



Diagnosis and Treatment of TB Infection

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Has the following disclosures to make:

- Consultant for Oak Therapeutics SBIR





Diagnosis and Treatment of TB Infection

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What We Will Cover

- Diagnosis of LTBI
 - Identifying those at risk of TB exposure
- Determining Who to Treat
 - Identifying those at risk of progression to TB disease
- LTBI Therapy – What Regimen is Best?

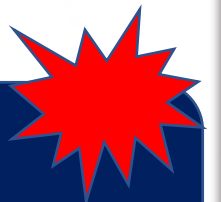


Latent TB Infection

- Persons are infected with *Mycobacterium tuberculosis* but:
 - No Active TB Symptoms
 - Chest X-ray may be normal, or show granuloma, **stable** pleural or parenchymal scarring
 - Positive TST or IGRA

The TST, the T Spot and the QuantiFERON -
All miss > 10 % of those with active TB

The % of those with true LTBI with negative tests unknown



Latent TB Infection

- Persons with LTBI are NOT infectious
- 90 +% chance of never getting Active TB Disease
- But the TB organism is in your body!



Latent TB Infection

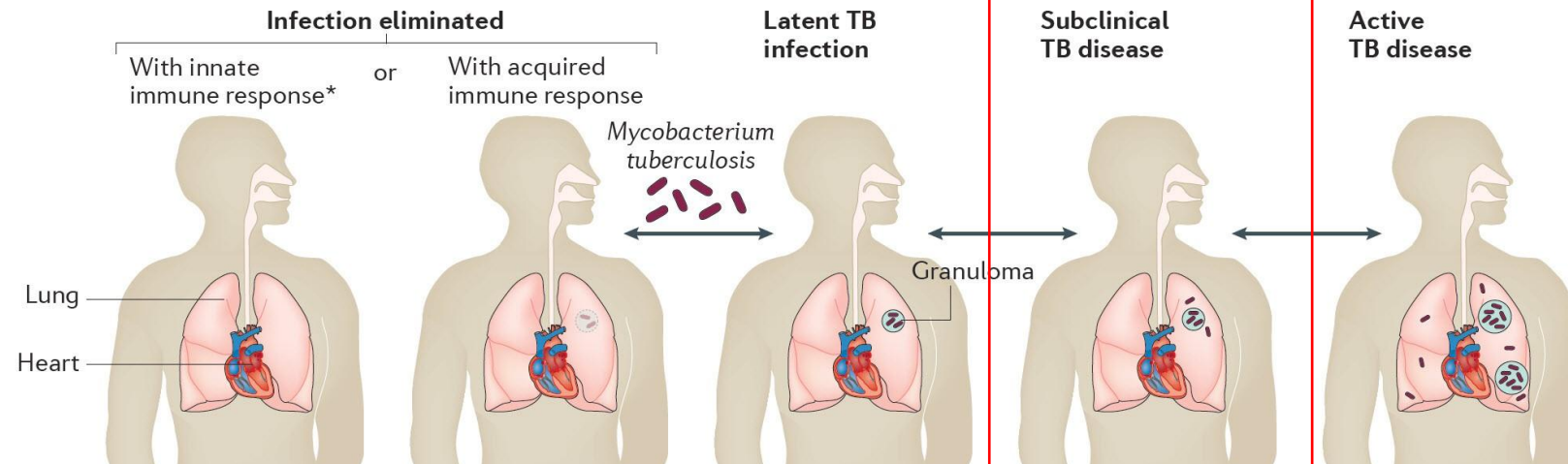
- We used to think the bacteria were in a resting state or dormant but
- TB Bacteria are metabolically **active and dividing**, but **infection is controlled** by the immune system.

