Substance Abuse and Tuberculosis
Oklahoma City, Oklahoma
November 17, 2010

Drug Interactions
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Drug Interactions
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Latent TB Infection

- Tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA) positive
- No signs/symptoms or physical findings suggestive of TB
- A normal or stable CXR
- Negative sputum smears and cultures
- **NOT INFECTIONOUS**
- Dormant TB bacilli place person at risk for development of TB disease
Pathogenesis of TB
Progression to Disease

Exposure (LTBI)
- 5% First Year
- 2-3% Second Year
- ~0.1% per year thereafter

Disease

No Disease (90%)

Who Should be Tested for LTBI?

- Contacts of persons with active TB
- HIV positive individuals
- Persons with medical risk factors that increase risk of progression to disease
- Targeted testing of high risk persons to identify those at risk of recent infection
Tuberculosis Disease

- Active infectious process involving the lungs and/or other areas of the body
- Patients are often sick unless they are identified as part of the contact investigation
- When disease involves the lungs, the person is usually infectious

Populations at High Risk for TB

- Contacts of infectious persons
- HIV-infected persons
- Foreign-born persons
- Homeless persons
- Those in congregate living situations
- Persons who inject illicit drugs
- Detainees and prisoners
ANTITUBERCULOSIS DRUGS (ATS/CDC/IDSA)

- **First-Line drugs**
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

*Not FDA approved for TB

- **Second-Line Drugs**
  - Cycloserine
  - Ethionamide
  - Levofoxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin
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Regimens for Treating LTBI

• 9-month regimen of isoniazid (INH) is the preferred regimen

• 6-month regimen of INH is less effective but may be used if unable to complete 9 months

• Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.

• In situations where Rifampin cannot be used, rifabutin may be substituted (e.g., HIV-infected persons receiving protease inhibitors, patients receiving methadone).
Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• General conclusions from the literature
  – 6 mo (26 wk) is the MINIMUM duration of RX
  – 6 mo regimens require rifampin and INH throughout and PZA for the first 2 months
  – 6 mo regimens are effective without INH if PZA given throughout
  – Intermittent regimens (2-3x/wk): DOT ONLY!
    • Drug susceptible isolate
    • Regimen contains INH and rifampin

Treatment of Patients with TB Disease

• Initiation phase of therapy
  – 8 weeks
  – INH, Rifampin and PZA +/-EMB

• Continuation phase of therapy
  – 16 weeks
  – INH and Rifampin
Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB
(Yee, AJRCCM 2003; 167: 1472)

- 37/430 Patients had major side-effects: 9 had a second major adverse event (46 total events)
  - Rash/drug fever 21
  - Hepatitis 12
  - Severe GI upset 11
  - Visual Toxicity 1
  - Arthralgia 1

- Associated with Female sex, age >60, Birthplace in Asia and HIV status

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Rash</th>
<th>Hepatitis</th>
<th>GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>(5.2)</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>(10.2)</td>
<td>9</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PZA</td>
<td>(24.2)</td>
<td>8</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>EMB</td>
<td>(16.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB
(Yee, AJRCCM 2003; 167: 1472)

- PZA: 1.48/100 person months of exposure
- INH: 0.49/100 person months
- Rif: 0.43/100 person months
- EMB: 0.07/100 person months

“The drug most likely responsible for the occurrence of hepatitis or rash during therapy for active TB is PZA”

Alcohol and LTBI treatment

- Isoniazid
  - Alcohol consumption appeared to more than double the rate of probable isoniazid hepatitis
  - Abnormal results were associated with alcohol use, but not with race, age, chronic hepatitis B infection, or HIV infection
  - A study in Spain found that only excessive alcohol consumption and a high baseline ALT concentration were independently associated with isoniazid hepatotoxicity

- Rifampin
  - Hong Kong Chest Service study showed none of 49 individuals, 20% of whom used alcohol and 8% of whom used injection drugs, treated with rifampin for 6 months had symptomatic liver injury
Isoniazid Drug Toxicities

- Increased toxicity when administered with INH due to increased serum levels
  - Phenytoin
  - valproic acid
  - Carbamazepine
  - disulfiram (Antabuse)
  - Serotonergic antidepressants
  - acetaminophen

Isoniazid Toxicity

- Central Nervous System Effects
  - irritability, seizures, dysphoria, inability to concentrate

- GI reactions (nausea, anorexia, abdominal pain)

- Peripheral Neurotoxicity
  - Dose Related
  - Uncommon (< 0.2%) at conventional doses
  - Increased risk with other conditions associated with neuropathy: malnutrition, diabetes, HIV, renal failure, alcohol
  - Pyridoxine 25 mg/kg (vitamin B6) recommended patients with above conditions
Alcohol and LTBI treatment

- For those with chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits.

- If LTBI treatment is undertaken, close monitoring is indicated.

- The decision to treat LTBI, or more likely defer, should be carefully made on a case-by-case basis, weighing the risk of progression to TB disease against the risk of INH or rifampin-related DILI.

