TUBERCULOSIS INTENSIVE
In a Nutshell

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OBJECTIVES

1. For Tuberculosis (TB), clarify the:
   - Epidemiology
   - Pathogenesis
   - Natural History

2. Differentiate the clinical manifestations of:
   - Latent TB
   - Active TB
   - Old, healed TB

3. Independently diagnose and manage Latent TB Infection (LTBI)

4. Case-find and co-manage Active TB Disease, and old healed TB

5. Facilitate prevention of TB transmission
Mycobacterium tuberculosis
a.k.a. “M. Tb”

- Not visible by Gram Stain due to waxy cell wall
- Need special **Acid-Fast** stain
  Thus Acid-Fast Bacillus: “AFB”
- Slow-growing:
  - Doubling-Time: 16 hrs.
    
    *E. coli*: 20 min.
  - Up to 60 days on traditional culture media
  - Newer technology can detect growth in 1-2 wks.

Other **Mycobacteria** (MOTT)

- *M. avium* Complex (MAC in AIDS)
- *M. leprae* (Leprosy)
- *M. bovis* (from raw milk)
- *M. kansasii*
- *M. chelonae*
- *M. gordonae*
- *M. fortuitum*
- >60 more species
“Consumption”

• Found in Mummies
• 1854 -- First Sanatorium
• 1882 -- M.Tb isolated by Robert Koch (Koch’s Postulates: germ theory)
• 1921 -- BCG Vaccine – (Bacillus Calmette-Guérin)
• 1944 -- Streptomycin
• 1952 -- Isoniazid (INH)
Estimated 1/3 of world’s population is infected with M.Tb (2 billion)
TB plus HIV

- HIV → greatly ↑ TB morbidity & mortality
  - T-helper lymphocytes key to TB control
- Worldwide: ~14,000,000 people co-infected
- TB causes 25% of AIDS-related deaths in world
  - Largest single cause
- 3rd World: Active TB may be Asymptomatic in HIV
  - 10% may have normal Chest X-Rays
  - Up to 25% pts presenting for HIV care have Un-Dx’d TB
Active TB -- U.S. Epidemiology
A “Focal” Disease

Reported TB Cases United States, 1982–2010*

No. of Cases
30,000
25,000
20,000
15,000
10,000
5,000

Year

*Updated as of July 21, 2011

TB Case Rates,* United States, 2010

National Average
3.6/100,000

1982 1993 2010

www.cdc.gov
Active TB Case Rates (per 100,000 population)

- U.S.: 3.6
- California: 6.4
- San Francisco: 13.4
Reported TB Cases by Origin and Race/Ethnicity,* United States, 2010

U.S.-born

- White (33%)
- Hispanic or Latino (19%)
- American Indian or Alaska Native (3%)
- Asian (3%)
- Native Hawaiian or Other Pacific Islander (2%)

Black or African American (40%)

Foreign-born**

- White (5%)
- Hispanic or Latino (37%)
- Asian (45%)

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 196 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.
Latent TB in USA

- Estimated >11,000,000
  - prevalence 4.2% (1999-2000)

- Higher Prevalence Among:
  - Foreign Born (18.7%)
  - African-Americans (7%)
  - Mexican-Americans (9.4%)
  - Poor (6.1%)
1) M.Tb is inhaled
2) Macrophages engulf, carry to lymph nodes
   *(innate immunity)*
3) M.Tb disseminates
4) During 2-10 weeks, Macrophages present M.Tb antigens to T-cells,
   → specific *adaptive cell mediated immunity* (CMI)

*Image credit: Curry International Tuberculosis Center, University of California, San Francisco*
IMMUNE CONTROL OF TB

• **Cell-Mediated Immunity** can **kill** the bacteria

• **Delayed-Type Hypersensitivity** $\rightarrow$ **granulomas**
  – Macrophages engulf bacteria $\rightarrow$ release cytokines
  – Cytokines recruit T-cells & more Macrophages
  – **Granuloma** = organized collection of macrophages

• **Granulomas** wall off M.Tb (good)

• **Granulomas** prevent CMI (T-cells) from killing off M.Tb (bad)
“Granulomatous”
“Caseating Granulomas”
Think TB
(“Caseating” = “cheesy”)

Non-Caseating Granulomas
• Sarcoid
• Parasitic
• Neoplasms

• Fungal
• Syphilis
• Foreign Bodies
• Other (Crohn’s etc.)
LATENT TB **INFECTION** (LTBI)

- M.Tb remains **dormant** in granulomas in areas of high oxygen tension:
  - Lung apices / upper lobes
  - Kidneys
  - Cervical nodes (scrofula)
  - Salpinx
  - Pleura
  - Virtually any organ
  - Larynx
  - Vertebrae
  - Meninges
  - Eye
  - Peritoneum
LATENT TB  **INFECTION** (LTBI)

- Completely **Asymptomatic**
- **Not contagious** (walled-off in granulomas)
- **Culture is Negative** (no multiplying bacilli)
- **Not pathologic:** wouldn’t find on autopsy
- Only finding: **PPD/IGRA Testing is Positive**

**Natural History of LTBI**

- 5% - 10% lifetime risk reactivation to Active TB
- Half of that occurs within 2 yrs. of infection
ACTIVE TB = DISEASE

- Patient is sick
- Active TB: **Pulmonary** and **Extrapulmonary**
  - Developed Nations: 85% is Pulmonary
  - Underdeveloped Nations /
  - Immunocompromised Pts: 50% is Pulmonary
- Contagious: **Pulmonary** & Laryngeal TB
- Culture **Positive** (bacilli multiplying)
- Pathology: “Caseating” Granulomas = TB
ACTIVE TB -- Symptoms

• PULMONARY
  – Cough (may be minimal, but persistent)
  – Hemoptysis (blood in sputum)
  – Weight loss, Fevers, Night Sweats (drenching)
  – Diagnose: X-ray (presumptive); Sputum Exam

