TUBERCULOSIS PATHOGENESIS
AND
LATENT TB INFECTION (LTBI)
Lynn L. Horvath, MD, FACP, FIDSA
November 17, 2015

Tuberculosis Intensive
November 17-20, 2015
San Antonio, TX

Lynn L. Horvath, MD, FACP, FIDSA has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
What We Will Cover

• TB Pathogenesis
  – LTBI
  – Active TB
    • Primary TB
    • Reactivation TB

• LTBI Diagnosis
• LTBI Therapy
Active TB Disease

- Active infectious process involving the lungs ± other organs
- Symptoms
  - Fever
  - Chills
  - Night Sweats
  - Weight Loss
  - Cough
  - Productive Cough
  - Hemoptysis
- When disease involves the lungs, the person is contagious

Latent TB Infection

- No Active TB Symptoms
- Normal Chest X-ray
- Positive PPD or IGRA
Tuberculosis Pathogenesis

TB EXPOSURE

• TB Exposure
  – You have been sharing the air you breathe with someone who has active TB
FACTORS DETERMINING TRANSMISSION OF *MYCOBACTERIUM TUBERCULOSIS*?

INFECTIOUS PARTICLES

- Droplet Nuclei
  - Particles with < 5 μM in diameter
  - Aerodynamic
  - Contain 1-3 tubercle bacilli
  - Particles > 5 μM captured by mucociliary defenses
- Approximately 5 to 200 droplet nuclei are thought to be needed to result in an infection
TB SOURCE PATIENT FACTORS

- Concentration of organisms in sputum
- Presence of Cavitary disease on CXR
- Frequency and strength of cough

AJCCRM. 2005: 170;1169-1227.

TB EXPOSED PATIENT FACTORS

- Immunosuppressed?
- Cavitary Lung Disease?
- Tobacco Abuse?
- Malnourished?
CHARACTERISTICS OF THE EXPOSURE

- Frequency and duration of Exposure
- Dilution effect (volume of air)
- Ventilation
- Exposure to ultraviolet light

AJCCRM. 2005: 170;1169-1227.

RISK OF TB INFECTION

Figure 2. Percentage of persons infected with Mycobacterium tuberculosis, by bacteriologic status of and proximity to the source case—British Columbia and Saskatchewan, 1966–1971. Source: Reference 57.

AJCCRM. 2005: 170;1169-1227.
TB INFECTION

• The TB organism is in your body!

• Outcome of TB Infection
  – Latent TB Infection (LTBI) (90%)
    • No Active TB Disease
  – Active TB Disease (10%)
    • 50% Primary Progression in first 2 years
    • 50% Reactivation later in life

PATHOGENESIS OF TB INFECTION
• Innate Immunity
  – First line of Defense:
    • Rapid acting
    • Non-specific
    • No Memory
  – Components:
    • Complement
    • Macrophages
    • Natural Killer Cells

• Adaptive Immunity
  – Second Line of Defense
    • Slower Acting
    • Very Specific
    • Generates Immune Memory
  – Components:
    • Humoral:
      – B cells
      – Plasma Cells
      – Immune globulins
    • Cell-Mediated
      – T cells
      – Activated Macrophages
      – Activated Natural Killer cells
INITIAL IMMUNE RESPONSE TO TB INFECTION

• Innate Immunity
  – Alveolar macrophages
    • Activated Macrophages
      – Ingest the TB bacilli
      – Can destroy TB bacilli
    • Non Activated Macrophages
      – Ingest TB bacilli
      – Don’t kill TB bacilli

INITIAL IMMUNE RESPONSE TO TB INFECTION

• Innate immunity
  – Non Activated macrophages
  – Can’t kill the TB bacilli
  – Allow TB to multiply inside the macrophage
  – The macrophage will ultimately burst, allowing the bacilli to infect other macrophages
**INITIAL IMMUNE RESPONSE TO TB INFECTION**

- Innate immunity
  - Non Activated macrophages
  - Can’t kill the TB bacilli
  - Allow TB to multiply inside the macrophage
  - The macrophage will ultimately burst, allowing the bacilli to infect other macrophages

