Selected Topics in LTBI
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Disclosures

• No disclosures or conflicts of interest to report

Outline

• Special LTBI situations
  – Pediatrics, pregnancy, contacts, drug resistance
• How to monitor and manage side effects
• Adherence to LTBI treatment
• How to handle drug interruptions
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LTBI in children

• Young children more likely to be recently infected, and are at higher risk for severe disease (ie meningitis)
• INH appears to be more effective in preventing TB disease in children
• Risk of INH hepatotoxicity lower in children
**LTBI in children**

- Diagnosis: Targeted just like in adults
  - TST: American Academy of Pediatrics guidelines
  - IGRA:
    - Insufficient data for use age < 5
    - Recommended if age 5+ and history BCG
  - “Window prophylaxis”
    - Contacts age < 5 at high risk for progression
    - If initial LTBI testing negative, initiate treatment and retest 8-12 weeks later (stop meds if 2nd test negative)

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**Table 3.75. Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induration 5 mm or greater</td>
<td>Children in close contact with known or suspected contagious people with tuberculosis disease, Children with a history of tuberculosis disease, Children receiving immunosuppressive therapy or with immunosuppressive conditions, including human immunodeficiency (HIV) infection</td>
</tr>
<tr>
<td>Induration 10 mm or greater</td>
<td>Children at increased risk of disseminated tuberculosis disease, Children born in high-prevalence regions of the world, Children who travel to high-prevalence regions of the world, Children incarcerated or institutionalized who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized</td>
</tr>
<tr>
<td>Induration 15 mm or greater</td>
<td>Children age 5 years or older with any risk factors</td>
</tr>
</tbody>
</table>

AAP Red Book 2012

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**LTBI in children**

- Treatment
  - INH X 9 months preferred regimen (daily, or twice weekly DOT)
  - RIF X 6 months AAP recommended alternative if INH intolerant
  - JAMA Pediatrics 2015: INH/RPT as effective and well tolerated in those age 2+
LTBI in pregnancy

• Treatment more hepatotoxic in pregnancy and post-partum period
• Pregnancy does not increase risk of TB disease
• So, only test and treat those at high risk
  – Close contacts
  – HIV, immunosuppressive therapy
• Otherwise, defer testing/treatment until 3 months after delivery (need to r/o active disease at that time!)

LTBI in pregnancy

• Testing: No special considerations
• Treatment:
  – INH X 9 months preferred (with pyridoxine)
  – RIF is alternative (INH intolerant, adherence)
  – INH/RPT not studied/recommended in pregnancy
• Monitoring:
  – Baseline LFTs, then monthly
  – Same guidelines for stopping medications
  – OK to breastfeed (infant should get pyridoxine)
LTBI in contacts

• High risk contacts warrant treatment even if negative LTBI test
  – Children <5 should start treatment and have follow up LTBI test in 8-12 weeks (“window prophylaxis”)
  – HIV (and other severely immunosuppressed) should be treated regardless of LTBI test results

LTBI in contacts (drug resistance)

• Limited data to guide therapy
• INH monoresistance: RIF
• RIF monoresistance: INH
• MDR (INH and RIF resistance):
  – Tailor towards susceptibility profile
  – Use 2 drugs, including quinolone if susceptible
  – Duration: 6-12 months (unstudied)
  – Expert consultation recommended
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Monitoring/managing SE

• We worry most about hepatitis (all drugs)
• You should also be aware of:
  – INH: peripheral neuropathy, rash
  – RIF: drug interactions, GI SEs, rash, flu-like syndrome, hemalogic effects, orange fluids
  – RPT: hypersensitivity reaction, drug interactions, GI SEs, flu-like symptoms, orange fluids

Monitoring/Managing SE

• Baseline LFTs if
  – Underlying liver disease
  – Regular alcohol use
  – HIV infection
  – Pregnant or within 3 months post-partum
  – Taking other hepatotoxic medications
  – Malnourished child
  – +/- age > 65
Monitoring/Managing SE

• If baseline LFTs > 3 times ULN, defer LTBI treatment until determine cause
  – Active hepatitis and ESLD are relative contraindications to treatment

Monitoring/Managing SE

• Who should get pyridoxine with INH?
  – Diabetic
  – Renal failure
  – Alcoholism
  – Malnutrition
  – HIV infection
  – Pregnant (and infants of breastfeeding mothers)
  – History of seizure disorder

Monitoring/Managing SE

• Monthly assessment (weekly if INH/RIF)
  – Symptom screen (especially hepatitis, neuropathy, hypersensitivity)
  – Basic exam (icterus, hepatic tenderness, rash)
  – Remind patients not to drink
  – Remind patients about signs/symptoms of hepatotoxicity (stop med, contact provider)
    • Anorexia, nausea/vomiting, dark urine, icterus, rash, weakness/fatigue lasting 3+ days, abdominal pain, bruising/bleeding, arthralgias
**Monitoring/Managing SE**

