Tuberculosis Infection Screening and Testing

Megan Devine, MD

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Megan Devine, MD

Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Tuberculosis Infection Screening and Testing

Megan Devine, MD
Heartland TB Center

Associate Professor
Pulmonary and Critical Care Medicine
University of Texas Health Science Center at Tyler

Latent TB infection

Latent TB Infection

- Infection with *Mycobacterium tuberculosis* without manifestations of active disease
  - Positive TST or IGRA
  - Asymptomatic
  - Normal or stable chest radiography
  - Non-infectious
- LTBI can be persistent for many years and lead to TB disease if untreated.
- 80% TB disease arises from prior infection.
- Treatment is up to 90% effective
- LTBI treatment is less costly with less morbidity

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**

Who should be tested for TB infection?

Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

The simplified version:

- Persons who are at increased risk for *M. tuberculosis* infection
- Persons at increased risk for progression to active disease if infected with *M. tuberculosis* (even if not at increased exposure risk)

And those who tend to be tested in addition:

- Persons tested for administrative reasons (e.g., mandatory employment testing)
- Persons with symptoms of active TB disease (fever, night sweats, cough, and weight loss)

Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

- Contacts of persons with active TB
- HIV positive individuals
- Immigrants from high prevalence countries
- People who use injection drugs
- Residents and employees of high-risk congregate settings:
  - Correctional facilities and homeless shelters
  - Hospitals, clinics, nursing homes, substance abuse facilities
- Immunosuppression:
  - Patients considering treatment with TNF-α antagonists
  - Organ transplant recipients
- Children exposed to high-risk adults or environments

Contacts of Individuals with Active TB

- Among close contacts to a TB Case:
  - 30% have TB Infection
  - 1-3% have active TB disease
- Without TB infection treatment:
  - 10% with TB Infection with develop Active TB
    - Approximately 5% of contacts with newly acquired TB Infection progress to TB disease within 2 years
    - The other 5% activate > 2 years after acquisition
- Examination of contacts is one of the most effective strategies for TB Infection diagnosis and TB control!

MMWR December 16, 2005 / Vol. 54 / No. RR-15

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%

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221

Progression of LTBI to Active TB Disease Increased By

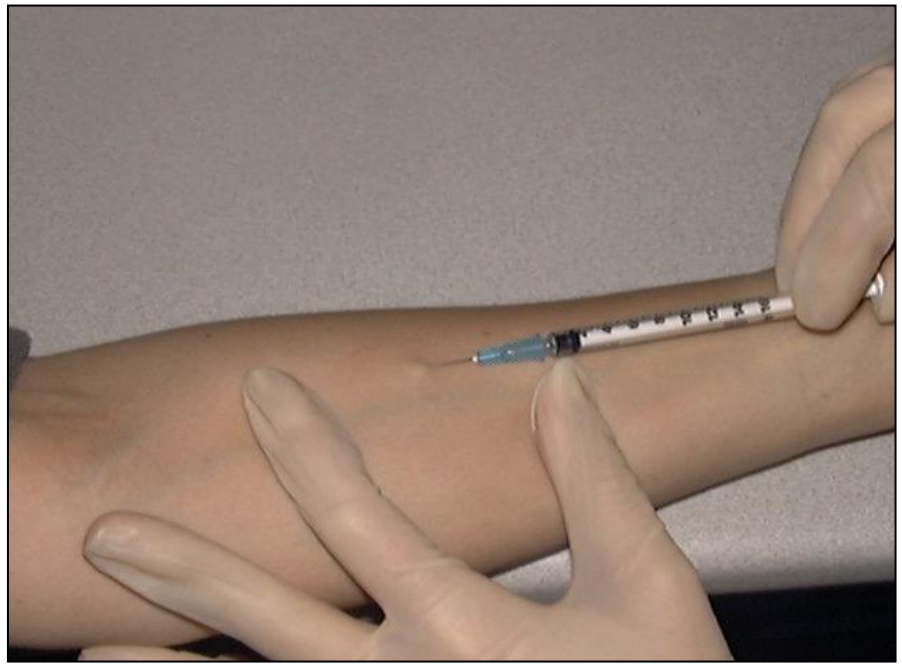
- Pregnancy and first three months post partum
- Immunosuppression
  - Hematologic cancers and head and neck cancers
  - Medications
    - TNFα inhibitors
    - Prednisone >15 mg, > 4 weeks
    - Chemotherapy
    - Other immunosuppressive drugs

How do we test for TB infection?

