic minorities
Abuse of EtOH or drugs

RISK GROUPS for ACTIVE TB
HIV +ve
Recent infection with *M. tb* (< 2 years)
DM, CKD, malignancy, ISDs
Hx of inadequate treatment
Children < 4 yrs

Mechanism of PPD skin test
The skin test does not actually elicit CMI, so it may be performed repeatedly
Activation of memory T cells → TH1 → secrete IFN-γ → macrophages → induration
False positives: BCG vaccination, *exposure to environmental mycobacteria*
    NOT specific to *M. tb*
False negatives: decreased immune response, CKD, malnutrition, transient anergy

If admitting to long-term care center: two-step boost PPD
    Administer after 1 – 3 wks if first test is negative
    If positive: presumed to be latent TB

Serum Tests for Latent TB AND active disease
    QuantiFERON Gold: *in vitro* assay. Detects IFN-γ production when host serum is incubated with TB antigens
        Highly specific to *M. tb*, single-visit, independent of prior BCG vaccination
        It is an ELISA
    T-SPOT: same mechanism as QuantiFERON

OTHER MYCOBACTERIA

M. leprae
    Causes leprosy. Involves granulomatous inflammation of peripheral nerves and superficial tissue.
Environmental Mycobacteria
    Non-tuberculosis mycobacteria (NTM) [atypical mycobacteria].
    Typically acquired from water.
    No horizontal TMX.
    Common presentation: pulmonary disease (similar to TB), lymphadenitis, cutanous and soft tissue infection, disseminated disease
    Resistant to Tx with first-line antimycobacterial agents

HIV CO-INFECTION

50% of developing active disease over within 2 years
5 – 10% chance of developing disease per year
1/3 isolated pulmonary dz, 1/3 isolated EPTB, 1/3 combined dz
Increased risk of infection with environmental TB
    Acquired through RT, and usually involves dissemination
    Causes chronic wasting in HIV
    Dx with blood plates and Tx with 2nd line drugs

PEDIATRIC TB

Pulmonary: endobronchial TB with lymphadenopathy
Disseminated: TB meningitis
Miliary TB
CXR: PA *and* lateral views

VACCINATIONS

BCG: protects against severe disseminated disease and pediatric military TB
    Prevents bacteremia by priming macrophages
    THIS IS A LIVE VACCINE derived from antigens from *M. bovis*
    CI: pregnancy
NOT routinely provided in the US since TB infection is rare, vaccine is not effective
Interpretation: assume the patient is not vaccinated, IF RISK FACTORS ARE PRESENT, since anergy occurs over times

TREATMENT

Active: Multidrug therapy for 6 – 9 mos. Patient is non-infectious after 2 – 3 wks. Routine cultures until two consecutive nagtive results.
Latent: INH 9 mos. High threshold for staring Tx due to toxicity of INH, so must r/o other primary diseases.
MDR: Resistant to INH and rifampin. Use second-line agents.
XDR: Resistant to INH, rifampin, FQ, > 1 IV second-line drug

INH

Cell-wall inhibitor: prevents synthesis of mycolic acid
Prodrug: requires conversion and trapping
Cidal
Delayed hepatotoxicity, peripheral neuropathy (co-treat with pyridoxine: B6)

Rifampin

Inhibits transcription by altering structure of RNAP
Cidal
Hepatotoxicity, numerous drug interacts due to induction of CYP450

Pyrazinamide
Unknown mechanism
Prodrug: requires hydrolysis within the organism
Arthralgia, hepatotoxicity, gout
CI: pregnancy

Ethambutol
Static
Inhibits incorporation of mycolic acid and chelates metals (inhibiting protein synthesis)
Optic neuritis and loss of color perception, gout

Drug Pearls
Primary RF for resistance is **non-compliance**
INH, Rifampin, Ethambutol, Ethionamide, and Cycloserine are effective against TB meningitis
INH is used for prophylaxis
It is possible to use Rifampin for prohylaxis
INH, Rifampin, and Pyrazinamide are cidal, and have significant hepatotoxicity
Pyrazinamide and Ethambutol cause hyperuricemia and may lead to gout
Second-line drugs are: ethionamide, aminosalicylic acid, cycloserine, aminoglycosides, capreomycin, and FQs

Strategy

ACTIVE DISEASE
Active phase: INH, rifampin, pyrazinamide, ethambutol for 2 mos.
If susceptible to all drugs, discontinue ethambutol.
Suppressive: INH and rifampin for 4 mos.

INH-resistance: all other drugs for 6 – 9 mos.
MDR: Use 5- 7 drugs, including parenteral antibiotic (e.g. FQ).
Use ≥ 4 drugs for 18 – 24 mos. once susceptibility is determined
HIV: standard 4-drug Tx + extended suppressive phase with **frequent dosing of rifamycins**
substitute rifabutin for rifampin dueto CYP450 induction and interference with antivirals
Pregnancy: INH + rifampin for 9 mos. CI: pyrazinamide
Pediatric: All drugs except ethambutol due to difficulty in screening for vision changes

LATENT DISEASE
Known exposure + aymptomatic: INH for 6 mos. With conversion of PPD: treat for 1 year.
Positive PPD (primary infection) + asymptomatic: INH for 9 mos.
Hx of TB with inadequate therapy: INH for 1 year.
Anergic patients from risk groups: INH for 1 year.