• EXTRAPULMONARY
  – Weight loss, Fevers, Night Sweats (drenching)
  – Other Symptoms depend on which organ
  – Diagnosis: culture / histology (often by biopsy)
  – Disseminated TB: “Miliary TB”
ACTIVE TB: NATURAL HISTORY

• “Natural History” = course if untreated
  – MUST KNOW the Natural History of any disease you’re going to deal with

• Untreated Active Pulmonary TB
  – 50% of patients die within 5 years
  – 32% cured on their own
  – 18% experience ongoing relapses & remissions
Latent TB (LTBI) -- Diagnosis

• Purified Protein Derivative (PPD)
  a.k.a. Tuberculin Skin Test (TST)
  a.k.a. Tuberculin Testing
  a.k.a. Mantoux Test

• Intradermal: MUST Raise a Bleb!!!
PPD TESTING

• **Type-4 Hypersensitivity Reaction**
  – T-Memory Cells → cell-mediated response

• **Type-4 = “Delayed-Type” Hypersensitivity**
  – Read at 48-72 hrs.
  – Non-Specific response at 24 hrs. *doesn’t count*
  – Later reactions **DO COUNT** (? even at 1 wk.)
PPD TESTING – Adverse Effects

• Large Local Reactions are Rare
  – Skin sloughing even rarer
• Not prognostic in terms of getting Active TB
• Do NOT Dx / Tx as “cellulitis”
• One reason never to repeat PPD in pt. who’s already Pos.
LTBI -- POSITIVE PPD

• ≥ 10 mm induration (NOT just erythema)
  – Any Vesicles = Positive
• 5 mm Positive: HIV, abnl. CXR, recent exposure
• 15 mm in person w/o risks for TB

BUT... DON’T TEST PEOPLE w/o RISKS

SO -- WHO SHOULD WE TEST ???
AT-RISK FOR GETTING LTBI

- Poor / Homeless
- Born in 3rd World
- Travel to 3rd World (for >1 mo., or 2x each yr.)
- Incarcerated / Institutionalized
- Native American / Alaskan
- Injection Drug User
- Contact w/ Active TB

[most HCW are low-risk, a few intermediate]

- Only Test These Persons

- Also Test if Risk of Reactivation

[See Next 2 Slides]
REACTIVATION: ACTIVE TB DISEASE

Patients with Decreased CMI

• **High Risk:**
  - AIDS
  - HIV
  - Post-Transplant
  - Silicosis
  - Renal Failure (dialysis)
  - Cancer: head & neck, lymphoma, leukemia
  - ChemoTx; TNF-Inhibitors
  - Malnutrition

• **Mod.:**
  - DM
  - Prednisone ≥15 mg/d x ≥1 mo.

• **Slight:**
  - Underweight (BMI <20)
  - Smoker
REACTIVATION: ACTIVE TB DISEASE

Other Risks

• **High:**
  – Abnormal CXR compatible with prior active TB that healed on its own
  – Recent infection *(PPD conversion in ≤2 yrs.)*

• **Moderate:**
  – ≤4-years-old
  – Puberty
False-Positive PPD

• Read Test before 48 hours

• Mycobacteria Other Than TB ("MOTT")
  – More common in rural Southeast USA

• Bacillus Calmette-Guérin (BCG) Vaccine
  – Invented in 1921
  – No standardization in potency
    • Each batch derived from a prior batch
  – Effect on PPD related to time from last booster
Bacillus Calmette-Guérin (BCG)

- Widely given in 3rd World at birth
  - Given in Europe until recently
  - All countries have different booster schedules
  - See country guide: www.bcgatlas.org

- Meta-analysis: 26 studies (of >1200 articles)
  - Protection: 50% for TB, 64% meningitis, 71% death
  - Rarely indicated in US
    - e.g. Child in home w/ drug-resistant TB
Foreign-Born HCW w/ + PPD

- **PPD Induration from BCG**
  - Common: <10 mm
  - Uncommon: >10 mm
  - Rare: >15 mm

- If Person from area w/ high TB Prevalence, is PPD more likely **FALSE** or **TRUE** Positive?

- **CDC:** “Ignore Hx BCG when interpreting PPD”
FALSE-NEGATIVE PPD ???

- Bad Technique (too deep, no bleb)
- Spoilage (solution left at room temp x 30 min)
- Recent TB Infection [takes 2-10 wks to convert]
- Recent measles / varicella -- or the vaccines
  - Place PPD simultaneously w/ vaccine, or in 3 mos.
- Anergy (HIV, malnutrition, neonate, CA, etc...)
- Waned Type-4 (Delayed) Hypersensitivity due to Remote Infection (many years ago)
WANING of Delayed-Type Hypersensitivity

• Over many years, DTH can wane
  - Therefore, no reaction to PPD
• BUT: The PPD primes DTH memory
• SO: Subsequent PPD will be positive
• This is called the booster phenomenon
• NOTE: CMI doesn’t wane
• Note: Frequent PPDs do NOT → Positive
BOOSTER TESTING

• a.k.a. “2-Step Testing”:
  – If very first PPD is Negative: Repeat in 1-3 wks.

• Only do for pts who requiring annual PPDs
  – e.g. health-care workers, institutionalized, etc.

