Overview: Treatment of Latent TB Infection

September 29, 2015
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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
- Considerations:
  - Risk of side effects
  - 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
  - When there is a recent CXR…
  - Immunocompromised? Young children? Prior abnormal CXR?

Daily Isoniazid

- Efficacy of INH:
  - 9 months: ~90%
  - 6 months: 60 - 70%

Comstock GW, IJTBLD; 1999; 3: 847

Twice weekly INH (DOT)

- 6 – 9 months of INH twice weekly (15 mg/kg, up to 900 mg per dose) by DOT
INH: side effects

- Hepatitis
  - Associated with advanced age

- Peripheral neuropathy
  - Pyridoxine supplement
    (25-50 mg daily)

Other 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

Effective but can be very toxic

- 2 months of daily rifampin and pyrazinamide
  - Original studies: the regimen was shown to be effective among the HIV infected.
  - Severe liver injury in HIV-negative LTBI patients
  - The CDC recommends against its use
3 months of weekly INH and Rifapentine

- aka “3 HP” or “the 12-dose regimen”
- CDC sponsored LTBI treatment trial (Sterling TR et al. NEJM 2011)
- Comparison of INH x 9 mo (self adm) vs RPT/INH once weekly DOT x 12 weeks
- 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

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<th>No. of Subjects</th>
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<th>per patient-yr</th>
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Once weekly INH-RPT

- Non-inferior to INH daily for 9 mo
- Higher completion rate of treatment
- Hepatitis less frequent but systemic drug reactions (SDR) can occur
- DOT
- Cost of drugs
- Drug interaction
Systemic Drug Reactions in 3HP trial

- 138/3893 (3.5%) had ‘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

Sterling: 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
- Of 73/138 pts with SDR underwent drug rechallenge.
  - 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
  - features differ from immunologically mediated drug reactions
  - most mild and resolved within 24 hrs

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

- Less serious side effects, including 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)