Contact Investigation
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Diagnosis and Medical Management of Latent TB Infection
Joshua Jones, MD
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Joshua Jones, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Diagnosis and Management of Latent Tuberculosis Infection

Joshua D. Jones, MD
Medical Director, TB Control
Chicago Department of Public Health
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Definition of terms

• PPD = TST (TB skin test)
• IGRA = Interferon-gamma release assay
  – Quantiferon Gold and Q-Gold In-Tube
  – T-spot (Elispot)
Latent TB Infection (LTBI)

- Infection with MTB without symptoms
  - Theoretical risk of developing active TB
- TST+ and/or IGRA+ (if done)
- Active TB ruled out (CXR not c/w active TB)
  - Sputum staining for AFB and culture, if warranted
  - Calcified granulomas are OK in LTBI
- Includes “healed TB” (inactive, never treated)
  - Abnormal CXR (usually scarring), negative sputa

Background on LTBI

- NHANES 1999-2000: 4.2% TST+ US population
- Risk of progression to active TB: 10% lifetime
  - 5% in the first year after infection
  - <2y after infection: 15x Abnormal CXR: 6-19x
  - HIV: 50-110x
  - CRF-HD: 10-25x
  - DM: 2-4x
  - Transplant: 20-75x
  - TNF-α inhibitors: 2-9x
  - Children: 2-5x
- 2002: 300-400,000 persons started LTBI Tx
  - Only ~70% agree to start therapy

Bennett, et al, AJRCCM 177:2008
Lobue and Menzies, Respirology 15: 2010
Who should be screened for TB?

- Those at high risk of exposure -> TB infection
  - Recent contacts to active TB, esp. kids
  - Born in/exposed to high-incidence countries
  - Prison, homeless, substance abusing

- Those at high risk of reactivation
  - Children
  - Recent immigration
  - Immunocompromised
    - HIV+, immunosuppressive meds, chronically ill

Diagnostic workup

- Always rule out active TB before starting LTBI therapy (monotherapy -> resistance)
  - Any abnormal CXR c/w active TB needs sputum
    - Infiltrates, scarring, volume loss, pleural effusion
  - Wait for culture results, not just smear
  - Get MTB PCR on sputum if possible
  - High suspect: empiric active TB treatment (RIPE)
  - Low suspect: no therapy until cultures final (neg)
TST or IGRA or both?

- TST or IGRA, not both (usually)
- TST > IGRA: when IGRA is not validated
  - Children < 5 y/o
    - Risk of active TB outweighs possible false + TST
- IGRA > TST: when BCG confuses issue
  - Foreign-born
  - If doubt return visit for TST reading

MMWR, 59:RR-5, 2010

TST/IGRA in active TB disease

- Role of TST/IGRA is to assess for LTBI
  - Not definitive testing, esp. for active disease
- Measure of the immune response
  - Active disease may alter immune response
- Negative test does not rule out active TB
  - If clinical picture fits, assume TB until ruled out
Recommended LTBI regimens

• INH 300 mg qd x 9 months (9H)
• Rifampin 600 mg qd x 4 months (4R)
• Rifapentine/INH weekly x 3 months (3HP)
• Rifampin/PZA qd x 2 months no longer recommended: unacceptable liver toxicity
  • Adequate LTBI tx if given to suspect cases x 2 m
  • Still might be OK in kids and HIV+
• Rifampin 600/INH 300 qd x 3 months
  • Not a CDC recommended regimen

Why is LTBI rx so long?

• Drugs work quickly; why so long needed?
  – Why longer than active TB??

• MTB goes dormant in lung macrophages
• Drugs don’t work unless MTB is active
  – Need drug present when MTB activates
• Serum levels not same as in granuloma
Different microenvironments

Caseous granuloma in active TB  
Fibrotic granuloma in latent TB


Measuring LTBI Tx outcomes

• Efficacy: under ideal conditions  
  – “Intention to treat”
• Effectiveness: under real-world conditions  
  – Incorporates adherence, ADEs, provider decision
• Goal: prevent reactivation TB  
  – Measure: % of active cases prevented
• “LTBI” is really a spectrum of MTB activity
Evidence for INH qd x 9 m (9H)

• Most data on 6H and 12H, from 1950-60’s
  – 60% effective reduction in active TB vs. placebo
• Efficacy (80% pills): 12H (93%) vs. 6H (69%)
• Extrapolated for 9H (Comstock 1999)
  – ~90% efficacy (assuming adherence)
  – Effectiveness lower (range 25-88%; TBESC 47%)
  – Quoted completion rate 61-64% (self)
• 6H is actually more cost effective (80% compl.)
  – WHO and UK recommend 6H

Comstock, IJTBLD 1999

Adverse drug events with INH

• 1972: 14,000 patient 9H: 1.3% hepatotoxicity
  – Age>35 and chronic alcohol use increased risk
• Meta-analysis: 0-2.9% hepatotoxicity
• Recent observational data: 0.1-0.3% with monitoring
• Peripheral neuropathy: 0.2% in otherwise healthy
  – Vitamin B6 is not routinely needed

Lobue and Menzies, Respirology 15: 2010
Twice weekly INH

• Alternate CDC regimen (up to 900 BIW)
• Extrapolated from active TB data
• No trial examined BIW vs. qd regimens
• MUST be DOT

CDC, LTBI Guide for Primary Care Providers, 2010

INH for LTBI in HIV+ persons

• Mixed results of trials in HIV+ (TST+ and -)
• Meta-analysis: 8000 HIV+ persons (TST+/-)  
  – 33% reduction in active TB vs. placebo
• Optimal duration less clear
  – 6H and 12H both efficacious, so 9H recommended
  – Protection 2.5-3.0 years (high burden countries)

Lobue and Menzies, Respirology 15: 2010
Is 9H an ideal LTBI regimen?