• Rationale: PPD neg. this year, pos. next year, implies new PPD conversion (Neg $\rightarrow$ Pos)
  ➢ Conversion = Recently Infected
    High risk of reactivation, requiring Tx
Interpreting 2-Step Testing

• PPD #1 → Negative
  > Repeat PPD in 1-3 weeks

• PPD #2:
  Negative = Not infected w/ M.Tb (No LTBI)
  Positive = LTBI, infection occurred long ago
POSITIVE PPD

You order CXR:

>> It’s read as “normal”

How Do You Explain to Patient What’s Going On???
LATENT TB INFECTION (LTBI)

• The bacterium *Mycobacterium tuberculosis* (M.Tb) *is inside the body* [probably the lung]
  – Undoubtedly contracted long ago
• It’s causing no harm  [CXR is normal]
  – Body defenses have walled it off
• It’s not contagious

• BUT: average 10% lifetime-risk of reactivating
  – Substantially decreased with Tx
Interferon-Gamma Release Assay (IGRA)

- QuantiFERON-TB Gold In-Tube®, T-Spot.TB®
- Pt’s blood incubated w/ MTb antigen, assayed to detect Interferon-Gamma from T-Cells
- Negative- and Positive-Controls

**RESULTS:** “Pos” / “Neg” / “Indeterminate”

- “Indeterminate” = Not Valid [NOT “almost pos”]
- Maybe can’t respond to Pos. Control (anergy)
- Maybe background IFN responds in Neg. Control
Interferon-Gamma Release Assay (IGRA)

• Logistics Problem: Must process < 8-12 hrs.
• **Specific:** No reaction to BCG
  – Maybe not to other Mycobacteria either
• **NOT MORE SENSITIVE THAN PPD**
• **BIG ADVANTAGE:** Single-visit only
• Prefer IGRA: Prior BCG Vaccine
• Prefer PPD: Children <5 y.o.
• Unsure: Serial testing for LTBI
PPD plus IGRA

• Not usually recommended (CDC)
  – More acceptable by Canadians, UK, Europeans

• PPD might boost the IGRA
  – Perform together, or draw IGRA w/ PPD reading

• Might Consider if:
  – High Risk for active TB (e.g. HIV, TB contact <5 y.o.)
  – Low Risk for true LTBI (BCG)

• PPD + IGRA Calculator:
  http://www.tstin3d.com
LATENT TB INFECTION (LTBI)

• Can be clinically diagnosed by either a positive PPD or IGRA

• BUT... What’s the Gold Standard for diagnosing LTBI ???

btw –

What does “Gold Standard” mean?
GOLD STANDARD for LTBI

• i.e. How do we know 10 mm induration of PPD really means LTBI?
• It’s purely epidemiologic !!!!!!!
  – Not by radiography, biopsy, or even autopsy
• Countless studies, diverse populations, have correlated 10 mm with ↑ risk of active TB
• 5 mm = pos.: HIV, abnl. CXR, or TB contact
• 15 mm: for low-risk pts [but DON’T even test!!]
ONLY TEST AT-RISK FOR LTBI !!!

• PPD has imperfect specificity
  – Can cause false-positives

• DON’T SCREEN low-prevalence populations:
  > Most “positives” are actually false !!!
  > Subsequent work-ups & treatments will cause harm !!!
What Happens if you Screen a Low-Prevalence Population

• Example: If a Given Test has 99% Specificity, then 1% of results are false pos.

• Suppose a prevalence in 2 populations:
  
  \[
  \text{Pop. “x”} = 10\% \quad \text{Pop. “y”} = 0.1\%
  \]

Test 1,000 people in Pop. “x”:
  
  \[
  \rightarrow 100 \text{ true pos}, 10 \text{ false pos} = 91\% \text{ true pos}.
  \]

Test 1,000 people in Pop. “y”:
  
  \[
  \rightarrow 1 \text{ true pos}, 10 \text{ false pos} = 91\% \text{ false pos. !!!!}
  \]
How Often to Test for LTBI?

• Based on exposure risk & local epidemiology

• **Test annually:**
  – Long-Term Care, Prisons, Drug Programs
  – Residents of congregate living facilities
  – Health Care Workers

• **Test every 6 months:**
  – TB workers, ER staff, bronchoscopists

• **Travelers >1 mo.** to endemic area, upon return
POS. PPD / IGRA = **ALWAYS POS.**

- **Never repeat**
  - Useless; we learn nothing new
  - Repeat PPD may cause worse local reaction

- **Future TB Screening: Chest X-Ray [???????]**
  - Employers, etc., care about Active TB, not LTBI
  - PPD/IGRA do NOT screen for Active TB, but serve the purpose
  - Pos. pts. NEVER need repeat CXR’s unless ill
    - But you can’t argue w/ the Boss
LATENT TB INFECTION (LTBI)

How do we Treat?
Why do we Treat?
Adverse Effects of Treatment?
Who do we Treat?
Isoniazid Hydrochloride (INH)

- **Dose:** 300 mg (10-20 mg/kg) daily
  - On empty stomach
  - Rx 30 pills, No Refills (monthly F/U)
- **Duration of Tx:** 9 months (recommended)
  - 6 months (acceptable alternative)
- **Goal:** Prevent TB Reactivation
- **Prior appellations:**
  - “preventive therapy” “chemoprophylaxis”
- **Current Conceptualization:** Treat (“cure”) LTBI
Rationale for INH Tx

TB germ walled-off by defenses

10% lifetime chance it escapes

Treatment kills germ
INH to Prevent Active TB

• 1970s Eastern Europe trial
  - Old, healed TB (“old scars” on CXR = “TB-4”)
  Among the very adherent subjects at 5 yrs:
    > 6 mos. Tx → 69% reduction active TB
    > 12 mos. Tx → 93% reduction

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536088/

• Cochrane Review 11 INH Trials: 6 mos. = 12 mos.
  > 0.44 relative risk of active TB at 2 yrs.

What About Missed Doses?

Treatment considered complete if

- 9 mos. of INH taken within 12 mos.
- 6 mos. of INH taken within 9 mos.
INH – Adverse Effects

• **Hepatotoxicity**  [!!!!!!]

