Treatment of Latent TB Infection

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Disclosures: None
Objectives

• Describe current treatment recommendations for LTBI

• Understand monitoring recommendations particularly related to INH treatment
Tuberculosis Screening Flowchart

At-risk person

TST or IGRA & symptom review

- Negative
  - Treatment not indicated
- Positive
  - Chest x-ray
    - Normal
      - Potential candidate for Rx of latent TB
    - Abnormal
      - Evaluate for active TB
...Back to SB, the case of LTBI

- Obtained:
  - TST (Mantoux) Positive
  - Chest x-ray Negative

- Do you need sputum smear and culture?

  Only if suspicious for active disease
  Not necessary in asymptomatic patient, positive TST, normal CXR
What Treatment for S. B.?

Optimal LTBI Rx…

• Short as possible to enhance completion rates (programmatic advantages)

• Minimally toxic
Treatment of Latent TB Infection
HIV Neg. & Pos. Adults
(Dept of Public Health provides meds)

1. Daily INH for 9 months (270 doses w/in 12 mos)*,+ 
2. Daily INH for 6 months (100 doses w/in 9 mos)+ 
   Exclude any w/ old healed fibrotic TB lesions on CXR 
3. 1*,+ or 2+ above, administered as DOT, twice weekly 
   76 doses w/in 12 months or 52 doses w/in 9 months 
4. Daily rifampin for 4 months (120 doses w/in 6 m) 
   Alternative for those who are known contacts with INH resistant TB or INH not feasible 

Completion = Total # doses, not duration alone 
If > 2 month interruption, re-evaluate for active TB before restarting 

ATS/CDC/IDSA 5/2000; Update 8/2003 

* Recommended for children < 18 years 
+ Recommended for pregnant women.
TB Case Rates vs. No. of Months INH Treatment (Bethal Data)
Even Shorter Treatment = Reality…

- **New regimen**: INH 900 mg plus Rifapentine 900 mg weekly x 3 months (12 doses, DOT)
- **Open Label, Randomized Noninferiority trial 2011**
  - New regimen (DOT) vs INH x 9 mos (not DOT)
  - N ~ 8000 US & Canada x 33 mos (few HIV, children)
  - Target population: TST converters & +TST old healed TB chest x-ray
  - Result: New Regimen equivalent to 9 mos INH
    - Drug d/c d/t adverse events 4.9 vs 3.7%
    - Increased hypersensitivity (New) vs hepatotoxicity (INHx9)
    - Trend toward New regimen better than INHx9
      - New Regimen group: TB rate ~50% lower
      - Rx completion rate 82% vs 69%

Sterling TR et al. NEJM 2011;365:2155-66
New Regimen vs INHx9

- Noninferiority margin (delta)
- Favors Isoniazid Only
- Upper limit of 95% CI
- Reference (no difference)
- Difference in rates
- Lower limit of 95% CI

Tuberculosis Rate Difference (%)

Days since Enrollment

No. at Risk
- Isoniazid only: 3745, 3644, 3599, 3555, 3513, 3484, 3454, 3405, 3394, 3310
- Combination therapy: 3986, 3866, 3827, 3799, 3783, 3752, 3726, 3675, 3661, 3577
Real World Recommendation

- **New Regimen** (DOT) does not replace INHx9, but equal option for Rx LTBI
- (Iowa) Dept Public Health provides INHx9 at no cost for anyone diagnosed w/ LTBI
- IDPH agrees **New Regimen** equivalent to INHx9
  - *New Regimen* costs **10x** the standard INHx9 regimen
  - IDPH able to cover high cost of *New Regimen* (not DOT)
  - Policy for your state?
- **New Regimen** not recommended for the following:
  - Child <2
  - HIV/AIDS taking HART
  - Pregnant women
  - Contacts of INH &/or Rif resistant TB
Real World Dosing

- **INH**: 900 mg max for those ≥ 60 kg or 15 mg/kg rounded up to the nearest 100 mg
  Formulations: 300 & 100 mg tabs

- **Rifapentine**: 900 mg max for ≥ 50 kg
  10.0–14.0 kg  300 mg
  14.1–25.0 kg  450 mg
  25.1–32.0 kg  600 mg
  32.1–49.9 kg  750 mg
  Formulation: 150 mg tabs (others in development)

- INH-Rifapentine combo being developed
Rifamycins Better Than INH?