- Low cost medication, simple
- Ample data on efficacy

- Long duration
- Low completion rate -> preventable TB cases
- Relatively high risk of hepatotoxicity
  - Lower with monitoring, which takes resources
- Costly in terms of staff time
  - Costs increases with serious ADE

Shorter regimens better?

- To demonstrate a regimen is better than 9H:
  - Completion rates need to be better
    - Dependent on convenience, tolerance
  - Safety must be equivalent or better
  - Efficacy to prevent TB must be non-inferior

  - Cost-effectiveness should be better

Menzies, et al, AJRCCM 2004
Evidence of Rifampin qd x 4 m (4R)

- Effectiveness not been well studied
  - 3R 46-50% effective (HK 1992 study)
  - 6R well-tolerated (case series)
- 116 patients (2004): 4R better than 9H
  - Completion: 91% (4R) vs 76% (9H)
  - ADE: 3% (4R) vs 14% (9H)
  - Cost: $17,000 (4R) vs $27,000 (9H)
- ↑completion/↓hepatotoxicity consistently observed

Uses of Rifampin qd x 4 months

- Contact of case with INH resistant TB
- INH intolerance, concern for hepatotoxicity
- Concern for poor compliance (?)
- Not rec for HIV (active TB more subtle)
Rifampin for LTBI in children

- No published studies evaluating RIF in kids
- Expert opinion: 6 months needed
- Definition of “child” not clear (<=15y best)
- Obvious choice if index case is INH resistant

Evidence of INH/Rifampin qd x 3m

- More data on effectiveness than 4R
  - Effectiveness and tox. comparable to 6H, 12H
  - Hepatotoxicity 2-5% (higher than 12H)
- Meta-analysis: Equivalent effectiveness (4.1%) and toxicity (4.9%) to 6H
- Not clear it is more effective than 4R (no head to head trial data)
  - Completion/toxicity lower with 4R vs. INH
Shorter regimens → ↑ completion?

• Not necessarily
  – 2RIF-PZA completion rates = 6INH
  – 3INH-RIF completion rates = 6INH, even 12H
• DOPT one option for daily regimens
  – Definitely improves adherence
  – Limited by cost, staff resources

Menzies, et al, AJRCCM 2004
Jasmer, et al, AJRCCM 2000

Rifamycins and rifapentine

• Rifamycins: best killing for dormant AFB
• Rifapentine (RPTN, P): weekly dosing, long t/2
  – Efficacious in mouse models
  – As good as RIF in active TB
  – RPTN tolerated at 900 qweek

Rifapentine for LTBI Tx

- Weekly dosing with INH
  - 12 weekly doses (3HP) within 16 weeks
  - Usually 900mg/900mg
  - Almost always DOT
- Brazil LTBI: 3HP qweek DOT vs RIF/PZA qd self
  - 3HP better tolerated (RP ↑ hepatotoxicity)
- S. Afr. LTBI (HIV+): 3HP qweek vs BIW vs 6H
  - 3HP not inferior to 6H
  - Some suggestion of induced RIF resistance

INH/Rifapentine qweek x 3 m (3HP)

- Study 26, PREVENT TB trial
  - TB Trials Consortium (PI Sterling)
- Compare 9H qd self vs 3HP DOT (900/900mg)
  - Open label, non-inferiority, ~10 years
- 8,000 persons w/LTBI, 19 sites
  - >2yo, TST+ contacts or recent converters
  - Exclude: active TB, MDR contacts, HAART, Hx Tx
- End point: active TB
Results of Study 26

- 7 TB cases after 3HP vs. 15 after 9H
  - Non-inferior effectiveness
  - Average 33 months of follow-up
- Completion: 82% 3HP vs 69% 9H
- Serious ADE: 1.6% 3HP vs 3% 9H
  - Any ADE: 8% 3HP vs 5.5% 9H
  - Meds d/c b/c of ADE: 4.9% 3HP vs 3.7% 9H
  - Reporting procedures different (DOT vs self)

CDC Recommendations

- Weekly RPTN + INH via DOT is approved
  - Any patient over 12 y/o, HIV+ not on HAART
  - Case by case in kids 2-11, DM, liver disease
- Not recommended (yet) in:
  - Kids <2 y/o
  - Pregnancy
  - HIV on HAART
- Baseline LFTs for some patients
- Assess at least monthly
Potential limitations to 3HP use

• ATS/IDSA/CDC revised guidelines in process
• RPTN cost
• RPTN availability
• DOT requirement
  – 3HP self or even 1HP self would be cost saving
  – But no data on effectiveness of self yet

Cost effectiveness of regimens

• Compared 9H (qd self), 9H (BIW DOPT), 4R (qd self), 3HP (qweek DOPT) and no treatment
  – Per pill: INH 2¢, RIF 46¢, RPTN $2.20
• Lifetime cost: 4R most cost effective
  – 4R < 9H < 3HP DOT < no TX < 9H DOT
  – 3HP more cost-effective if high likelihood of non-adherence
• Repeated with 9H, 4R, 3HP DOT, 3HP self
  – 4R < 3HP self < 3HP DOT < 9H self
    • 4R could be 17% less effective than 9H and still save $
Questions?

joshua.jones@cityofchicago.org