• **Peripheral Neuropathy** (interferes w/ Vit. B6)
  > Rx Pyridoxine (Vitamin B6) 25-50 mg daily to:
    – Pts >50 y.o., children
    – Diabetics, HIV, Pregnant/Lactating, Malnourished, Alcoholic, Renal Failure, other risks for neuropathy

• Rare: joint pains, drug-induced Lupus, rash, N/V, diarrhea (from sorbitol in liquid prep)
INH – Drug Interactions

• Antacids: interfere with absorption
• INH → Toxic Levels of:
  – Warfarin: monitor levels
  – Anticonvulsants: monitor levels
  – Clopidogrel (Plavix): avoid
  – Citalopram (Celexa): ↓ citalopram dose
• INH may ↓ efficacy of Tamoxifen
INH Hepatotoxicity -- Risks

- <35 y.o.: 0.1% to 0.4%
- >65 y.o.: 0.3% to 4.5%
  - lower numbers are more recent

- Increased Risk:
  - Daily EtOH
  - Pre-existing Liver Dz
  - IDUs
  - Pregnancy/Post-Partum
  - Women of Color
  - Other Hepatotoxic Meds
  - Prior INH Intolerance

- Children: virtually NO risk
INH Hepatotoxicity -- Management

• Good pt. ed. / monthly review [does pt recall?]
  – anorexia, nausea, malaise, upper abd. pain
  – Barely mention jaundice !!!

• If symptoms occur x2 days:
  1. Stop the INH
  2. Return to Clinic ASAP (for LFTs)

• Fatalities mainly occur among patients who continue INH despite Sx
INH Hepatotoxicity -- Management

- No routine baseline or follow-up LFTs
  - ALT ↑ x2 in 20% pts [ignore]
- Order them only if:
  - Underlying liver disease
  - HIV on meds / other hepatotoxic meds
  - Pregnant / Post-partum

Remember

• Only Rx INH 30 days at a time, No RF’s
INH Contraindications (relative)

• Pregnancy
  – Start 12 wks. post-partum to avoid hepatitis risk
  – INH is NOT teratogenic
  – OK in pregnancy for high-risk pt. (e.g. HIV+)
  – Certainly OK to give INH in pregnancy for Active TB

• Daily Alcohol intake
  – Rx INH & strongly urge to limit EtOH
  – Close F/U

• Hx of INH Hepatotoxicity [absolute contraindic.]
WHO SHOULD GET INH ???

Old Guidelines (pre-2001)

• Anyone <35 y.o. if PPD-Pos. [or IGRA-Pos.]

• Following persons regardless of age:
  – Pts w/ conditions that → high risk of reactivation
  – New conversion (Neg → Pos in last 2 yrs)
  – Close contacts of newly-Dx’d Active TB pt., even if PPD-Negative
    • Tx x3 mos, repeat PPD, d/c if still neg. [usually]
High Risk of TB-Reactivation

- **High Risk:**
  - AIDS
  - HIV
  - Transplant Meds
  - Silicosis
  - Renal Failure (dialysis)
  - Cancer: head & neck, lymphoma, leukemia
  - ChemoTx; TNF-Inhibitors
  - Malnutrition
  - CXR w/ “old scars” of prior healed TB
  - Infected (LTBI) within last 2 yrs (“conversion”)

- **Mod.:**
  - DM
  - Prednisone $\geq 15$ mg/d x 1 mo.

- **Slight:**
  - Underweight (BMI <20)
  - Smoker
WHO SHOULD GET INH ???

Current Guidelines

• Age is no longer a consideration
• Pos. Immigrants from high-prevalence countries who have been in U.S. ≤5 years
• Anyone w/ risks for TB-Reactivation (of course)

BUT, What about the....

• 90-y.o. newly-arrived immigrant?
• 20-y.o. who’s been in U.S. for 6 yrs?
WHO SHOULD GET INH ???
Informal Consensus

<35 y.o. -- • Everyone with Positive PPD/IGRA (regardless of time in U.S.)

<50 y.o. -- • Immigrants in U.S. <5 yrs.
  • Smokers
  • BMI <20

<65 y.o. -- • Diabetes
  • Prednisone ≥15 mg/d for ≥1 mo

Regardless of Age: High risks for TB-reactivation
Alternative Regimen for LTBI

- INH 900 mg + Rifapentine 900 mg (adult doses)
  > INH 300 mg 3 tabs. + RPT 150 mg 6 tabs.
  > one time per week for 12 weeks
  > by Directly Observed Therapy (DOT)
- Caveats: ≥12 y.o., not pregnant, not on HIV meds
- Rifapentine Adverse Effects:
  - Reddish urine (harmless)
  - Stains contact lenses
Alternative Regimens for LTBI

- **Rifapentine: off-label** (approved to Tx Active TB)
- Based on 3 open-label studies
  - [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm)
- INH-intolerant, or suspect INH-resistant strain:
  - Rifampin 600 mg daily x4 mos. [also off-label]
  - Do NOT use Pyrazinamide + Rifampin x2 mos. as noted in latest (2000) MMWR recommendations
REINFECTION

- Well-documented, but uncommon
  - Cell-mediated immunity offers protection
- More common among immunocompromised
- Clinical diagnosis impossible
  - PPD / IGRA remain positive for life
  - Might consider re-treating “reinfected w/ LTBI” if immunocompromised w/ strong exposure risk
REACTIVATION: ACTIVE TB DISEASE

• Also called “Post-Primary”
• Can occur in any organ
• Only contagious if pulmonary or laryngeal
  – NOT pleural [ignore “pleural thickening” on CXR]

HOW DOES ACTIVE TB USUALLY PRESENT?
COUGH !!!