Alcoholics with TB

### Table 2: Differences in disease characteristics between North Carolina tuberculosis cases reported 1994–2006 with and without excess alcohol use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excess alcohol use</th>
<th>Prevalence ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No/Unknown</td>
</tr>
<tr>
<td>Site of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary (nonextrapulmonary)</td>
<td>1227 (92.5%)</td>
<td>3366 (77.2%)</td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>99 (7.5%)</td>
<td>964 (22.8%)</td>
</tr>
<tr>
<td>Chest radiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td>452 (34.8%)</td>
<td>920 (28.2%)</td>
</tr>
<tr>
<td>Non-cavitary</td>
<td>775 (63.2%)</td>
<td>2346 (71.8%)</td>
</tr>
<tr>
<td>Sputum smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>809 (65.9%)</td>
<td>1495 (45.8%)</td>
</tr>
<tr>
<td>Negative</td>
<td>418 (34.1%)</td>
<td>1771 (54.2%)</td>
</tr>
<tr>
<td>Sputum culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1038 (84.6%)</td>
<td>2270 (69.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>189 (15.4%)</td>
<td>996 (30.5%)</td>
</tr>
</tbody>
</table>

Chest radiographic, sputum smear, and sputum culture data are for cases with pulmonary involvement only.
Alcohol and Hepatotoxicity in the Treatment of TB Disease

Table 5  Dichotomous variables in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 56)</th>
<th>Controls (n = 406)</th>
<th>( \chi^2 )</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High alcohol intake</td>
<td>19-8%</td>
<td>4-9%</td>
<td>20-4</td>
<td>4-76 (2-25 to 10-05)*</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>14-0%</td>
<td>3-5%</td>
<td>13-6</td>
<td>4-5 (1-88 to 10-93)*</td>
</tr>
<tr>
<td>Slow acetylator</td>
<td>82-9%</td>
<td>64-2%</td>
<td>5-60</td>
<td>2-72 (1-16 to 6-57)**</td>
</tr>
<tr>
<td>Jaundice in past</td>
<td>11-6%</td>
<td>10-8%</td>
<td>0-001</td>
<td>1-08 (0-49 to 2-35)</td>
</tr>
<tr>
<td>Pyrazinamide in regimen</td>
<td>62-8%</td>
<td>25-1%</td>
<td>44-78</td>
<td>5-03 (2-99 to 8-47)**</td>
</tr>
</tbody>
</table>

* p<0-001; ** p<0-01; *** p<0-1 x 10^-3.
† Yates’ corrected \( \chi^2 \).

Pande Thorax 1996;51:132-136

Rifampin Drug Interactions

- Interactions due to induction of hepatic microsomal enzymes that accelerate metabolism of multiple drugs

- Major concern is reduction in serum concentrations of common drugs (oral contraceptive pills, warfarin, etc.) to ineffective levels

- Bi-directional interactions between rifamycins and antiretroviral agents
Rifampin and Opioids

• Methadone
  – Rifampin lowers the serum concentration of methadone by 33-66%
  – Administration of rifampin to patients on methadone has led to opioid withdrawal in patients on methadone replacement therapy
  – Need to increase methadone dose and monitor carefully to prevent withdrawal with co-administration of rifampin and methadone


• Codeine
  – Administration with rifampin leads to decreased biotransformation to morphine (which is responsible for most of the analgesic effects)
  – Decreased serum concentration with rifampin

• Morphine
  – 28 % decrease in serum levels when given with rifampin
  – Loss of analgesic effect

Rifampin and Benzodiazepines

- Diazepam
  - Reduction of half-life by 76%
  - Enhanced total body clearance by 300%
  - May require a 2-3 fold increase in dose for effect

- Midazolam and Triazolam
  - Decreased serum concentration to 2-4% of controls
  - Ineffective during co-administration with rifampin

Rifampin Drug Toxicities

- Significant decrease in serum levels
  - Phenytoin
  - Valproic acid
  - Carbamazepine
  - Serotonergic antidepressants

Rifampin Drug Interactions

- It is imperative to be aware of all medications a patient is taking when that patient is placed on rifampin.
Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs

Second-Line TB Drugs

- Cycloserine
  - Central Nervous System Effects:
    - headaches, restlessness, suicidal ideation psychosis, seizures (3% 500 mg/day),
    - May exacerbate underlying seizure disorders or mental illness.
    - Pyridoxine at 100-200 mg/day may help prevent neurotoxic side-effect.
  - Peripheral neuropathy
  - Cycloserine does not appear to be associated with hepatotoxicity, but should be used with caution in patients at risk for alcohol withdrawal seizures
Second-Line TB Drugs

• Linezolid
  – Bone marrow suppression
  – Peripheral Neuropathy
  – Optic Neuritis
  – Gastrointestinal Disturbance
  – Rash

Adverse Drug Events
Neurotoxicity

• Peripheral neuropathy
  – Drugs: INH, EMB, (ethionamide, cycloserine)
  – More common in patients with
    • Diabetes
    • Alcoholism
    • HIV infection
    • Hypothyroidism
    • Pregnancy
    • Inadequate dietary intake of pyridoxine (Vitamin B6)
  – Usually symmetrical
  – Initial symptoms: tingling, prickling, burning in balls of feet/tips of toes
    • May progress to sensory loss, loss of reflexes, unsteady gait
    • May also involve hands and fingers
Thanks!!

Questions?

1-800-TEX-LUNG