TB PREVENTION:
TREATMENT OF LATENT TB INFECTION
AND BCG VACCINATION

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Denver Public Health
DISCLOSURES

• No relevant financial relationships
OBJECTIVES

• Understand evidence supporting treatment of latent TB infection (LTBI)

• Understand advantages/disadvantages of current treatment options for LTBI

• Understand efficacy of BCG vaccination & potential complications
26 year old woman. Her IGRA is positive and chest radiograph is normal. Risk factors for TB infection include prior residence in a TB endemic area. What LTBI treatment would you select?

- 9 months daily isoniazid
- 4 months daily rifampin
- 12 weekly doses of isoniazid / rifapentine
- It depends - we need more information!
LTBI TREATMENT
KEY CONSIDERATIONS

Efficacy
• Ability to prevent disease among individuals adhering to medication

Effectiveness (adherence)
• Ability to prevent disease when used in public health practice

Drug interactions & adverse events

Monitoring requirements, cost, availability
INH: BETHEL DISTRICT ALASKA

- RTC in 1957-1959
  - 1 year INH versus placebo
  - 69% reduction in TB
- Community-wide prophylaxis began in 1963
- 12-months INH recommended for LTBI treatment in 1970

IF 12 MONTHS IS EFFECTIVE, THEN HOW ABOUT 9 MONTHS OR 6 MONTHS?

• IUAT trial
  • 28,000 adults with fibrotic pulmonary lesions followed 5y

<table>
<thead>
<tr>
<th>Group</th>
<th>Intention to treat</th>
<th>Completers/compliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>3 months INH</td>
<td>21%</td>
<td>31%</td>
</tr>
<tr>
<td>6 months INH</td>
<td>65% *</td>
<td>69%</td>
</tr>
<tr>
<td>12 months INH</td>
<td>75% *</td>
<td>93%</td>
</tr>
</tbody>
</table>

* Not significantly different

IUAT Bull WHO 1982; 60:555
IF 12 MONTHS IS EFFECTIVE, THEN HOW ABOUT 9 MONTHS OR 6 MONTHS?

- Lower TB rates among those who took 0-9 months
- No significant increase among those who took >9 months

Comstock Int J Tuberc Lung Dis. 1999 3; 10:847
OUR PATIENT STARTS ISONIAZID... SHE LIKELY DOES NOT NEED LABORATORY MONITORING

• Check baseline labs if:
  - HIV-positive
  - History of liver disease
  - Regular alcohol use
  - Age >35
  - Pregnant or post-partum (within 3 months)
  - H/o injection drug use
  - On hepatotoxic medications

• Labs during follow-up only if baseline labs elevated or symptomatic
Monthly visits include

- Education regarding purpose of treatment
- Assessment of adherence
- Education regarding drug-related symptoms

- Fever
- Headache
- Rash
- Nausea, RUQ pain
- Dark urine
- Numbness

Our patient starts ISONIAZID... she likely does not need laboratory monitoring
One month later, another provider checked an ALT which was 105 (upper limit of normal = 40). She feels fine. Which of the following is not indicated?

<table>
<thead>
<tr>
<th>A</th>
<th>Consider other causes of elevated ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Continue isoniazid - recheck ALT at intervals</td>
</tr>
<tr>
<td>C</td>
<td>Discontinue isoniazid immediately</td>
</tr>
</tbody>
</table>
ISONIAZID
A SPECTRUM OF LIVER INFLAMMATION

“Adaptation” seen in 10-20%

- Increase in ALT
  - <3 x ULN with symptoms
  - <5 x ULN without symptoms
- Not an indicating for stopping Rx
- Generally normalizes despite continued Rx
Mild-moderate hepatocellular injury

- Increase in ALT
  - 3-10 x ULN with symptoms
  - 5-10 x ULN without symptoms
- Stop treatment – follow at weekly intervals
- 0.2% in patients <35 y/o; 1.8% in patients ≥ 35 y/o

Severe hepatocellular injury
- >10 x ULN ALT
- ↑ bilirubin, ↑ INR
- Hospitalize, monitor for fulminant hepatic failure

ISONIAZID
A SPECTRUM OF LIVER INFLAMMATION
INH HEPATOTOXICITY
CDC SURVEILLANCE FOR SEVERE HEPATITIS

• 17 persons treated for LTBI with INH during 2004-2008
  • All monitored according to guidelines
  • 5 transplants; 5 deaths
  • Among 15 adults, age ranged from 19-64
  • Symptom onset 1-7 months after initiating INH
  • 80% continued taking INH for more than a week after symptom onset

INH ADVERSE EVENTS

- Neurologic - interference in vitamin B₆ absorption
  - Higher risk in DM, renal insufficiency, alcoholism, malnutrition, HIV, pregnancy, seizure disorder
- GI
  - Hepatotoxicity
  - Nausea/vomiting
- Skin rash
- Drug interactions—always check!