• **Hallmark of Active TB**

• **Persistent; BUT May be Minimal**

• Any cough x 3 wks. duration, not improving, should get CXR (unless other Dx, e.g. asthma)

• **Other symptoms get W/U sooner:**
  * Fever   * Hemoptysis   * Wt. Loss
  * Night Sweats (drenching)
CLASSIC ERROR

• Cannot R/O Active TB with a PPD / IGRA
• 20% of pts. with Active TB are PPD-Negative
  – Probably because Active TB is immunosuppressive
  – PPD often reverts to positive after Tx
• PPD / IGRA only used to diagnose Latent TB
• Diagnosing Active Pulmonary TB
  1) Suspect by CXR
  2) Confirm by Sputum smear & culture for AFB
ACTIVE PULMONARY TB -- Nodules

ncbi.nlm.nih.gov

hss.edu
ACTIVE PULMONARY TB --
Cavities

Curry International TB Center
ACTIVE PULMONARY TB --
Infiltrates

Obvious
Curry International TB Center

Subtle
(Left Apex)

Courtesy University of Wisconsin Board of Regents
ACTIVE PULMONARY TB --
Left Apical Nodule

Hard to see on PA view  Easy on “Apical Lordotic”

Curry International TB Center  Curry International TB Center
NOT ACTIVE TB:

“Calcified Granuloma”

• “Ghon Lesion”
  Blue Arrow
  Calcified parenchymal nodule
  Where MTb first entered lung, engulfed by innate immunity

• “Ranke Complex”
  Blue + White Arrows
  Calcified nodules in parenchyma & hilum

Curry International TB Center
ACTIVE PULMONARY TB -- Primary

- Innate immune response weak
- AIDS, nursing home pts, malnourished, infants, etc.
- Middle / Lower lobe (mimics classic pneumonia)
ACTIVE PULMONARY TB -- AIDS

• Only Lymphadenopathy!
• Lung lesions are caused by body’s immune cells
• AIDS pt. has few T-Cells
• So normal parenchyma, maybe even normal CXR
• BUT… overwhelming number of bacilli

hiv.va.gov
ACTIVE TB -- PEDIATRICS

Lymphadenopathy on Lateral CXR

Normal Lateral CXR

Lymphadenopathy

Curry International TB Center
Diagnosing Active TB

1. Suspect by **Symptoms**
   - Cough ≥3 wks., not improving, no other Dx
   - Sooner if fever, night sweats, hemoptysis, wt. ↓

2. Obtain **CXR**, pursue Dx if suspicious
   - Apical / Upper Lobe, nodules / infiltrates
   - Cavities
   - Lymphadenopathy (esp. in AIDS, Peds)

3. Confirm by **Sputum analysis**
Dx Active TB -- SPUTUMS

• Order “Sputums for AFB x 3”
  – 3 separate days
  – Early AM best: Pt. coughs whatever they can into cup, brings specimen in same day
  – If obtain 1\textsuperscript{st} specimen in clinic, send pt. outdoors to cough

• Lab will do “smear” + culture & sensitivities
Dx Active TB -- SPUTUMS

- **Smear**: See AFB on Microscopy (24-hr. results)
  - 50% of Active TB is “Smear-Positive”
- **Prove by Culture**: 6-8 wks. conventional media
  - 1-2 wks. radiometric technology (e.g. Bactec®)
- **Susceptibility Tests**: 2 more weeks
- False-Positive Smears:
  - AIDS pt. w/ Mycobacterium avium complex (MAC)
Sputum for Nucleic Acid Amplification Testing

• **PCR** (Polymerase Chain Reaction):
  – amplifies DNA
  – Must order separately (single specimen)

• 80% of Active TB is NAAT-Positive

• 1-2 day results
  – Expensive
  – Only order if high suspicion (e.g. patient with hemoptysis, night sweats, or weight loss)
Xpert® MTB/RIF Assay

• **New molecular test that:**
  – ↑ Dx yield for active TB by 45% over smears
  – Detects Rifampin resistance (= Multi-Drug Resist. TB)
  – Performs in 2 hrs.

• **Being used in 67 high-prevalence countries**
  – Especially useful to Dx TB in HIV

• **Cost to drop to < $10**
  – Special agreement bet. manufacturer (Cepheid) & B&M Gates Foundation, USAID, PEPFAR (U.S.), & UNITAID (int’l global health initiative)
Deciding Whether to Treat vs. Await Results

- Often Tx for Pneumococcus pending results
- Smear-Positive (or NAAT-Pos) → Treat !!!
- Smear-Negative: Judgment call, based on
  - Clinical picture
  - X-Ray

But Best of All...
Let TB Experts at DPH Decide

- **Directly Observed Therapy (DOT)**
  - Cornerstone of TB Management
- **M. Tb mutates → Drug Resistance**
  - Occurs within 1 month of inadequate Tx
  - **Adherence is essential**
- If your HT pt. is non-adherent, tough for them
  - They get an M.I. & die
- If your TB pt. is non-adherent, they transmit !!
Treatment of Active TB

• **MUST** always be taking **at least 2 drugs** to which M.Tb strain is susceptible

• Shortest course is 6-months:
  – INH + Rifampin + Pyrazinamide x2 mos.
  – INH + Rifampin for 4 more mos. (7 more if HIV)
  – Usually add ethambutol / streptomycin at first, until susceptibility results back

• Any other regimens are longer
  – Some 2\textsuperscript{nd}-Line drugs require >2 yrs. of Tx
Some Drugs for TB

First-Line Tx
• INH
• Rifampin *
• Pyrazinamide
• Ethambutol
• Streptomycin

* May substitute rifabutin for HIV pt. on anti-retrovirals

2nd-Line Tx ‡
• Para-aminoosalicylic acid
• Ethionamide
• Ciprofloxacin
• Amikacin
• Cycloserine
• Etc.