**LATER IMMUNE RESPONSE TO TB INFECTION**

- **Adaptive Immunity**
  - All Cell-Mediated Response
    - T cells
      - Th1 cells
      - Interleukin 12
      - Interferon gamma
    - Activated Macrophages
    - Activated Natural Killer cells
- **No Humoral Response**
  - No B cells
  - No Plasma cells
  - No Immunoglobulins
  - No Lasting immunity for future infections!!!!
GRANULOMA FORMATION

- Delayed Type Hypersensitivity
  - Destroy bacilli laden macrophage
  - Caseous Necrosis
  - Very Tissue Damaging
- Some Bacilli may be dormant
  or minimally metabolically active within macrophages
GRANULOMA FORMATION

Good Cell Mediated Immunity (CMI)
Active Macrophages
surround caseous center
and contain disease

Stage 4b
Poor Cell Mediated Immunity (CMI)
Non Activated Macrophages allow disease to progress
CAVITIES AND DISSEMINATION

- Cavity Formation
- Dissemination
  - Hematogenously spread
  - Bronchial Spread
- Replication
  - In tissues
  - Not just in Macrophages

FROM GRANULOMA TO CAVITY
LATENT TB INFECTION

• The TB organism is in your body!
• Asymptomatic
• Outcome of TB Infection
  – About 90% chance of no Active TB Disease

Latent TB Infection (LTBI)

• What is LTBI?
  – We used to think the Bacteria were dormant
  – Hence the name Latent TB

More data now reveals that you are asymptomatic, but the bacteria are not Dormant!!!!!
– State of bacterial viability, but controlled by the host’s immune system

LATENT TB INFECTION

1) TB Bacteria are metabolically active and dividing, but infection is controlled by the immune system.

2) Active TB Disease develops when immunity wanes.

3) Current methods of LTBI diagnosis are less than perfect

Our Terminology is Outdated!

• Names should be
  – TB Infection (old name LTBI)
  – TB Disease (old name Active TB)

• TBI transformation to TBD is:
  – Difficult to Detect
  – Not Black and White
  – Continuum or Gray scale
Latent TB Infection (LTBI)

A Quiescent or Latent State

Active TB Infection

B Exacerbated Inflammation; Proliferation of M. tuberculosis
LATENT TB INFECTION

- No symptoms or signs of infection
- NOT infectious
- Positive tuberculin skin test
- T-cells respond to mycobacterial antigens
- Chest x-ray may be normal, or show granulomata, pleural or parenchymal scarring

Pathogenesis of Pulmonary Acquired Tuberculosis

Latent Tuberculosis Infection
Inhalation of Droplet Nuclei

Localization to mid and lower areas of lung

Multiplication

Immune Response

Organisms killed

Organisms Dormant/walled off
LTBI → ACTIVE TB DISEASE

- HIV infection
- Chest x-ray abnormality
- Underweight by >10%
- Intravenous drug use
- Immunosuppression

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221
**LTBI → ACTIVE TB DISEASE**

- **Immunosuppression**
  - Pregnancy
  - Hematologic cancers
  - Medical Comorbidities
  - Medications
    - TNFα inhibitors
    - Prednisone >15 mg, > 4 weeks
    - Chemotherapy
    - Other immunosuppressive drugs

---

**LTBI → ACTIVE TB DISEASE**

<table>
<thead>
<tr>
<th>High-Risk Group</th>
<th>Incidence of Active Tuberculosis</th>
<th>Prevalence of Latent Tuberculosis Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median rate per 1,000 population (range)</td>
<td>median percentage (range)</td>
</tr>
<tr>
<td>Persons with HIV infection</td>
<td>16.2 (12.4–28.0)</td>
<td>14.5 (2.7–21.5)</td>
</tr>
<tr>
<td>Adult contacts of persons with tuberculosis</td>
<td>0.6%</td>
<td>21.1 (6.6–55.1)</td>
</tr>
<tr>
<td>Patients receiving tumor necrosis factor blockers</td>
<td>1.4%</td>
<td>11.8 (4.0–22.3)</td>
</tr>
<tr>
<td>Patients undergoing hemodialysis</td>
<td>26.6 (13.3–52.0)</td>
<td>33.4 (17.4–44.2)</td>
</tr>
<tr>
<td>Patients undergoing organ transplantation</td>
<td>5.1%</td>
<td>21.9 (15.4–23.5)</td>
</tr>
<tr>
<td>Patients with silicosis</td>
<td>32.1%</td>
<td>46.6%</td>
</tr>
<tr>
<td>Prisoners</td>
<td>2.6%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Health care workers</td>
<td>1.3%</td>
<td>14.1 (0.9–76.7)</td>
</tr>
<tr>
<td>Immigrants from countries with a high tuberculosis burden</td>
<td>3.6% (1.3–41.2)</td>
<td>30.2 (9.8–53.8)</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>2.2%</td>
<td>53.8 (18.6–75.9)</td>
</tr>
<tr>
<td>Illicit-drug users</td>
<td>6.0%</td>
<td>63.0 (1.4–46.4)</td>
</tr>
<tr>
<td>Elderly persons</td>
<td>1.3%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

