Disclosures

• None
Disclosures

As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of CPD) must ensure balance, independence, objectivity and scientific rigor in its educational activities. Course Director(s), Planning Committee Members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so those participants in the activity may formulate their own judgments regarding the presentation.

No Relationships

Course Director - Stacey Rizza, M.D

Relevant Financial Relationships

None

Off Label/Investigational Uses

None

Accreditation

Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Mayo Clinic College of Medicine designates this live activity for a maximum of 1 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Mayo Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

Participants can earn up to 1.0 nursing contact hours (accredited).
Drugs FDA Approved for TB

- Aminosalicylate sodium (PAS)
- Capreomycin
- Cycloserine
- Ethionamide
- Ethambutol
- Isoniazid
- Pyrazinamide
- Rifampin
- Rifapentine
- Streptomycin
Drugs not FDA approved for TB

Other Aminoglycosides:
- Amikacin
- Kanamycin

Fluoroquinolones:
- Moxifloxacin
- Levofloxacin
Drugs not FDA approved for TB

Macrolides - generally poor TB drugs:
  Azithromycin
  Clarithromycin
  (indicated for, and primarily useful for, MAC)

Amoxicillin-clavulanate (role not established)
Clofazimine (role being re-evaluated)
Rifabutin (used for TB and MAC)
Linezolid, newer agents Sutezolid and AZD-5847
Outside US: prothionamide, thiacetazone, viomycin
PA-824

- Unique mechanism of action\(^1\)
- Narrow spectrum of activity\(^1\)
- Bactericidal activity in mouse models\(^1-3\)

<table>
<thead>
<tr>
<th></th>
<th>MIC vs. <em>M. tuberculosis</em> H37Rv (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.05</td>
</tr>
<tr>
<td>PA-824</td>
<td>0.25</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.25</td>
</tr>
</tbody>
</table>

\(1\) Stover et al, *Nature* (2000); 405:962
\(2\) Tyagi et al, *AAC* (2005); 49:2289
\(3\) Lenaerts et al, *AAC* (2005); 49:2294
OPC-67683 = Delamanid

- Nitroimidazo - oxazole
- Cross-resistant with PA-824
- Up to 20x more potent than PA-824
- As with PA-824, best companion drug is PZA

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L)</th>
<th>MBD (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>RIF</td>
<td>0.4</td>
<td>10</td>
</tr>
<tr>
<td>OPC-67683</td>
<td>0.012</td>
<td>2.5</td>
</tr>
<tr>
<td>PA-824</td>
<td>0.2</td>
<td>20+</td>
</tr>
</tbody>
</table>

MIC = Minimum inhibitory concentration
MBD = Minimum bactericidal dose (ie, to kill 99% of bacteria)

Otsuka Pharmaceutical Inc.,
Presented at ICAAC, December, 2005
TMC207 = Bedaquiline

Class: Diarylquinoline

• Median MIC = 0.06 µg/ml
• New target: ATP synthase
• Selective activity vs. mycobacteria (including NTM)
• No cross-resistance

Cole & Alzari, Science 2005; 307:214
Isoniazid (INH)

**Role:** primary drug, along with rifampin

**Action:** inhibits cell wall synthesis

**Dosage:** oral, I.M., I.V. (in normal saline only)

**Dose:** 300 mg QD // 10-20 mg / Kg for kids

**Cleared:** liver >> kidneys

**Toxicity:** hepatotoxicity, peripheral neuropathy
Rifampin (RIF)

role: primary drug, along with INH
action: DNA-dependent RNA polymerase
dosage: oral, I.V.
dose: 600 mg QD // 10-20 mg / Kg for kids
cleared: liver >> kidneys
toxicity: hepatotoxicity, flu-like syndrome
Rifabutin (RBN)

- **role:** instead of RIF for HIV+ patients
- **action:** DNA-dependent RNA polymerase
- **dosage:** oral
- **dose:** 300 mg (150 - 450 mg) QD
- **cleared:** liver >> kidneys
- **toxicity:** neutropenia, thrombocytopenia, uveitis
## Rifamycins

<table>
<thead>
<tr>
<th></th>
<th>MIC * (µg / ml)</th>
<th>Cmax ^ (µg / ml)</th>
<th>Ratio</th>
<th>t ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>0.25</td>
<td>12</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.06</td>
<td>0.6</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Rifapentline</td>
<td>0.06</td>
<td>12</td>
<td>200</td>
<td>15</td>
</tr>
</tbody>
</table>

* 7H12 broth ^ total Rx (free and bound)
## Rifamycins

<table>
<thead>
<tr>
<th></th>
<th>CYP 3A4 induction</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>1.00</td>
<td>flu-like syndrome</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.40</td>
<td>uveitis, neutropenia</td>
</tr>
<tr>
<td>Rifapentidine</td>
<td>0.85</td>
<td>98% protein bound</td>
</tr>
</tbody>
</table>
Pyrazinamide (PZA)

role: primary drug, first 2 months
action: via metabolite pyrazinoic acid
dosage: oral
dose: 25 - 30 mg / Kg QD (adults and kids)
cleared: liver, then metabolites via kidneys
toxicity: hepatotoxicity, elevated uric acid
Ethambutol (EMB)