- “...a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB”

- **WHO Guidelines on the management of Latent Tuberculosis Infection 2015**



Tuberculosis Spectrum of Disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Progression of LTBI to Active TB Disease Increased By

- HIV infection
- Chronic kidney disease
- Silicosis
- Recent exposure
- Diabetes
- Chest x-ray abnormality c/w previous inadequately treated TB (TB IV)
- Intravenous drug use
- Smoking – active and passive
- Underweight by >10%



Progression of LTBI to Active TB Disease Increased By

- Pregnancy and first three months post partum
- Immunosuppression
 - Hematologic cancers and head and neck cancers
 - Medications
 - TNF α inhibitors
 - Prednisone >15 mg, > 4 weeks
 - Chemotherapy
 - Other immunosuppressive drugs



TB Infection Diagnostics

- TB Skin Test (TST)
- Interferon Gamma Release Assays (IGRA)



Active TB Disease or TB Infection?

The Clinical Evaluation

The single most important thing prior to starting treatment for TB Infection is to exclude active TB disease.

If in doubt – wait!

Evaluate for TB disease

Consider consultation with TB expert



Evaluate to Exclude Active TB Disease

- If the TST or IGRA is Positive –
 - **OR**
- Patient has been exposed and is symptomatic
 - At least 10 % of persons with active TB disease are IGRA/TST negative
- Child < 5 or immunocompromised person with recent exposure **even if TST/IGRA negative** –
- Evaluation includes:
 - ✓ History
 - ✓ Physical examination
 - ✓ Chest X-Ray



Is There Evidence of Disease?

- Symptoms*

- Fever
- Chills
- Night Sweats
- Weight Loss
- Cough (dry/productive)
- Hemoptysis
- Fatigue

* **only one may be present**

Is Patient at Risk of Progression to Disease?

- Medical History:

- HIV
- Silicosis
- Chronic Kidney Disease
- Diabetes
- Immunosuppression
- Drug/alcohol/tobacco
- TB exposure



Physical Exam

- General assessment – does person look well?
- Lung exam
- Check for lymph nodes
- Palpate liver
- *In children* look at growth curve/weight/activity
- Look for anything that will complicate therapy!



Radiologic Exam

- CXR must be done **before treatment of TB Infection**
 - Must be read as normal
- Or
- IF abnormal:
 - Not consistent with Active TB
 - Stable abnormality confirmed over a 3 month period



Mycobacteriological Laboratory Exam

- If you suspect TB disease due to an abnormal CXR and/or symptoms – collect sputum specimens:
 - Gene Xpert (1) AFB smear (3), and culture(3)
- If Gene Xpert and AFB smears are negative, don't start TB Infection treatment until cultures are negative – 6 weeks
 - Remember you suspected possible TB disease and you cannot exclude this without a negative culture
 - May be appropriate to start RIPE for disease



Deciding When to Treat LTBI

Groups Who Should be Given High Priority for LTBI Treatment

People with a positive IGRA result or a TST reaction of ≥ 5 mm

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on CXR c/w old TB
- Organ transplant recipients
- Persons immunosuppressed for other reasons
 - taking the equivalent of >15 mg/day of prednisone for ≥ 1 month,
 - taking TNF- α antagonists
 - receiving chemo/radiation therapy

People with a positive IGRA result or a TST reaction of ≥ 10 mm

- Persons from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology lab personnel
- Children < 4 years of age,
- Children and adolescents exposed to adults in high-risk categories



Children Who Should Be Treated Following Recent Exposure Once TB Disease Excluded:

- Contacts < 5 y/o identified during an investigation surrounding an identified case
 - Treat even if initial TST or IGRA is negative
- Those > 5 y/o who are TST or IGRA positive
- Recent immigrants and refugee children with positive IGRA



Why Should Small Children Who Are Exposed to Active TB Disease Be Treated Even When TST or IGRA is Negative?