LTBI → ACTIVE TB DISEASE

- Smoking
  - Never Smoked OR 1
  - Current Smoker OR 2.73
  - Ever Smoked OR 2.69

Am J Respir Crit Care Med 2009;180:475-480.
LTBI $\rightarrow$ ACTIVE TB DISEASE

- Passive Smoking
  - RR 1.64

![Graph showing cumulative hazards for active tuberculosis with respect to passive smoking after adjustment for potentially confounding variables by Cox proportional hazards analysis.](image)


ACTIVE TB

- 10% Lifetime Risk
- Symptomatic
  - Primary TB
  - Reactivation TB
Pathogenesis of Pulmonary Acquired Tuberculosis

Primary Disease

Inhalation of Droplet Nuclei

↓

Localization to mid and lower areas of lung

↓

Pneumonia \[\rightarrow\] Multiplication With poor CMI \[\rightarrow\] Pleurisy

↓

Dissemination

↓

Acute hematogenous disease \[\rightarrow\] Meningitis

Miliary Tuberculosis
PRIMARY TUBERCULOSIS

[Image of chest X-ray]

PRIMARY TUBERCULOSIS

[Image of chest X-ray]
PRIMARY TUBERCULOSIS

Pathogenesis of Pulmonary Acquired Tuberculosis
Post-Primary or Re-Activation Disease

Inhalation of Droplet Nuclei

Localization to mid and lower areas of lung

Multiplication

Immune Response
Good CMI

Organisms killed

Organisms walled off

Immune Function Decreases

Active disease
REACTIVATION TB

SUMMARY

• TB Exposure can result in:
  – No infection
  – Infection without active disease (LTBI)
  – Primary TB
  – Reactivation (post-primary) TB

• Factors that increase likelihood of infection
  – Duration of exposure
  – AFB+/Cavitary source patients
  – Poor Ventilation/Prolonged Contact
SUMMARY

• Immune Response
  – Innate immunity: First Line of Defense
    – Alveolar Macrophages
    – Natural killer cells augment macrophage killing of TB bacilli
  – Adaptive immunity: Second Line of Defense
    – T-cells, Th1 responses
    – IL-12
    – IFN-gamma

• LTBI:
  – Bacteria divide actively during clinical latency but are contained by the immune system

---

SUMMARY

• Risk Factors for Progression to Active TB
  – Recent TB Infection
  – Low Body Weight
  – IV Drug Abuse
  – Immunosuppression/HIV/Transplant/Meds
  – Abnormal CXR/Silicosis
  – Comorbidities/DM/Renal Disease
  – Active or Passive Smoking
QUESTIONS?

DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)

Lynn L. Horvath, MD, FACP, FIDSA
Infectious Disease Physician, Texas Center for Infectious Disease
Medical Consultant, Heartland National TB Center
Associate Professor of Medicine
University of Texas Health NorthEast
Why Do We Care about LTBI?

Latent TB Infection

• If we identify an LTBI case,
  – We can treat it & prevent an active TB case
  – We can prevent all the secondary cases that one active TB case would have caused
• Ultimately, should be a cost effective approach
• Is this combination approach working?
Active TB Infection in USA

- USA has aggressive program for TB treatment
  - TB is a reportable disease
  - Ensure all patients take their medications
    - DOT – Directly Observed Therapy
  - Ensure all patients complete their TB treatment
  - Contact Investigations
    - Identify contacts with Active TB
    - Identify contacts with LTBI

Reported TB Cases
United States, 1982–2014*

*Updated as of June 5, 2015.
TB Elimination in USA

- Treatment of LTBI is an important part of TB elimination!