‡ NOTE: Lab won’t perform susceptibility tests unless specifically requested
Active TB Tx -- Response

• Patients usually improve rapidly
• **Smear-Negative TB** rendered non-contagious in 5-7 days

**Smear-Positive TB** is rendered non-contagious in 2-3 wks

• But BEWARE:
  – Pt. may develop drug-resistance in 2-4 wks.
  – Follow with serial sputum exams & CXRs
“Culture-Negative TB”

• Clinical picture & CXR look like Active TB
  Sputum smear is negative
• Tx for TB x2 mos, sputum Cx returns negative !!
• Repeat CXR → abnormalities have resolved !!!
• Diagnosis: “Culture-Negative TB”
  – Constitutes ~2% of Active TB
  – Continue Tx for total 4-6 mos.
DRUG RESISTANCE

• INH: ~10% worldwide (1999)
  – In US: 4% among US-born, 10% foreign-born

• Highest Prevalence INH Resistance:
  -- Vietnam -- Haiti -- Philippines

• CLASSIC ERROR
  – Adding single drug to failing regimen
  – MUST add 2 new drugs strain susceptible to
MDR- and XDR-TB

• Multi-Drug Resistant (MDR-TB)
  – Resistance to INH & Rifampin

• Extensively Drug-Resistant (XDR-TB)
  – Resistant to INH + Rifampin + 2 More

• Totally-Drug Resistant
  – Some case reports, require confirmation
  – So no abbreviation yet
MDR- and XDR-TB

- Multi-Drug Resistant (MDR-TB)
  - 60% of cases occur in China, India, Russia, Pakistan, & South Africa
- Extensively Drug-Resistant (XDR-TB)
  - Has been reported in 84 countries
- Require extremely long courses of Tx.
  - Various destructive surgical options have been used, esp. in pre-antibiotic era
“Old Scar”

- Asymptomatic pt. screened ➔ Pos. PPD ➔ Obtain a CXR

- Radiology report: “right upper lobe scars, compatible with old granulomatous disease. No active TB.”

Curry International TB Center
WRONG !!!!!

• It’s *impossible* to distinguish Active TB from Old Healed TB by x-ray !!!

• If another film available, can say “fibronodular infiltrates unchanged, stable over ___ yrs.”
  – “Stability” is the operative term

• **NOTE:** If obtained CXR for another reason, before PPD, place a PPD and consider it “positive” if ≥5 mm.
CLASSIC ERROR

• Treating LTBI with single drug (INH) if there are actually active bacilli multiplying
  – Guaranteed to generate drug-resistance in 2-4 wks.

• **Must have recent normal CXR to give INH**

• **If abnormal CXR, & no comparison film:**
  – collect 3 sputum specimens
  – Cultures back in 2 mos., & repeat CXR then
  – Negative sputum Cx + stable CXR = “Old Scar”
CASE -- 85-y.o. Cuban Woman

- Long Hx asthma (lots of coughing)
- Hx TB as child, cured on own
  - CXR w/ extensive fibronodular infiltrates
- Sent to TB clinic
  - Elicited Hx “always” on Prednisone [“siempre”]
  - Obtained 3 sputum Cx, Rx’d 4 Drugs
    → severe N/V
- “always” = 5 mg/d x 10d, q3mos → d/c’d meds
  - Cx → Neg at 2 mos. → Rx’d INH alone for TB-4
Ms. G: 44-Yr.-Old Latina

- Screening PPD positive
- Never remembered having had a cough or any symptomatic illness in her life [!!!!!!!!!!]

©stevenleiner
Classification of Tuberculosis

- **TB-2 = Latent TB Infection** (Pos. PPD / IGRA)
  - Asymptomatic, non-pathologic, non-infectious
  - Normal chest x-ray (so no multiplying bacilli)

- **TB-3 = Active TB Disease**
  - Symptomatic, pathologic, infectious
  - Abnormal CXR, positive sputum culture

- **TB-4 = Old, healed TB** (previously active)
  - Asymptomatic, non-infectious, pathologic
  - Abnormal but **stable** CXR, negative sputum cultures
  - **High-Risk of Reactivation**
Classification of Tuberculosis

• **TB-0** = No true exposure
  – Don’t even bother doing a PPD or IGRA

• **TB-1** = Exposure (temporary classification)
  – e.g. Household contact of active TB pt.
  – Needs PPD / IGRA (PPD “pos” = ≥5 mm induration)

• **TB-5** = R/O Active TB (temporary classification)
  – Awaiting sputum results
  – Tx in meantime depends on index of suspicion
Contact Tracing

• “Concentric circle” testing (PPD/IGRA)
  – Closest contacts first (home)
  – If no positives → STOP
  – If positives → EXPAND FURTHER
  – Etc.
Contact Tracing

• PPD = Positive if ≥ 5 mm. induration
  – If Pos. → INH x9 mos.

• If Neg. → INH anyway
  – Takes 2-10 wks. from infection for PPD to convert
  – Retest in 10 wks. → d/c INH if still Neg.
    • BUT BEWARE: 1960s study (TB outbreak on Navy ship)
      – PPD conversions to Pos. got INH immediately
      – At 3 mos, 100% reverted to Negative PPD
    • In young children (high risk TB meningitis), maybe continue full INH course (also in immunocompromised)
TB Transmission --
NOT SO CONTAGIOUS !!!

• 50% to 75% persons living in same house with Active TB pt. become infected
  = 25% to 50% don’t (maybe even after months)

• Measles: 90% transmission in a week
  – Transmitted in waiting rooms

• Pertussis: 85% transmission in ~3 weeks

• Varicella: 75% in ~1 week
TB Transmission -- DROPLET NUCLEI

- Droplets 1-5 μm
- M. Tb rods: 3 x 0.3 μm
- Suspended in air for several hours
- 3,000 droplet nuclei:
  - 1 cough
  - Singing 1 min.
  - Talking 5 min.
TB Transmission -- DROPLET NUCLEI

• We get infected w/ M.Tb by hanging around a closed space where Active TB pt. had been
  – Droplets suspended in air, waiting to be inhaled
  – TB pt. need not be present at time

• Some locales M.Tb has been transmitted:
  – Local bars -- Submarine -- Jails
  – Rehearsal room at opera -- Drug houses
  – Strip Clubs -- Homeless Shelters
TB Transmission on Airplanes

• Very contagious pt. on 4 flights
  – Data for 760/1025, 6 likely infected (8.75 hr. flight)
  – All in rear section, 4 within 5 seats of index pt.