Offer B6 at 25-50mg daily to individuals at higher risk for peripheral neuropathy
### INH

"ONE OF THE PREFERRED REGIMENS"

<table>
<thead>
<tr>
<th><strong>ADVANTAGES</strong></th>
<th><strong>DISADVANTAGES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Large body of evidence</td>
<td>Intermittent regimens must be directly observed</td>
</tr>
<tr>
<td>Regimen of choice for children aged 2-11 years</td>
<td>Adherence is poor</td>
</tr>
<tr>
<td>Efficacy shown in HIV + and -</td>
<td></td>
</tr>
<tr>
<td>Intermittent regimens useful for DOPT in high-risk children</td>
<td></td>
</tr>
</tbody>
</table>
SELF-ADMINISTERED RIFAMPIN EFFICACY FOR LTBI

- 679 patients with silicosis & LTBI in Hong Kong
- Randomized to:
  - Placebo - 27% developed TB within 5 years!
  - 6 months INH
  - 3 months INH/RIF
  - 3 months RIF

Hong Kong Chest Service  Am Rev Resp Dis 1992;145:36

4 months
10mg/kg = 600mg daily unless underweight

Inhibits RNA synthesis
Potent activity against slow-growing MTB
SELF-ADMINISTERED RIFAMPIN EFFICACY FOR LTBI

H = isoniazid
R = rifampin
Pl = placebo

Hong Kong Chest Service  Am Rev Resp Dis 1992;145:36
Self-administered rifampin: better adherence than INH

847 adults with LTBI in Canada, Brazil & Saudi Arabia
Randomized to:
- 4 months RIF (n=420)
- 9 months INH (n=424)

Menzies D, Ann Intern Med 2008; 149:689

Proportion Still Receiving Therapy

Days after Randomization

<table>
<thead>
<tr>
<th></th>
<th>Rifampin</th>
<th>INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Grade 3-4 Hepatotoxicity</td>
<td>0.7%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

Rifampin: 78% completion
INH: 60% completion
# Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults


<table>
<thead>
<tr>
<th>Variable</th>
<th>Isoniazid (N = 2989)</th>
<th>Rifampin (N = 3023)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completed — no. (%) †</td>
<td>1890 (63.2)</td>
<td>2382 (78.8)</td>
<td>15.1 (12.7–17.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Within allowed time</td>
<td>1727 (57.8)</td>
<td>2136 (70.7)</td>
<td>12.1 (9.6–14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not within time allowed by protocol</td>
<td>163 (5.5)</td>
<td>246 (8.1)</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Treatment not completed for any reason — no. (%) ‡</td>
<td>1099 (36.8)</td>
<td>641 (21.2)</td>
<td>−15.1</td>
<td></td>
</tr>
<tr>
<td>Death during treatment period deemed to be not related to therapy</td>
<td>3 (0.1)</td>
<td>0</td>
<td>−0.1</td>
<td></td>
</tr>
<tr>
<td>No. of confirmed or clinically diagnosed cases of active tuberculosis per 100 person-yr (95% CI)</td>
<td>0.11 (0.05 to 0.27)</td>
<td>0.09 (0.04 to 0.22)</td>
<td>−0.02 (−0.30 to 0.26)</td>
<td>0.77</td>
</tr>
<tr>
<td>Adverse event, with trial drug restarted without symptom recurrence — no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2 adverse event</td>
<td>4 (0.1)</td>
<td>5 (0.2)</td>
<td>&lt;0.1 (−0.2 to 0.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event †</td>
<td>4 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>−0.1 (−0.3 to −0.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Adverse event, with trial drug stopped permanently — no. of patients (%) ‡</td>
<td>153 (5.4)</td>
<td>74 (2.6)</td>
<td>−2.9 (−3.9 to −1.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
SELF-ADMINISTERED RIFAMPIN