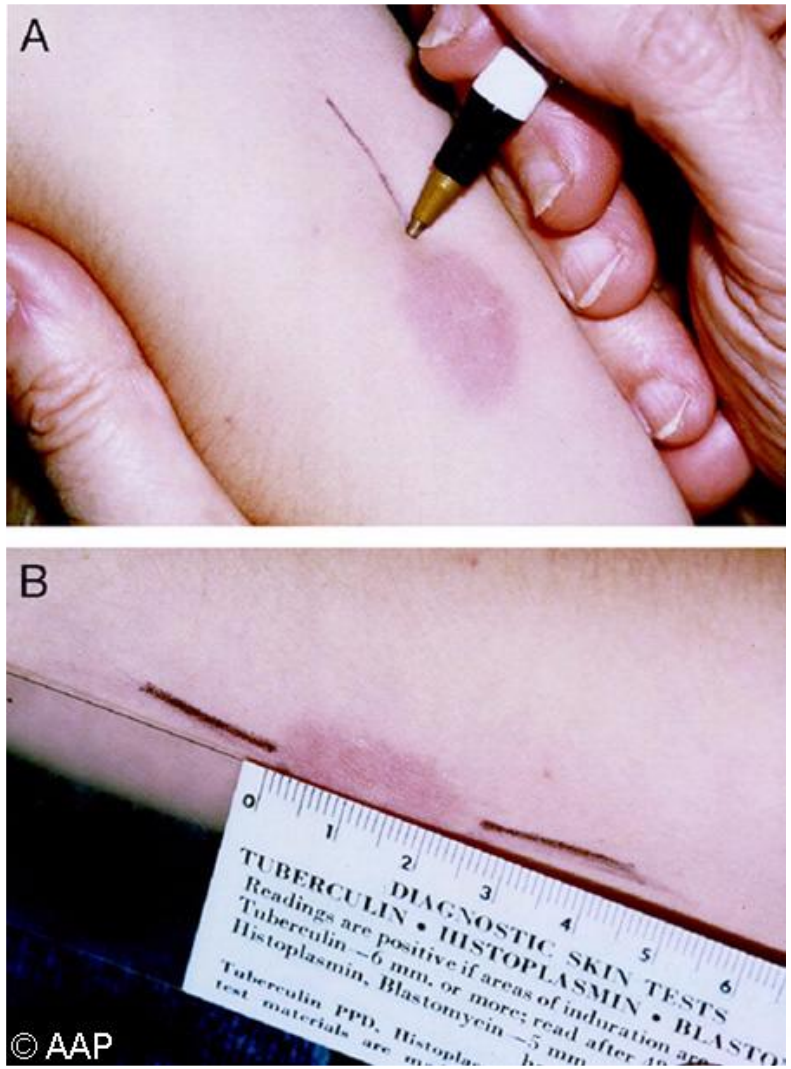
Tuberculin skin test or gamma-interferon release assay (IGRA)

The Tuberculin Skin Test (TST)

0.1 ml of 5 TU PPD tuberculin injected intradermally



Induration in mm read 48-72 hours after injection



TB Skin Test (TST)

Pros:

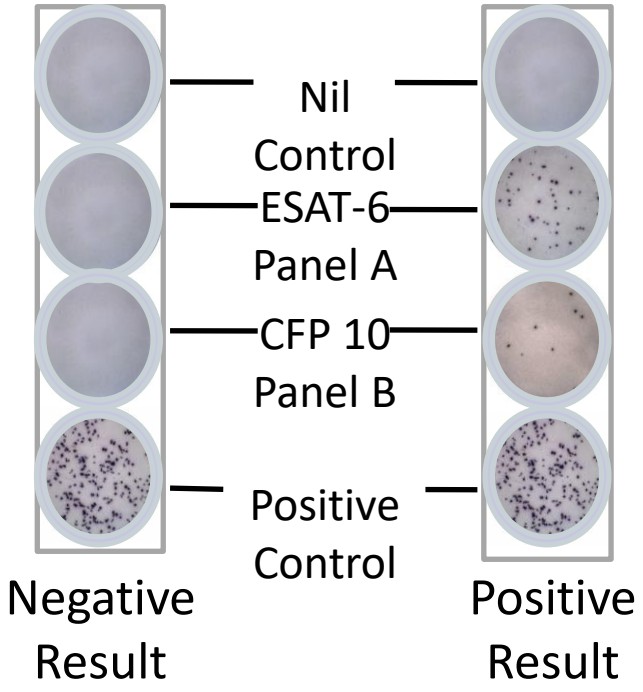
- Inexpensive
- Simple to perform
  (if you know what you are doing….
  and know how to herd cats……)

- Cons:
  - Must return in 48-72 hrs
  - Interpretation is somewhat subjective
  - False Negatives:
    - Elderly
    - Immunosuppressed
  - False Positives:
    - Low risk populations
    - Non-tuberculous mycobacteria
    - BCG vaccination