• Very contagious pt on 2 flights of 75 min. ea.
  – No likely infections occurred (160 exposed)
  – Moore M. Aviat Space Environ Med. 1996;67:1097
TB Transmission on Airplanes

• **WHO guidelines for contact tracing:**
  – Passengers >8 h, rows adjacent to pt. w/ Pulm TB

• **Systematic review 13/39 identified studies**
  – Only 2 suggest possible transmission
  – “…reason to doubt the value of actively screening air passengers …resources [might be better spent on] other priorities for the control of TB”
Prevent Transmission

Treat Active TB !!!

• Smear-Positive → non-infectious in 2-3 wks
• Smear-Negative in 5-7 days

• Treatment: Directly Observed Tx (D.O.T.)
  – 4 Drugs x2 months until susceptibility tests back
  – 2 effective drugs for 4-7 additional months
  – Second-Line drugs require longer Tx
ISOLATION – Hardly Necessary

• Others at home have already been exposed for some time
• M. Tb is NOT transmitted OUTDOORS
• Best to avoid indoor locales other than the home until Meds on Board long enough
• **BUT...** Isolation critical in Healthcare Facility
  – If no isolation room available, do not reuse pt. room for 2-3 hrs. after “suspicious pt.” leaves
Airborne Infection Isolation (AII)

- Negative Pressure Room (vent to outdoors)
- If anteroom, don’t open both doors simultaneously
MASKS

**N95**
- Filters 1-micron particles with 95% efficacy
  - Worn by whoever enters isolation room (where droplet nuclei float in air)
  - NEVER worn by patients

**SURGICAL**
- Forced covering mouth: bats droplets to floor
  - Worn by patients when leave isolation room
  - Useless for visitors to patient’s room
Some Studies (ca. 2000)

• 19% TB pts. not isolated on first hospital day
  – Of pts isolated, only 8% proved to have TB
  – ~50% people entering AII room wore surgical masks even though N95 masks available

• 19% of R/O TB pts. placed in rooms w/o negative pressure
  – 11% of pts in negative pressure rooms, the negative pressure not activated or functional
N95 Masks -- Tight Fit

• Several mask sizes available
  – Leave them outside isolation room for visitors

• Health Care Workers: fit-test for size
  – OSHA: Annual fit-testing required
  – But this stems from regulations protecting workers from industrial aerosols
  – Necessary for healthcare facilities??????????

• If N95 Mask can’t fit well...
Got a Beard?

Wear a Powered Air-Purifying Respirator (PAPR)!
RESOURCES

• Medical Consultation for Providers:
  – Curry International TB Center  (415) 502-4700

• Continuing Ed, etc.: Curry International TB Center
  510-238-5100 / www.currytbccenter.ucsf.edu/

• LTBI: A Guide for Primary Health Care Providers

• Recent Review: Zumla A et al. Tuberculosis.
An Educational Blogsite

DiagnosisDude.com

The How’s & How-Not’s of Medical Diagnosis
Summary Handouts

The following slides are useful summary pages conducive to printing as hard copies

– Print in landscape format

1. Public Health Classification System for TB
2. Persons who Warrant Testing for LTBI (with PPD or IGRA)
3. Persons with LTBI who Warrant Treatment
4. Drugs Used to Treat Active TB
## PUBLIC HEALTH CLASSIFICATION SYSTEM FOR TUBERCULOSIS

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB-0</strong></td>
<td>No exposure. No risk of having been infected with M. Tb. No need to test with PPD or IGRA.</td>
</tr>
<tr>
<td><strong>TB-1</strong></td>
<td>Exposure. May have been infected with M. Tb. [temporary classification] Example: Household contact of Active TB pt. Immigrant from high-prevalence area. Needs PPD / IGRA. Pos = ≥10 mm induration. If recent contact, Pos = ≥5 mm induration.</td>
</tr>
<tr>
<td><strong>TB-2</strong></td>
<td>Latent TB Infection (LTBI). Defined by Pos. PPRD / IGRA. MUST have normal CXR (Calcified Granuloma, i.e. Ghon lesion / Ranke complex, is compatible w/ LTBI) Asymptomatic. Non-Pathologic. Non-Infectious. No multiplying bacilli.</td>
</tr>
<tr>
<td><strong>TB-3</strong></td>
<td>Active TB Disease. May be Pulmonary or Extra-pulmonary. Symptomatic. Pathologic. Infectious (pulmonary / laryngeal) Suspect by symptoms: cough ≥3 wks w/o improvement or other Dx is most common -- More severe: fever, night sweats, wt. loss, hemoptysis Confirm Suspicion by CXR (cavities, upper lobe infiltrates / nodules. Lymphadenopathy in AIDS &amp; Peds) Presumptive Dx: AFB smear Pos (50% cases); Histology: Caseating Granulomas. Definitive Dx: Culture. Shortest Tx course: 3 1st-Line drugs x2 mos, 2 drugs x4 more mos. 2nd-Line Drugs: longer courses.</td>
</tr>
<tr>
<td><strong>TB-4</strong></td>
<td>Old, healed TB (previously active). Asymptomatic, non-infectious. Pathologic (scars on CXR). Dx: abnormal but stable CXR (no change over 2 mo. period), Neg. Sputum Cx (60 d, conventional media) High risk of reactivation. INH x9 mos, regardless of age.</td>
</tr>
<tr>
<td><strong>TB-5</strong></td>
<td>R/O Active TB. Work-up in progress (sputum cultures pending) [temporary classification] Further categorized as “high likelihood” or “low-likelihood” (“High-5” or “Low-5”) Treatment while cultures pending is judgment call based on index of suspicion.</td>
</tr>
</tbody>
</table>
PERSONS WHO WARRANT TESTING for LTBI (with PPD or IGRA)  *