- Adverse effects
  - Dyspepsia
  - Orange discoloration to body fluids
  - Rash
  - Thrombocytopenia
  - Rare: neutropenia, hemolytic anemia, thrombocytopenia

- Drug interactions
  - Hormonal anti-contraceptives
  - Coumadin
  - Thyroid hormone
  - Anti-seizure agents
  - Antihypertensives
  - Antipsychotics
  - Plus many more
RIFAMPIN—MONITORING

• Check baseline labs if:
  ▪ HIV-positive
  ▪ History of liver disease
  ▪ Regular alcohol use
  ▪ Age >50
  ▪ Pregnant or post-partum (within 3 months)
  ▪ On hepatotoxic medications

• Labs during follow-up only if baseline labs elevated or symptomatic
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection


High risk LTBI in US, Canada, Brazil & Spain

Randomized to:
- 9 months daily self-administered INH (9H)
- 12 weekly doses INH/Rifapentine (3HP)

Outcome: TB over 33 months f/u

A non-inferiority trial
ISONIAZID WITH RIFAPENTINE

- Adverse effects
  - Dyspepsia
  - Nausea/vomiting
  - Fatigue
  - Flu-like illness
  - Headaches
  - Hepatotoxicity
  - Rash

- Drug interactions—some overlap with rifampin
  - Hormonal anti-contraceptives
  - Coumadin
  - Antihypertensives
  - Antiretrovirals
ISONIAZID AND RIFAPENTINE BOTH ONCE WEEKLY FOR 12 DOSES

- Isoniazid: 15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum
- Rifapentine
  - 10 to 14 kg: 300 mg
  - 14.1 to 25 kg: 450 mg
  - 25.1 to 32 kg: 600 mg
  - 32.1 to 49.9 kg: 750 mg
  - >50 kg: 900 mg maximum
- Obtain LFTs:
  - if aged >35
  - has underlying liver disease
  - pregnant/or within 3 months post-partum, o
  - Regular EtOH consumption or taking other hepatotoxic agents
SELF-ADMINISTERED INH/RIFAPENTINE: IADHERE STUDY

Adherence trial with three arms:
- DOT
- SAT
- eSAT (with weekly text reminders)

USA (75%), Spain, Hong Kong, South Africa

Outcome: completion

Measured by self-report, pill count, MEMS

15% non-inferiority margin

IADHERE RESULTS

- Overall
  - Non-inferiority not established for SAT or eSAT
- In US
  - iAdhere supports use of INH/rifapentine via SAT

<table>
<thead>
<tr>
<th></th>
<th>DOT</th>
<th>SAT</th>
<th>Difference from DOT</th>
<th>eSAT</th>
<th>Difference from DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>86.9%</td>
<td>74.4%</td>
<td>12.4 (6.6, 18.2)</td>
<td>75.4%</td>
<td>11.8 (5.9, 17.6)</td>
</tr>
<tr>
<td>USA</td>
<td>85.0%</td>
<td>78.3%</td>
<td>6.8 (0.1, 13.4)</td>
<td>76.0%</td>
<td>9.5 (2.6, 16.4)</td>
</tr>
</tbody>
</table>

DOT = directly observed therapy; SAT = self-administered therapy.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Efficacy</th>
<th>Mean completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months INH</td>
<td>90-92%</td>
<td>53-63%</td>
</tr>
<tr>
<td>6 months INH</td>
<td>41-76%</td>
<td>49-79%</td>
</tr>
<tr>
<td>4 months Rifampin</td>
<td>Equivalent to 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>months of INH</td>
<td>72-79%</td>
</tr>
<tr>
<td>3 months INH - Rifapentine</td>
<td>Equivalent to 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>months of INH</td>
<td>78%</td>
</tr>
</tbody>
</table>

• No standard regimen
• Contact MDR-TB expert
• Follow for 2 years
• “PT be considered in selected high-risk contacts of patients with MDR-TB, based on “individualized risk” and “sound clinical justification””
**CONTACT TO MDR-TB: LITTLE DATA, SOME CLINICAL EXPERIENCE**