FDA Approved IGRAs

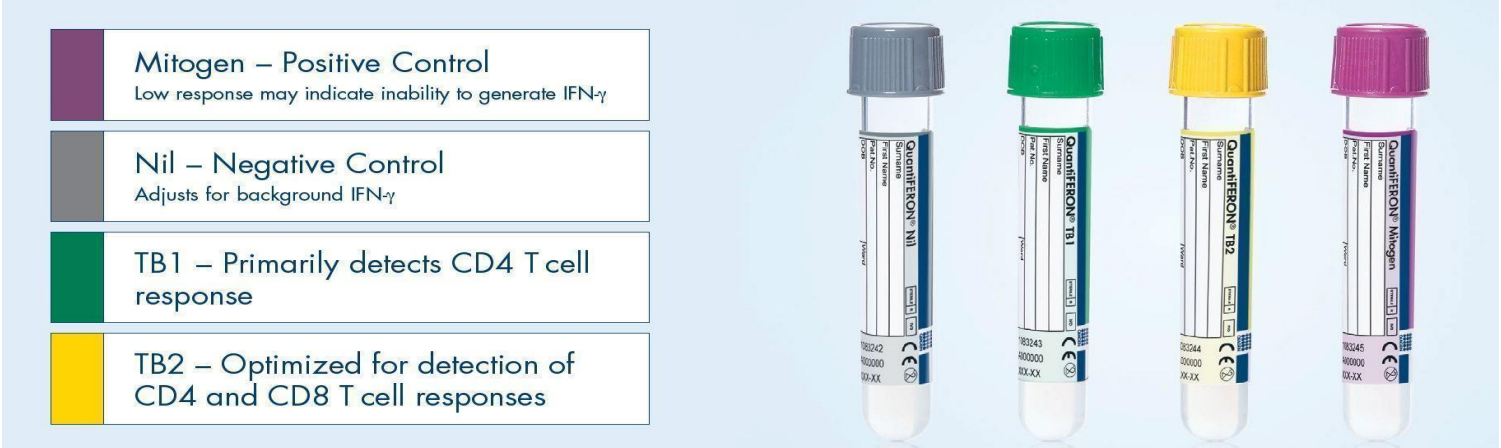
T-Spot®.*TB* (T-Spot)

FDA approved July 2008



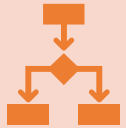
QuantiFERON®-TB Gold Plus (QFT-Plus)

- FDA approved 2017



Antigens for Newer Generation IGRAs

Negative control or nil (e.g., saline, heparin)



Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)

M. tuberculosis-specific antigens

Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)

Antigens for Gamma-Release Assays

Tuberculosis complex	Antigens ESAT	CFP	Environmental strains	Antigens ESAT	CFP
M tuberculosis	+	+	M abcessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG substrain			M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	M marinum	+	+
pasteur	-	-	M oenavense	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M xenopi	-	-

Indeterminate and Borderline Results

Indeterminate

- Negative control result is too high
  - High background production of IFN-γ
- Positive control result is too low
  - Immunocompromised patients may not respond to mitogen

Borderline (T-Spot only)

- Falls within borderline zone close to negative/positive cut point

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

David M. Lewinsohn,[1,a] Michael K. Leonard,[2,a] Philip A. LoBue,[3,a] David L. Cohn,[4] Charles L. Daley,[5] Ed Desmond,[6] Joseph Keane,[7] Deborah A. Lewinsohn,[1] Ann M. Loeffler,[8] Gerald H. Mazurek,[3] Richard J. O'Brien,[9] Madhukar Pai,[10] Luca Richeldi,[11] Max Salfinger,[12] Thomas M. Shinnick,[3] Timothy R. Sterling,[13] David M. Warshauer,[14] and Gail L. Woods[15]

[1]Oregon Health & Science University, Portland, Oregon, [2]Emory University School of Medicine and [3]Centers for Disease Control and Prevention, Atlanta, Georgia, [4]Denver Public Health Department, Denver, Colorado, [5]National Jewish Health and the University of Colorado Denver, and [6]California Department of Public Health, Richmond; [7]St James's Hospital, Dublin, Ireland; [8]Francis J. Curry International TB Center, San Francisco, California; [9]Foundation for Innovative New Diagnostics, Geneva, Switzerland; [10]McGill University and McGill International TB Centre, Montreal, Canada; [11]University of Southampton, United Kingdom; [12]National Jewish Health, Denver, Colorado, [13]Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee, [14]Wisconsin State Laboratory of Hygiene, Madison, and [15]University of Arkansas for Medical Sciences, Little Rock

Lewinsohn et al. CID. 2016

New in the Diagnosis Guidelines

- Decisions to test or treat are based on likelihood of infection and likelihood of progression.
- Testing in low-risk populations is still not recommended. When it is necessary, such as required HCW screenings, use an IGRA.
- IGRAs are recommended for testing:
  - Individuals ≥ 5 years old
  - Those with low or moderate risk if infection or progression
  - When TST administration is questionable
  - In BCG vaccinated populations (increased specificity)
  - In populations with a poor rate of return
- In populations at high risk for infection or progression, either a TST or IGRA is appropriate.

How do we diagnose latent TB infection?

We exclude active TB disease

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%

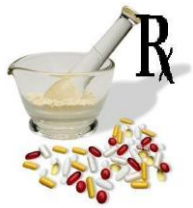
Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402

“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)

ATS/IDSA/NTCA. November 2018.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

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

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
- 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.

- 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?

1-800-TEX-LUNG