Disclosures: None
Objectives

• Describe the current guidelines for LTBI treatment

• Describe monitoring recommendations for patients on LTBI 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
M Proudfoot sputum TB NAAT positive

Contact: 56 yo girlfriend, no symptoms...

- 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
Tuberculosis Screening Flowchart

At-risk person

TST or IGRA & symptom review

Negative

Chest x-ray

Normal

Potential candidate for Rx of latent TB

Abnormal

Evaluate for active TB

Positive

Treatment not indicated
What Treatment for M Proudfoot GF?

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
TB Case Rates vs. No. of Months INH Treatment (Bethal Data)

Comstock GW: *Int J Tuberc Lung Dis* 1999
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

Sterling TR et al. *NEJM* 2011;365:2155-66
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?

Stagg et al. *Ann Int Med* 2014;161:419-26
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

ATS/CDC/IDSA 5/2000
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 HIV patient seropositive for Hep C
  - 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

ATS/CDC/IDSA 5/2000
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**

- Inhibit TNFα activity required for granuloma formation & containment of *M tuberculosis*
- Used for RA, Crohn’s disease, Psoriasis & 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-α 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

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

2. 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
Case 3

Questions

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

2. 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