TB Elimination: If TB and LTBI is treated at Current Rates

Hill Et al. Epidemiology and Infection. 2012 (140) 1862-1872.
TB Elimination: If rate of LTBI Therapy is doubled or quadrupled

Hill Et al. Epidemiology and Infection. 2012 (140) 1862-1872.

TB Elimination: If rate of LTBI Therapy is doubled or quadrupled and Foreign born rates of TB are decreased by 75%

Hill Et al. Epidemiology and Infection. 2012 (140) 1862-1872.
LTBI Diagnosis

Latent TB Infection

• How can we tell you have LTBI?
  – Positive TST or IGRA
    • Tuberculin skin test (TST)
    • Interferon Gamma Release Assay (IGRA)
  – No Symptoms suggestive of Active TB
  – A normal or stable CXR
Latent TB Infection Diagnosis

• Who should be tested?

Why Is TB Testing Recommended Only For Select Groups?

• Declining TB resources
  – Identify LTBI in those most likely to progress to active TB disease (most likely to benefit)
  – Treat those with
    • Risk of disease > than risk of toxicity from LTBI Meds
Who Should be Tested for LTBI?

- Contacts of persons with active TB
- HIV positive individuals
- Recent immigrants (<5 yrs) from high prevalence countries
- Injection Drug Users
- Residents and Employees of high risk congregate settings:
  - Correctional facilities and Homeless Shelters
  - Hospitals, Clinics, Nursing Homes, Substance Abuse Facilities
- Newest Category:
  - Patients considering treatment with TNF-α Antagonists

Contacts of Active TB Case

- Among close contacts to a TB Case:
  - 30% have LTBI
  - 1-3% have active TB disease

- Without LTBI treatment:
  - 10% with LTBI with develop Active TB
    - Approximately 5% of contacts with newly acquired LTBI 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 LTBI diagnosis and TB control!
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2014*

Tests for LTBI Diagnosis
LTBI Diagnostics

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

TB Skin Test (TST)

• Purified Protein Derivative (PPD): Concentrated Filtrate of heat killed TB
• PPD is given via intradermal injection
• Read induration, not erythema, at 48-72 hrs
TB Skin Test (TST)

- Pros:
  - Inexpensive
  - Simple to perform
  - More Sensitive than IGRA

- Cons:
  - Must return in 48-72 hrs
  - Difficult to interpret
  - False Negatives:
    - Elderly
    - Immunosuppressed
  - False Positives:
    - Low risk populations
    - NonTuberculous Mycobacteria

Reading the TB Skin Test

Measure induration, not erythema!!!
Induration of $\geq 5\text{mm}$
Considered a Positive TST

- HIV positive persons
- Recent contacts of TB cases
- Fibrotic Changes on CXR c/w prior TB
- Patients with organ transplants or other immunosuppression
  - Prednisone therapy 15 mg/day $> 1$ month

CDC. June 2000

Induration of $\geq 10\text{mm}$
Considered a Positive TST

- Recent arrivals (<5 yrs) high prevalence countries
- IVDU
- Residents/employees - high-risk congregate facilities (health care, prisons, shelters, etc.)
- TB lab personnel
- Children <4 yrs or exposed to adults at risk
- Persons with “high-risk” medical conditions

CDC. June 2000
Induration of $\geq 10\text{mm}$
Considered a Positive TST

- Persons with “high-risk” medical conditions
  - Silicosis
  - Diabetes
  - Chronic Renal Failure
  - Hematologic Disorders/Leukemia/Lymphoma
  - Cancers, particularly Head/neck and Lung
  - Low Body weight less than 10% below Ideal body weight
  - Gastrectomy
  - Jejunal Bypass

CDC. June 2000

Induration of $\geq 15\text{mm}$
Considered a Positive TST

- Persons with no risk factors

- Why did you even place the PPD????