Those With Likelihood of Having Latent TB Infection

- Immigrants from countries with high TB prevalence
- Travelers to such areas (for >1 mo., or 2x each yr.)
- Residents of urban areas with a high incidence of active TB
- Low-income and medically-underserved
- Staff and residents of institutions w/ high TB prevalence (nursing homes, psych. institutions, prisons, homeless shelters)
- Close contacts of newly-diagnosed active TB ‡
- Injection Drug User
- Native American / Alaskan
- Fibro-nodular scars on x-ray suggesting prior healed active TB (now inactive) ‡

Those With High Likelihood of Reactivation, If They Were to Have Latent TB Infection

High Risk:  
- HIV / AIDS ‡
- Renal Failure (dialysis)
- Chemotherapy
- Cancer: head & neck, lymphoma, leukemia
- Tumor Necrosis Factor inhibitors (TNF-I)
- Fibro-nodular scars on x-ray suggesting prior healed active TB (now inactive) ‡

Mod. Risk:  
- Diabetes
- Prednisone ≥15 mg/d x ≥1 mo.

Slight Risk:  
- Underweight (BMI <20)
- Smoker

NOTES:  
* Read PPD at 48-72 hrs.  Consider “positive” if ≥10 mm induration
Reactions later than 72 hrs. are considered “positive”.
Vesiculation = positive (regardless of amount of induration)
= 5 mm induration of PPD is considered “positive”
PERSONS with LTBI (Pos. PPD / IGRA) who WARRANT TREATMENT with INH
(Clinical Consensus; Not a Formal Guideline)

REGARDLESS OF AGE -- Persons With High Likelihood of Developing Reactivation TB:

- HIV / AIDS
- Renal Failure (dialysis)
- Chemotherapy
- Post-Transplant on Anti-Rejection Meds
- Cancer: head & neck, lymphoma, leukemia
- Tumor Necrosis Factor inhibitors (TNF-I)
- Silicosis
- Malnutrition
- Fibro-nodular scars on x-ray suggesting prior healed active TB (now inactive)
- Newly infected (documented Tuberculin test conversion Negative to Positive within last 2 years)

≤65 yrs. old:  •  Prednisone ≥15 mg/d x ≥1 mo.  •  Diabetes

≤ 50 yrs. old:  •  Underweight (BMI <20)  •  Smoker
- Immigrants from countries with high prevalence of TB who have resided in the US for <5 yrs.
- Travelers to areas with high prevalence of TB for >1 mo., or making repeated visits >2x / yr.

≤35 yrs. old:  •  Anyone testing positive for Latent TB Infection

Treatment for Latent TB Infection

- INH 300 mg (Peds: 10-20 mg/kg), daily for 9 mos. [6 mos. acceptable alternative if not high risk as above]
  --  plus Vit. B6 25-50 mg if risk of Neuropathy (>50 y.o., HIV+, diabetes, pregnant/nursing, renal failure, alcoholism, other)
  --  Rx 30 d at a time, no refills. Monthly visits for education re Sx of hepatotoxicity
- INH 900 mg PLUS Rifapentine 900 mg weekly for 12 weeks, by D.O.T. (>12 y.o., non-pregnant)
- If INH-intolerant / contraindicated: Rifampin 600 mg daily for 4 mos. (Peds: 10-20 mg/kg)
## DRUGS USED TO TREAT ACTIVE TB

<table>
<thead>
<tr>
<th>First Line</th>
<th>Usual Adult Dose (q.d. unless noted)</th>
<th>Prominent Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong> *</td>
<td>300 mg</td>
<td>hepatitis; peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Rifampin</strong> *</td>
<td>600 mg</td>
<td>nausea, discoloration of body fluids (stains contact lenses), rash, hepatitis, numerous drug-drug interactions</td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong> *</td>
<td>1.5 – 2.0 g</td>
<td>hepatitis, arthralgias, hyperuricemia</td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>15-25 mg/kg</td>
<td>visual disturbances</td>
</tr>
<tr>
<td><strong>Streptomycin</strong></td>
<td>1.0 g IM</td>
<td>ototoxicity, nephrotoxicity</td>
</tr>
</tbody>
</table>

* essential components of 6-month Tx

<table>
<thead>
<tr>
<th>Second Line</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Para-aminosalisylic Acid</strong></td>
<td>10-12 g</td>
<td>nausea, vomiting, diarrhea, hypersensitivity reactions, hepatitis</td>
</tr>
<tr>
<td><strong>Ethionamide</strong></td>
<td>1.0 g</td>
<td>nausea, vomiting, anorexia, abdominal pain, hepatitis, metallic taste, arthralgias, impotence, gynecomastia, hypothyroidism, photodermatitis</td>
</tr>
<tr>
<td><strong>Cycloserine</strong></td>
<td>1.0 g</td>
<td>emotional disturbances, psychosis, peripheral neuropathy, convulsions</td>
</tr>
<tr>
<td><strong>Capreomycin / Kanamycin</strong> or <strong>Amikacin</strong></td>
<td>1.0 g IM or 15 mg/kg IM</td>
<td>ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td>nausea, vomiting, hypersensitivity</td>
</tr>
<tr>
<td>(Ciprofloxacin / Ofloxacin / Monifloxacin / Gatifloxacin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiacetazone</strong></td>
<td>150 mg</td>
<td>nausea, vomiting, rash (contraindicated in HIV)</td>
</tr>
</tbody>
</table>

not available in US; very cheap, widely used in poor countries

<table>
<thead>
<tr>
<th>Potentially Effective (not widely used)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clofazamine</strong></td>
<td>100-300 mg</td>
<td>skin/eye discoloration, nausea, vomiting, fatal abdominal pain</td>
</tr>
<tr>
<td><strong>Rifabutin</strong></td>
<td>300 mg</td>
<td>same as rifampin</td>
</tr>
<tr>
<td>“Augmentin”</td>
<td>500 mg TID</td>
<td>diarrhea, hypersensitivity reactions</td>
</tr>
</tbody>
</table>