- Very high rate of infection
- Takes up to 3 months for the skin test to turn positive
 - Small children can very quickly become very sick
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household are treated
- WHO standards – children <5 years old exposed in a TB household should be treated



Percent Risk of Disease by Age

Age at Infection	Risk of Active TB
Birth – 1 year*	43%
1 – 5 years*	24%
6 – 10 years*	2%
11 – 15 years*	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults ⁺	30-50% lifetime

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

⁺WHO, 2004



Risk of Progression to TB Disease by Age

Age @ primary infection

Risk of Disease

- Birth - 12months

TB Disease

up to 50%

Pulmonary Disease

30-40%

Miliary or TB Meningitis

10-20%

- 1-2 years

Disease

20-25%

Pulmonary Disease

75%

Miliary or TB Meningitis

2-5%



“Window Period” TB Prophylaxis After Exposure

- Household contact with infectious person
 - Initial TST negative
 - ❖ **Window period** for TST/IGRA conversion (8-12 weeks)
 - CXR and physical exam normal
- ❖ **‘Window’ prophylaxis recommended:**
 - For children <5 yrs of age
 - Immunosuppressed patients, especially HIV positive
 - Patients on tumor necrosis factor-alpha blockers or other biologics
 - May prevent progression to disease during window period
- Repeat TST or IGRA 8-12 wks after exposure
- May stop treatment if 2nd TST (<5mm) or IGRA is negative in immunocompetent patients
- Consider completion of full course of treatment in HIV + and other immunosuppressed or children < 6 months



TB Infection Treatment Options

- CDC Recommended Treatment regimens:
 - INH/Rifapentine x 3 months (3HP)
 - Once weekly DOT x 12 weeks
 - Average of 10 pills at once
 - Rifampin x 4 months
 - Daily (10 mg/kg: 600 mg max)
 - INH +rifampin x 3 months
 - INH daily (5 mg/kg: 300 mg max) + rifampin daily (10 mg/kg: 600 mg max)
 - INH x 6-9 months
 - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)



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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

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Active TB disease: 7/3986 in 3 HP arm; 15 of 3745 in 9H arm

Completion of treatment: **82.1% 3HP arm; 69% 9 H arm**

Hepatotoxicity: 0.4% 3HP arm; 2.7% 9 H arm.

Conclusion: Use of 3 HP x 3 months was as effective as 9 months of INH and had a higher treatment completion rate.



Dosing for 3HP

Adults and children > 50 kg

- 900 mg INH once weekly
- 900 mg Rifapentine once weekly
- Vitamin B 6 50 mg once weekly
- **Completion** - 11 to 12 doses in 16 weeks
- Adults and children < 50 kg
 - INH 15 mg/kg (round to nearest 50 or 100 mg tablet)

Children 2 – 12 years*

- INH 25 mg/kg (round to nearest 50 or 100 mg tablet)
- Rifapentine
 - 10-14 kg: 300 mg
 - 14.1-25 kg: 450 mg
 - 25.1-32 kg: 600 mg
 - 32.1-49.9 kg: 750 mg
 - ≥ 50 kg: 900 mg

* Especially when short course is desirable; pill burden may be a problem



Pill Burden With 3HP is Currently a Problem for Some

- Current: 10 pills (6 rifapentine, 3 INH, 1 Vit B6)
- Future: 4 pills (3 RPT/INH + 1 B6)



2xPriftin® 150mg

+



Isoniazid®

=



PH 300/300

INH + RPT (3HP) is NOT Recommended For:

- Children under 2 y/o....yet
- HIV infected persons on Antiretroviral Therapy with drug drug interactions
- Presumed INH or Rifampin Resistance in the source case
- Pregnant women



Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Open label trial in 9 countries comparing 4 months rifampin vs 9 months INH:
 - study endpoint: prevalence of TB 28 months after randomization
- Rifampin: 3443 patients:
 - 4 active TB, 4 clinical TB
- INH: 3416 patients:
 - 4 active TB, 5 clinical TB



Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Treatment completion:
 - Rifampin 79%,
 - INH 63% ($p < 0.001$)
- Clinically significant (drug stopped) hepatotoxic events:
 - Rifampin 0.3%,
 - INH 1.7% ($p < 0.001$)
- 4 months of rifampin was not inferior to 9 months INH for preventing development of active TB but with significantly higher completion rates and greater safety than INH.