- Prospective observational study
- 1/2019-2/2012
- 119 contacts of MDR-TB patients:
  - 15 declined
  - 104 began treatment for MDR LTBI
  - 93 (89%) completed treatment, none developed active TB
- 4 contacts discontinued due to adverse effects
- 3/15 (20%) who declined treatment developed MDR-TB
- 15 unidentified contacts developed MDR-TB

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**12-month fluoroquinolone (FQ) based MDR LTBI treatment**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Patients who started treatment</th>
<th>Patients who completed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>5–11</td>
<td>20</td>
<td>19 (95)</td>
</tr>
<tr>
<td>12–17</td>
<td>17</td>
<td>17 (100)</td>
</tr>
<tr>
<td>18–25</td>
<td>17</td>
<td>14 (82)</td>
</tr>
<tr>
<td>26–40</td>
<td>14</td>
<td>11 (73)</td>
</tr>
<tr>
<td>41–55</td>
<td>17</td>
<td>15 (88)</td>
</tr>
<tr>
<td>&gt;55</td>
<td>13</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
<td>93 (89)</td>
</tr>
</tbody>
</table>

**Treatment regimen**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Patients who started treatment</th>
<th>Patients who completed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFX only</td>
<td>46</td>
<td>36 (83)</td>
</tr>
<tr>
<td>MFX + EMB</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>LVX only</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>LVX + EMB</td>
<td>17</td>
<td>16 (94)</td>
</tr>
<tr>
<td>LVX + ETH</td>
<td>12</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
<td>93 (89)</td>
</tr>
</tbody>
</table>

PREGNANCY, BREASTFEEDING AND PEDIATRICS

- Pregnancy does not increase TB risk
  - INH and Rifampin
    - Safe in pregnancy, no contraindication to breastfeeding
    - Higher hepatitis risk postpartum
- Pediatrics:
  - INH-rifapentine may be considered if ≥ 2 years old
  - Preferred by most experts for children aged 5 and older (DOT only)
  - Rifampin (self-administered)
  - INH

Red Book: 2018-2021
TNF-ALPHA ANTAGONISTS

• Treat if
  • TST ≥ 5mm — or —
  • Positive IGRA — or —
  • Epidemiologic risk [even if TST and IGRA are negative]— somewhat controversial

• Initiate TNF-α inhibitor after one months of LTBI treatment

• Based on expert opinion
BCG VACCINATION
BCG VACCINES
HISTORICAL PERSPECTIVE

- Bacillus of Calmette and Guerin
- Live attenuated *M. bovis* strain
  - Derived by serial passage (231 times during 1906-1919) until less virulent in animals
- First given to human in 1921
- Subsequently sub-cultured and distributed worldwide
  - >3 billion doses administered
BCG VACCINATION
CUTANEOUS REACTIONS

- Papule at 2-3 weeks
- Ulceration at 6-8 weeks
- Scar by 3 months
BCG VACCINES
HIGH EFFICACY IN CHILDREN

• TB meningitis in children
  • 73% effective (95% CI: 67-79%)
• Miliary TB in children
  • 77% (95% CI: 58-87%)

Trunz Lancet 2006; 367:1173
BCG VACCINE EFFICACY
VARIABLE EFFICACY FOR ADULT PULMONARY TB

Study Location
England
Native Americans
Chicago
Haiti
Puerto Rico
Mandanapalle, India
Georgia
Chingleput, India
Georgia
Illinois
England
Cameroon
Argentina
Indonesia
Papua New Guinea
Kenya
Colombia
Karongla, Malawi
BCG VACCINES
WHY THE DIFFERENCES IN EFFICACY?

• A collection of different vaccines
  • Diversity of strains producing different antigens

• Geographic difference in NTM exposures
  • Exposure to environmental NTM may protect against TB

  --- or alternatively ---

• Pre-existing immunity to NTM may interfere with BCG vaccine viability, reducing immune response

Behr MA  Lancet Infect Dis  2002; 2: 86–92
BCG VACCINES
WHY THE DIFFERENCES IN EFFICACY?

• Methodological flaws
• Differences between *M. tuberculosis* strains
• Differences between human populations
  • Genetics, environment, nutrition
BCG VACCINATIONS
CONTRAINDICATIONS

• Immunosuppression
• Pregnant Women
157 of 180 countries surveyed recommend universal BCG vaccination
THANKS!
Questions?

Thank you!