CDC. June 2000
Easy PPD Reading Summary

- > 5 mm = Immunosuppressed
- > 10 mm = “Normal” immune system with a risk of TB exposure
- > 15 mm = Normal immune system and essentially no risk of TB exposure

The Horvath Rules

Interferon Gamma Release Assays

- Blood tests for detecting *M. tuberculosis* infection
  - Sensitized white blood cells will release IFN-gamma in response to contact with TB antigens

- Two Tests currently available:
  - T-SPOT TB (Oxford Immunotec)
  - Quantiferon TB-Gold In-Tube (Cellestis)
Interferon Gamma Release Assays

Pros

• Patient does not have to return for second visit
• No Cross reactivity with BCG Vaccination
• Less Cross reactivity with other NTMs
• More Specific than TST

Cons

• Expensive
• Does not differentiate LTBI from active disease

No Cross-reactivity to BCG and Most NTMs

<table>
<thead>
<tr>
<th>Complex</th>
<th>Tuberculosis Complex Antigens</th>
<th>Environmental Strains Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT-6</td>
<td>CFP 10</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. africanum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. bovis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BCG substrain</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>gothenburg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tice</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tokyo</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>danish</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>glaxo</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>montreal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pasteur</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Within-Subject Variability and Boosting of T-Cell Interferon-γ Responses after Tuberculin Skin Testing

• Boosting:
  – A significant increase in mean QFT-Gold IFN-γ responses was noted by day 7 post-TST that persisted for up to 3 months after the TST

• Author proposals for QFT-Gold interpretation:
  – Borderline or uncertainty zone: 0.2-0.7 IU/ml
  – Conversion threshold: Increase from <0.35 to >0.7 IU/ml

Should I use TST or IGRA?

• Neither test is perfect
• Pick one and use it only!
• Do not use both to confirm!!!
Active TB or LTBI?
The Clinical Evaluation

Standard Components of TB/LTBI Evaluation

• If TST or IGRA Positive
  – Patient History
  – Physical examination
  – Radiologic evaluation
  – Laboratory?
Patient History

- Symptoms
  - Fever
  - Chills
  - Night Sweats
  - Weight Loss
  - Cough
  - Productive Cough
  - Hemoptysis

- PMH:
  - Diabetes
  - HIV
  - Other Immunosuppression
  - Silicosis
  - Drug/alcohol/tobacco
  - TB exposures or Risk?

Physical Exam

- Lungs
- Palpate liver
- Look for anything that will complicate therapy!
Radiologic Exam

• CXR must be done
• Must be normal
• Or
• IF abnormal:
  – Not consistent with Active TB
  – Stable abnormality confirmed over a 3 month period

Laboratory Exam

• Not “Required” by CDC – some states require
• But, if you have the funding
  – CBC
  – Chem 7
  – LFTs
  – Hepatitis B/C testing
Before Treatment of LTBI: Exclude Active Tuberculosis!

- Absence of symptoms
- Negative CXR
- Negative medical evaluation
- Order and wait for sputum culture if any question

Laboratory Exam

- Sputum AFB smear and culture
  - Only get if you suspect active disease
  - If you order, and AFB smear is negative, don’t start LTBI rx until cultures are negative – 6 weeks!!!!!
Management of TST+/IGRA + With Abnormal CXR

• If Patient has no symptoms of Active TB:
  – Collect 3 sputa for smears and culture
  – Evaluate for symptoms
    • If no symptoms - Wait
  – Repeat CXR in 2 – 3 months
• If CXR stable at 2 – 3 months and cultures negative, treat LTBI

Management of TST+/IGRA + With Abnormal CXR

• If patient has any signs or symptoms of TB disease:
  – The patient is a TB Suspect
  – Collect 3 sputa for smears and culture
  – Consider starting 4 drugs!
• Never start a single drug in a patient with possible active TB
LTBI Treatment

Rationale for Treatment of LTBI

• Prevent progression of infection to disease

• Interrupt transmission of disease

• Evidence that this works?
  – 1953: 52.6 cases/100,000 US Population
  – 2014: 3.0 cases/100,000 US Population
Who should be treated for LTBI?

- **A decision to test is a decision to treat!**
  - Tests should only be placed on persons who would benefit from treatment
  - Occasional tests placed for administrative reasons and these individuals should be evaluated on a case by case basis regarding initiation of treatment

What should you do with Negative IGRA/TST in Immunosuppressed Persons?

- Empiric treatment for LTBI is warranted even when TST or IGRA is negative on initial or repeat testing 8-10 weeks after exposure
  - Close contacts to Active TB case with
    - AIDS
    - Children < 5 years
    - Contacts with significant immunosuppression
      - Prednisone ≥ 15mg/day for 1 month
      - Persons receiving treatment with TNF alpha antagonists
LTBI Treatment Options

• CDC Recommended Treatment regimens:
  – INH 300mg daily x 9 months Daily (9H)
  – Rifampin 600mg daily x 4 months (4R)
  – INH/Rifapentine x 3 months (3HP)
    • Once weekly DOT x 12 weeks

CDC. November 2011.

