Treatment of Latent TB Infection

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Outline

- General concept of LTBI treatment
- Regimens
  - INH daily or twice weekly
  - INH and Rifapentine once weekly
  - Rifampin daily
LTBI treatment

- LTBI treatment: prevention of progression to active TB disease

- **Efficacy vs. Effectiveness**

- **Consider:**
  - Risk of progression to active TB (lifetime)
  - Risk of side effects
  - Likelihood of adherence and completion
  - Cost
  - Feasibility of DOT if indicated
CXR after positive TST / IGRA

- Prior to the initiation of LTBI treatment, the patient should undergo clinical evaluation including a CXR to rule out active TB disease
  - Repeat CXR when there is a recent one?
    - ✓ Consider: Immunocompromised? Young children? Prior abnormal CXR?
How much Isoniazid is needed to prevent active TB?

- Longer durations of therapy corresponded to lower TB rates among those who took 0-9 months.
- No extra increase in protection among those who took >9 months.

*Comstock GW, IJTBLD 1999; 3: 847*
INH: drug-induced liver injury (DILI)

- 10-20% of those who take INH will develop mild elevation of liver function tests.
  - Often resolves despite continuation
- Key: Monthly clinical evaluation and education for patients about signs and symptoms of hepatitis
INH-induced Hepatitis: Pre-treatment Evaluation

- Increased risk
  - HIV
  - daily alcohol use, chronic liver disease (e.g., hepatitis B & C)
  - Concurrent potentially hepatotoxic drugs
  - pregnant woman, postpartum within 3 months of delivery
  - Age over 65 (CMAJ 2011;183:E173)

→ Obtain baseline SGOT, SGPT and bilirubin if (+) hepatitis risk
INH: drug-induced liver injury

- Routine (e.g., monthly) LFT if:
  - Abnormal baseline LFT
  - Risk factors for drug-induced liver injury
    - Daily alcohol use, chronic liver disease (e.g., hepatitis B & C), HIV
    - Concurrent potentially hepatotoxic drugs
    - Pregnant woman, postpartum within 3 months of delivery
    - Age over 65 (CMAJ 2011;183:E173)
  - If no risk factor, check LFT only if drug-induced hepatitis is clinically suspected
Withholding LTBI treatment

- INH should be withheld when:
  - transaminase levels exceed 3 times the upper limit of normal if associated with symptoms
  - 5 times the upper limit of normal if the patient is asymptomatic
Twice weekly INH

- 6 – 9 months of INH twice weekly (15 mg/kg, up to 900 mg per dose)
- The guidelines recommend that DOT be used.
Besides INH: Recommended Regimens

- **In the U.S.**
  - 4 months of daily rifampin
  - 3 months (or 12 weeks) of weekly INH and Rifapentine

- **In the U.K.**
  - 3 months of daily INH and rifampin

- **WHO guidelines (2015)** recommend all of them, plus
  - 3 – 4 months of daily rifampin
CDC sponsored LTBI Treatment Trial: Sterling TR et al. NEJM 2011

- Comparison of self-administered INH x 9 mo vs. RPT/INH once weekly DOT x 3 mo
- Age ≥ 12 yr and high-risk (e.g. close contact)
  - Later included age between 2 and 11 yo
- 8053 enrolled
- Followed for 33 months
INH/rifapentine is non-inferior to INH

### Table 2. Number of Subjects with Tuberculosis and Event Rates.*

<table>
<thead>
<tr>
<th>Population and Study Group</th>
<th>No. of Subjects</th>
<th>Subjects with Tuberculosis</th>
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<td>Modified intention-to-treat analysis</td>
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<td>Combination therapy</td>
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<td>Per-protocol analysis</td>
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<tr>
<td>Isoniazid only</td>
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<tr>
<td>Combination therapy</td>
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</table>
Pros and Cons: INH-RPT

- Non-inferior to INH
- Higher completion rate
- ? Less serious adverse events

- DOT
- Cost of drugs
- Drug interaction
Systemic Drug Reactions in 3HP trial

- 138 of 3893 (3.5%) experienced ‘SDR’
  - 17% “cutaneous”: angioedema, urticaria, rash, itching, anaphylaxis
  - 63% “flu-like”: fevers/chills, fatigue, muscle pain, syncope (n=6), palpitations, flushing, dizziness, conjunctivitis

- 13 (0.3%) had severe reactions
  - 4 hospitalized, 7 hypotensive/syncope

Clinical Infectious Diseases 2015; 61: 527-35
Systemic Drug Reactions in 3HP trial

- SDR occurred after median of 3 doses
  - Median onset: 4 hrs
  - Median time to symptom resolution: 24 hrs
- 73 of 138 patients with SDR underwent drug re-challenge.
  - 51 took rifapentine as the first rechallenge drug and 36 tolerated
  - ultimately 8/73 were able to tolerate RPT/INH
Systemic Drug Reactions in 3HP trial

Authors conclusions:

- SDR were
  - mostly flu-like
  - Likely due to rifapentine
  - different from immunologically mediated drug reactions
  - mostly mild and resolved within 24 hrs

*Clinical Infectious Diseases* 2015; 61: 527–35
Rifampin daily for 4 months

- Less serious side effects, including drug-induced hepatitis, compared to INH
- Watch for drug-drug interaction (e.g. warfarin, some HIV meds)
- More expensive (~$100/mo) than INH
- DOT is not necessary
- A few cost analyses showed RIF x 4 mo is the most cost-saving if they are not extremely high-risk patients. (Am J Respir Crit Care Med 2009;179:1055, Thorax. 2010;65:582)