- INH monotherapy (6 or 9 mos) plagued by low completion rates, programmatic challenges & hepatotoxicity

From > 20 yrs of studies (~1500 trials), 53 RCTs LTBI Rx systematically selected & reviewed

- Each included relative efficacy & adverse events
- Applied Bayesian network meta-analysis
  [Allows comparison two distinct Rx regimens when no trials directly compare them]
LTBI Rx: Rifamycins Better Than INH?

Comparison to standard INH monotherapy:

- Rifampin x3-4 months ranked highly for both efficacy & hepatoxicity
- INH & Rifampin x3-4 months also ranked well
- INH & Rifabutin trended well but data NS
- Surprise: INH & Rifapentine not as well as above

Regimens containing rifamycins more effective alternative?
More Real Data Coming

• HALT trial: Evaluates Non-DOT Rifapentine vs INH monotherapy

• CDC trial: INH x 9 mos vs Rifampin x 4 mos
Treatment for S.B.

- INH daily x 9 months
- County public health department supervised treatment:
  - PHN performed Clinical Monitoring
  - 30 day supply aliquots of INH provided
  - Completed 9 months w/in 9 months
Monitoring on INH Treatment

• Educate the patient
  Liver disease symptoms & signs
  Stop meds until contact made with health care

• The critical element for preventing INH toxicity is Clinical monitoring…PHN
  Absolutely necessary to do, absolutely necessary to do well & absolutely necessary to document well.

• LFTs (ALT, AST) at baseline in selected cases
  – Hx of liver disease, EtOH, pregnancy, HIV
  – Repeat monthly if abnormal at baseline, symptomatic, or pregnant
  – Stop meds:
    • Symptomatic, LFTs 3x upper limit of normal (ULN)
    • Asymptomatic, LFTs 5x
Clinical Monitoring

• Instruct patient to report following adverse drug reactions (ADRs):
  - Rash
  - Anorexia, nausea, vomiting, or pain in RUQ
  - Fatigue or weakness
  - Dark urine
  - Persistent numbness in hands or feet

• Monthly visits should include review of:
  - Rationale for treatment
  - Adherence to therapy
  - Symptoms consistent with ADR(s)
  - Plans to continue treatment
Liver Safety Issues for INH

- Deaths from INH hepatitis in 1960s
- 1971-72 PHS Study (14,000 pts)
  - 1% overall rate of INH related hepatitis
  - Age related increase
    - 0.3% (<35)
    - 2.3% (>50)
  - 4x increase a/w EtOH
  - 8 deaths due to INH hepatitis
- Review of PHS data (Comstock JAMA 1986)
  - 7/8 deaths occurred in Baltimore
  - Death certificate review: XS deaths due to cirrhosis in 1972
  - Unidentified co-factor related to cluster of cirrhosis cases?
- Subsequent studies: risk is lower
Latest CDC Data on INH Liver Toxicity

- SAEs during LTBI Rx, 2004-2008
  - 17 patients with SAEs, all hepatotoxicity
    - 2 children < 15 yrs of age; Adults median age 39
    - One patient HIV seropositive for Hep C, HIV
    - 5/17 liver transplant (one child), 5/17 died (one transplant)
- 10/17 patients with CDC on-site investigation
  - Prescribers followed ATS/CDC guidelines for Clinical Monitoring
  - Symptoms 1-7 months after INH started
  - Fatigue, nausea, abdominal pain in 7 patients who waited for jaundice to seek medical attention
  - 2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset; all after medical instruction
- Death & liver transplantation ~1/150,000 - 1/220,000
- SAEs idiosyncratic reaction, independent of dosing, possible anytime during treatment, can occur in children
Deaths from INH Hepatitis

- Rates in women increased
  - Pregnancy & immediate post-partum period (3 mos)

- Concurrent acetaminophen questionable

- INH death rate reduced by Clinical Monitoring
  - Stopping INH at symptom onset reduces deaths
  - 7/8 liver transplants for INH hepatitis: Pts continued INH >10 d beyond symptom onset
    (CDC: MMWR 1993)
Safety Issues for INH: 
Current Practice Outcomes

• Most PHD practice Clinical Monitoring vs. biochemical monitoring

• Clinical Monitoring:
  – Educate for Rx related ADRs & Reviews adherence
  – Stop INH if any question until consult with clinician
  – CDC: “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.”
Monitoring on Treatment

• Educate the patient
  – Liver disease symptoms & signs
  – Stop meds until contact made with health care

• Clinical monitoring monthly…PHN

• LFTs (ALT, AST) at baseline in selected cases
  Hx of liver disease, EtOH, pregnancy, HIV
  Repeat monthly if abnormal at baseline, symptomatic, or pregnant
  Stop meds:
    Symptomatic, LFTs 3x upper limits of
    Asymptomatic, LFTs 5x ULN
Summary Points

• LTBI treatment update
  Can be shortened to 3 months (INH/rifapentine x 12 doses)
  Data re-evaluation → Rifamycin better than INH?