So which regimen should you choose?

• Efficacy
• Duration
• Cost
Efficacy

• Short term efficacy is equivalent
• Long term efficacy:
  – 9H (most data)
  – 4R
  – 3HP (least data)

Duration of Therapy

• 9H
• 4R
• 3HP

• 9 months (270 doses)
• 4 months (120 doses)
• 12 weeks (12 doses)

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

Fewer than 60% complete 9 months of INH!
Cost

- 9H
- 4R
- 3HP
- $30
- $110
- $250*

Medication costs – *DOT cost not included!

INH LTBI Therapy
INH LTBI Therapy

• “The standard treatment regimen for LTBI is nine months of daily INH. The regimen is very effective and is the preferred regimen for HIV infected people taking antiretroviral therapy, and children aged 2-11 years.”

CDC. November 2011.

How Much Isoniazid Is Needed for the Prevention of Tuberculosis?

• Longer durations of therapy corresponded to lower TB rates
• No extra increase in protection among those who took >9 months


Community based study. Bethel Alaska
LTBI Treatment Acceptance and Completion in the U.S. and Canada

• Employees at health care clinics more likely to decline therapy

• Risk factors for failing to complete treatment:
  – 9 month INH regimen
  – Residence in a congregate setting
  – Injection drug use
  – Age ≥ 15 years
  – Employment at health care facility

• Overall, fewer than half of the people starting LTBI therapy completed treatment

INH Side Effects

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

Chest 2010, 137; 401
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).


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

- CDC project to monitor SAEs with treatment of LTBI 2004-2008
- 17 patients with SAEs, all hepatotoxicity
  - 2 children < 15 yrs of age
  - Adults median age 39
  - Diagnosed between 2nd and 9th month
  - One patient HIV seropositive for Hep C, HIV
  - 5/17 liver transplant (one child), 5/17 died (one transplant)
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 Toxicity Monitoring

• The critical element for INH toxicity monitoring is CLINICAL MONITORING.
• My recommendation:
  – Only prescribe 30 day supply at a time/no refills
  – Communicate with patient every 30 days
    • Ask about Nausea, vomiting, Abdominal pain, Jaundice
  – Document a note about this communication
  – Only refill INH if the patient is OK
  – Stop INH and/or check LFTs if not OK
Rifampin LTBI Therapy

4 Mos Rifampin vs 9 Mos INH for Treatment of LTBI

- Menzies et al AJRCCM 2004, 170; 445
  - Completion of therapy significantly better with rifampin with fewer side effects than INH

- Lardizabal et al Chest 2006, 130; 1712
  - Patients receiving rifampin were significantly more likely to complete therapy than those receiving INH

- Menzies et al Ann Int Med 2008, 149; 689
  - Significantly higher rate of treatment completion with fewer serious adverse events
Rifampin Treatment of LTBI

• Pros:
  – Higher Completion Rates
  – Less Side Effects
  – Less Hepatotoxicity

• Cons:
  – Drug Interactions
    • Hormone Contraceptives
    • Warfarin
    • Prednisone
    • HIV Antiretrovirals
    • And many more...must look up all drugs for interactions!!!!!
  – Orange Body Fluids
  – Other Side Effects:
    • Rash
    • Thrombocytopenia
    • Anemia
    • Leukopenia
    • Allergic Interstitial Nephritis

INH/Rifapentine LTBI Treatment (3HP)
INH/Rifapentine LTBI Therapy

• “The 12 dose regimen of INH and RPT does not replace other recommended LTBI treatment regimens. It is another effective regimen option for otherwise healthy patients aged ≥ 12 years who have a predictive factor for greater likelihood of TB developing including”
  – Recent TB contacts
  – TST/IGRA Converters
  – Radiographic findings of healed pulmonary TB

CDC. November 2011.