- LFTs during treatment (ie monthly) if ...  
  - Baseline abnormal  
  - At risk for hepatotoxicity  
  - Symptoms suggestive of hepatitis  
- Stop medication only if  
  - Symptomatic and LFTs > 3 times ULN  
  - Asymptomatic and LFTs > 5 times ULN  
  - Don’t restart the same medication, even when LFTs normalize

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**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  
- 13/3893 (0.3%) had severe reactions  
  - 4 hospitalized, 7 hypotensive/syncope

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**SDR 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 who were re-challenged  
  - 2 tolerated both drugs on re-challenge  
  - None completed treatment  
- Unable to determine any early clinical predictors of SDR (but adverse events collected monthly)
SDR in 3HP trial

- Authors conclusions: SDR were
  - mostly flu-like
  - Likely due to rifapentine (but can’t be sure)
  - did not meet objective hypersensitivity criteria
  - features differ from severe immunologically mediated drug reactions (but can’t rule out)
  - most mild and resolved within 24 hrs
  - Ongoing post-marketing surveillance necessary

Monitoring/Managing SE

- Important to report potential adverse effects
  - Remember that for both INH and INH-PZA, fatal hepatitis identified only after widespread use
- Hospital admission or death:
  - Report to local/state health department for inclusion in CDC database

Monitoring/Managing SE
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**Adherence**

- Reported completion rates vary from 16% to 96% (Getahun NEJM 2015)
- Difficult to predict
  - Previous non-adherence, drug/alcohol, mental illness likely strongest predictors
- Even physicians poorly compliant: <15% completed INH in one study (Miller ARRD 1987)

**Adherence: Barriers**

<table>
<thead>
<tr>
<th>Factor affecting adherence</th>
<th>In TB disease</th>
<th>In LTBI</th>
<th>Impact on TUBD adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication side effects</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Negative financial impact</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Fear of infection</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Usually 6 months</td>
<td>Usually 6 months</td>
<td>Similar to TB disease</td>
</tr>
<tr>
<td>Compliance with treatment</td>
<td>Standard of care</td>
<td>Asymptomatic</td>
<td>Hinders</td>
</tr>
<tr>
<td>Motivation to take drugs</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Medication accessibility</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Toxicity concerns</td>
<td>Strong</td>
<td>Weak</td>
<td>Hinders</td>
</tr>
<tr>
<td>Public health threat</td>
<td>Threat</td>
<td>Indirect threat</td>
<td>Hinders</td>
</tr>
</tbody>
</table>

Hirsh-Moverman IJTD 2008
Adherence: What works?

- Directly observed therapy (DOT) is the most likely intervention to ensure adherence
- Other interventions show inconsistent results (for LTBI or anything else!)
  - Education, case management, incentives, enablers, reminders (I-ADHERE)
- Interventions can be costly
- Intervention must be tailored to individual patients and communities

Adherence: Example

- Pioneer Square Clinic (Seattle homeless)
  - Incentive based DOT program
    - DOT with 12 dose, once weekly INH/RPT
    - Incentives: discounted food vouchers and clothing
  - Money for intervention from:
    - Expanded Medicaid (ACA) for meds
    - Fundraiser (to purchase incentives)
  - Published feasibility, adherence rates forthcoming

Gupta NEJM 2015

Adherence: Providers

- Hypertension
- Liver TB adhesions

- Acute psychiatric
- Vary severe complications
- Mental disability
- Treatment in years
- Expensive medications
- Potential serious side effects
- Requires close monitoring and follow up

- Acute psychiatric
- Vary severe complications
- Mental disability
- AND treatment
- Treatment in years
- Expensive medications
- Potential serious side effects
- Requires close monitoring and follow up

- RCT – no decline about Treating
- Gupta NEJM 2015
- Menzies 2011
Adherence

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Drug Interruptions

• Treatment completion defined as:
  – INH 9 months: 270 doses within 12 months
  – INH 6 months: 180 doses within 9 months
  – Rifamin 4 months: 120 doses within 6 months
  – INH/RPT: Not defined. 12 doses within 4 months?
Drug Interruptions

• Restart therapy from the beginning if
  – INH 6 or 9 mo regimens: > 3 months missed
  – RIF 4 mo regimen: > 2 months missed
  – INH/RPT 3 mo regimen: > 2 months missed?

• Remember: If therapy restarted after a period of > 2 months, need to r/o active disease

Questions?