• Clinical vs Biochemical monitoring for INH hepatotoxicity

• (Iowa) Department of Public Health provides TB Rx at no cost to patient
More Case Examples & Discussion
How Should Immunosuppressed Persons at Risk for TB Be Managed?

Empiric treatment for LTBI even when TST or IGRA neg on repeat testing 8-10 weeks after exposure

- Advanced HIV infected contacts
- Children < 5 years who are contacts
- Contacts with other causes of immunosuppression
- Persons who are to receive treatment with TNF alpha antagonists
TNFα Antagonists

• Block TNFα activity which is required for granuloma formation & containment of *M tuberculosis*

• Used for RA, Crohn’s disease, Psoriasis and a variety of other immune mediated diseases
  - Remicaid (inflixamab)
  - Embril (entanercept)
  - Humira (adalimumab)
  - Cimzia (certolizumab)

• Patients should be evaluated for LTBI w/ IGRA or TST

• Treatment of LTBI should be initiated prior to therapy
Questions Remain

• Unknown
  – Does treatment of LTBI need to be completed prior to use of TNF-\( \alpha \) antagonist?

• Unknown
  – Does a person at risk of TB who is TST negative need to be treated?
    • Consider treatment of high risk TST negative patients

• No need to continue INH after completion of treatment for LTBI
Case 2

• 36-year-old Native American female
• History of diabetes
• 35 weeks pregnant
• TST = 18 mm of induration
• No symptoms of TB disease
• CXR, CBC, LFTs normal
• No known contact with TB patient
Case 2

Questions

What are this patient’s risk factors for TB infection or disease?

What is the appropriate management for this patient?
Case 2

Discussion of risk factors

• Persons with diabetes mellitus are 2 to 4 times more likely to develop TB disease than those without diabetes

• Risk may be higher in insulin-dependent diabetics and those with poorly controlled diabetes
Case 2

Discussion of management

• Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease

• Pregnant women should be targeted for TB testing only if they have specific risk factors for LTBI or progression to disease

• Some experts prefer to delay treatment until after the early postpartum period, unless the woman has recent TB infection or HIV infection
Case 3

- 41-year-old Hispanic male
- Moved to U.S. from Mexico 4 years ago
- Known contact of infectious TB case
- TST = 5 mm of induration
- 3 months later TST = 23 mm of induration
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin
Questions

What are the patient’s risk factors for TB infection or disease?

Has the management of this patient to date been appropriate?
Case 3

Discussion of risk factors

- Patient is a contact of an infectious TB case
- Recent immigrant to the U.S. from a country with a high prevalence of TB. Such persons have increased rates of TB
- If the patient had not been a contact, the recent immigration (less than 4 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive
Case 3

Discussion of management

• Should be treated for LTBI if TST reactions $\geq 10$ mm of induration
• As a contact of an active TB case, 5 mm of induration is considered positive
• This patient should have been treated for LTBI immediately after the first TST
Case 4

• 56-year-old White male
• Works in a mycobacteriology lab
• TST result negative 1 year ago
• M. *marinum* infection in his hand 8 months ago
• TST result 5mm
• QFT-G test positive
• No symptoms of TB disease, CXR normal
• No known contact with a TB patient & no known spills or accidents in the lab
Question 1
You diagnose a student with LTBI and discuss treatment options. Which of the following is the most appropriate treatment regimen?

A. INH daily for 9 months
B. INH daily for 6 months
C. DOT Rifapentine and INH once a week x 12 weeks
D. Rifampin daily for 4 months
E. Any of the above
Question 2

A 56 year-old white male who is working in mycobacteriology lab for 5 years and over the last 5 years his health record documents his annual TST has been 0 mm. Eight months ago he suffered \textit{M. marinum} infection in his hand and he recovered completely. This year his TST is 5 mm and he gets a QFT-G test which comes back 1.95. He is asymptomatic, has a normal chest x-ray, comes from a lab known for a perfect safety record (no spills/accidents) and he denies contact with a known TB patient. You are asked to recommend the best course of action:

A. INH daily for 9 months
B. INH daily for 6 months
C. DOT Rifapentine and INH once a week x 12 weeks
D. Rifampin daily for 4 months
E. None of the above