INH + RPT is NOT recommended for:

• Children under 2 yo
• HIV infected on Antiretroviral Therapy
• Presumed INH or Rifampin Resistance
• Pregnancy
If you choose to prescribe INH + RPT

- The regimen must be administered via DOT
- Be vigilant about Rifamycin drug interactions:
  - Coumadin
  - Hormonal contraception
  - HIV Antiretrovirals
If you choose to prescribe INH + RPT

• Use caution!
• INH + RPT has been well tolerated and effective in 3 clinical trials
• “However, with both INH and Rif-PZA, fatal liver injuries came to attention only after the regimens were widely adopted.”
• Report any adverse events to the FDA at http://www.fda.gov/medwatch

The Unknowns of INH + RPT

• Long term efficacy?
• Will it increase MDRTB?
• Will it be safe?
TBTC 26 (3HP in Peds)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No.</th>
<th>TB Cases*</th>
<th>TB per 100 Patient-Years</th>
<th>Cumulative TB Rate, %</th>
<th>Difference in Cumulative TB Rates</th>
<th>One-sided 97.5% CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid only</td>
<td>434</td>
<td>3</td>
<td>0.27</td>
<td>0.74</td>
<td>-0.74</td>
<td>0.32</td>
</tr>
<tr>
<td>Combination drug therapy</td>
<td>471</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TBTC 26 (3HP in HIV+)

Table 5. Safety and tolerability. Safety population except as noted.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3HP N=207</th>
<th>9H N=186</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion (MITT)</td>
<td>183/206 (89%)</td>
<td>123/193 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinue—adverse drug reaction</td>
<td>7 (3%)</td>
<td>8 (4%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Grade 3 toxicity</td>
<td>14 (7%)</td>
<td>18 (10%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Grade 4 toxicity</td>
<td>4 (2%)</td>
<td>10 (5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Grade 5 (death)</td>
<td>6 (3%)</td>
<td>5 (3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatotoxicity → drug discontinuation</td>
<td>2 (1%)</td>
<td>8 (4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Possible hypersensitivity</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

TBTC 26 (3HP in HIV+)

Table 3. TB Cases and Event Rates by Treatment Arm: MITT Population

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>#TB Cases</th>
<th>TB per 100 p-y</th>
<th>Cumulative TB Rate (%)</th>
<th>Difference in Cumulative TB Rate</th>
<th>Upper bound of 95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9H</td>
<td>193</td>
<td>6</td>
<td>1.25</td>
<td>3.50</td>
<td>-2.49</td>
<td>0.60</td>
</tr>
<tr>
<td>3HP</td>
<td>206</td>
<td>2</td>
<td>0.39</td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. TB Cases and Event Rates by Treatment Arm: PP Population

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>#TB Cases</th>
<th>TB per 100 p-y</th>
<th>Cumulative TB Rate (%)</th>
<th>Difference in Cumulative TB Rate</th>
<th>Upper bound of 95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9H</td>
<td>123</td>
<td>2</td>
<td>0.63</td>
<td>1.81</td>
<td>-1.25</td>
<td>1.47</td>
</tr>
<tr>
<td>3HP</td>
<td>133</td>
<td>1</td>
<td>0.21</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TBTC 33 (3HP Self Administered)

I-Adhere - Protocol Synopsis

- Phase IV open label, randomized design
- Target Population: adults with LTBI
- All patients received 3HP
  1. DOT (control)
  2. Standard SAT
  3. SAT with weekly SMS reminders
- Sample size to detect a difference in study arms of 15% or greater based on cost modelling
- Enrollment targeted ≥ 75% from U.S.

TARGETED TESTING FOR LTBI

- TST or IGRA, Not Both!
- Rule out active Disease before starting LTBI Rx
- Treatment Options
  - INH daily x 9 mo preferred over 6 mo
  - Rifampin daily x 4 mo
  - INH/Rifapentine weekly x 3 mo – DOT

Summary

DOT completion was higher than in Study 26
SAT completion varied by country of enrollment
Case 1

- 57 yo female
- Husband diagnosed with Cavitary PTB
- Contact investigation September 2013
  - PPD+
  - Asymptomatic except “Smoker’s Cough”
  - CXR report = Normal
- What would you do?

Case 2
Case 2

- Dx: LTBI
- Rx: Rifampin daily
- But: Cough is worse in December 2013...
Case 3

April 22, 2010

Case 3

April 22, 2010
Case 3

July 21, 2010

Case 3

June 8, 2011
Questions?