Rifampin Dosing for TB Infection

- Adults
 - 10 mg/kg daily
 - 600 mg daily x 4 months
- Children:
 - 10 – 20 mg/kg daily x 4 months
 - Capsules 150mg/300 mg round up - use higher range
 - Higher rifampin doses well tolerated



Rifampin Treatment of TB Infection

- Pros:

- Higher Completion Rates
- Equally effective
- Fewer Side Effects
- Less Hepatotoxicity
- Cost effective
- Rifampin resistance uncommon
 - Globally 3%

- Cons:

- Drug Interactions
 - Hormone Contraceptives
 - Warfarin
 - Prednisone
 - **HIV Antiretroviral agents**
 - And many more...must look up all drugs for interactions
 - Orange Body Fluids
- Other Potential Side Effects (rare):
 - Rash
 - Thrombocytopenia
 - Anemia
 - Leukopenia
 - Allergic Interstitial Nephritis



INH TBI Therapy

- The standard treatment regimen for TBI has been nine months of daily INH.
 - The regimen is effective and is the preferred regimen for HIV infected people taking antiretroviral therapy with drug-drug interactions that do not allow a rifamycin
 - Is the option when drug-drug interactions with rifamycins are significant and must be avoided
- **But less than 60% complete**
 - Primarily due to long duration of treatment but also increased adverse effects



INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure)
 - Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).



Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229



“Medical providers should emphasize to patients that *INH treatment should be stopped immediately upon the earliest onset of symptoms* (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice.”

INH Side Effects

- Hepatotoxicity
- Migraine Headaches
- Gastrointestinal
 - Nausea, Diarrhea, Constipation
- Rash
- Peripheral Neuropathy
 - Pyridoxine 50mg daily can help prevent this



Isoniazid (INH) Dosing

- Adults: 300 mg single daily dose or 900 mg twice weekly*
- Children: 10-15 mg/kg single daily dose (max dose 300 mg daily)
 - 20-30 mg/kg twice weekly*
- Duration of treatment for TB Infection: 6 - 9 months
 - 9 month regimen more effective
 - 9 month regimen is very difficult to complete
 - 6 months is considered adequate therapy by ATS/IDSA/CDC guidelines
- *** twice weekly treatment must be given by directly observed therapy through health department**



Treatment Options for LTBI

- INH +RPT once weekly
- Rifampin daily
- INH 9 daily
- INH 6 daily
- 12 weeks (12 doses)
- 4 months (120 doses)
- 9 months (270 doses)
- 6 months (180 doses)

The longer the duration/more doses, the less likely your patient is to complete treatment

Fewer than 60% complete 9 months of INH



Should Pregnant Women Be Treated for TB Infection during Pregnancy?

- A prior study showed increased risk of serious, even fatal hepatotoxicity **with INH** during pregnancy and the immediate post-partum period (3 months following delivery)
- No study has shown increased risk of hepatotoxicity with daily rifampin
- In pregnant persons who have reason for treatment of LTBI, consider daily rifampin
- Monitoring should be close
 - Blood work for any symptoms and hold medication
 - Monitor liver enzymes and patient at every monthly visit.



Monitoring for Toxicity and Progression to Active Disease

- Baseline liver enzymes - all with risk of liver toxicity
 - Those with underlying liver disease due to Hepatitis B or C or alcohol
 - Those taking other potentially hepatotoxic medications
 - Those with a medical co-morbidity
 - Pregnant women and those in immediate post-partum (3 months) period
 - Elderly
 - Generally not needed for children; healthy young adults
- Monitor monthly “in person” for toxicity and for evidence of progression to TB disease
 - Monthly liver enzymes if baseline LFTs abnormal or above risks



Pearls of Wisdom for Treating TBI



- Consider the shortest regimen possible to increase the odds of completion
- Be vigilant
- Be supportive.....and forgiving

Thank you for being here.

Thank you for all that you do every single day.

You make a difference.

Questions?

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