- **Role:** “fourth drug” in case of resistance
- **Action:** inhibits cell wall synthesis
- **Dosage:** oral, (I.V. in Europe)
- **Dose:** 15 - 25 mg / Kg QD (adults and kids)
- **Cleared:** kidneys >> liver
- **Toxicity:** ocular toxicity, rashes
Streptomycin (SM)

role: “fourth drug” in case of resistance

action: inhibits protein synthesis

dosage: I.M., I.V.

dose: 12 - 15 mg / Kg QD (adults and kids)

cleared: kidneys

toxicity: ototoxicity, nephrotoxicity, cation loss
Amikacin (AK)
Kanamycin (KM)
Capreomycin (CM) *

role: drug resistant TB
action, PK, toxicity: same as streptomycin

* CM is a polypeptide
Levofloxacin (Levo)

**role:** drug resistant TB

**action:** inhibits DNA gyrase

**dosage:** oral, I.V.

**dose:** 750 - 1000 mg QD

**cleared:** kidneys

**toxicity:** caffeine like effects, GI, tendonitis
Moxifloxacin (Moxi)

- **Role:** drug resistant TB
- **Action:** inhibits DNA gyrase
- **Dosage:** oral, I.V.
- **Dose:** 400 mg QD
- **Cleared:** kidneys and liver
- **Toxicity:** caffeine like effects, GI, tendonitis
Ethionamide (ETA)

role: drug resistant TB

action: inhibits cell wall synthesis

dosage: oral

dose: 250 - 500 mg BID //

10 - 20 mg / Kg divided BID for kids

cleared: liver

toxicity: GI upset, hypothyroidism
p-Aminosalicylic Acid (PAS)

role: drug resistant TB

action: not known

dosage: oral

dose: 4000 mg BID - TID //

150 mg / Kg divided BID - TID for kids

cleared: liver >> kidneys

toxicity: GI upset, hypothyroidism
Cycloserine (CS)

role: drug resistant TB

action: inhibits cell wall synthesis

dosage: oral

dose: 250 - 500 mg BID //

10 - 20 mg / Kg divided BID for kids

cleared: kidneys

toxicity: lack of concentration, altered behavior
How Do Antibiotics Work?

For every drug with a proven mechanism of action, this action involves the drug entering the organism, binding to a target, and producing an inhibitory or lethal effect.
How Do Antibiotics Work?

For every drug given orally or parenterally, the only way for the drug to reach the bug is through the blood stream.
How Do Antibiotics Work?

If it ain’t in the blood,

it ain’t in the bug.

Therefore, pharmacokinetics matters…
How Do Antibiotics Work?

For most patients, drug treatment makes up 100% of the TB treatment.

If you get the drug treatment wrong, you just got 100% of the TB treatment wrong.
Pharmacokinetics (PK)

The study of the movement of drugs through the body.

Most commonly based on the study of serum concentrations in relation to dose, with interpretation and dose adjustment.
PK: Plasma Elimination Half-Life

t\( \frac{1}{2} \) is defined as the time for concentrations (in plasma) to decline by 50%.

After 7 \( t\frac{1}{2} \)'s, nearly all of the drug is gone, regardless of the starting concentration.

t\( \frac{1}{2} \) is independent of dose and concentration.
INH Slow Acetylator over 24 h

Ln Conc (mcg / ml) vs Time (h)

- 300 mg
- 900 mg
t 1/2 is inversely proportional to the clearance of a drug (Cl).

Clearance can be thought of as the size of the drain in the bathtub.

A big drain will empty the tub faster.
PK: Clearance

**Clearance organs:**
- **Kidneys:** especially water soluble drugs
  - creatinine clearance might predict
- **Liver:** metabolize drugs to make water sol.
  - AST, ALT usually do not predict

[ minor: lungs, skin, saliva… ]
PK: Volume of Distribution

t_{1/2} is directly proportional to the volume of distribution (V).

V can be viewed as the size of the bathtub. Big tubs take a longer time to drain.

t_{1/2} is viewed as a proportionality constant, dependent upon Cl and V.
**PK: Volume of Distribution**

Large volumes of distribution typically reflect drug penetration into tissues which return the drug to the plasma space only slowly.

Drug molecules inside of tissues are unavailable to the organs of clearance.
The most common parameters clinically are Cmax (peak), Cmin (trough), Tmax, & t1/2.

Simple kinetics can be done with a calculator, or with a spreadsheet.

The most common calculations involve linear regression (fitting a straight line to data).
Example: Amikacin Kinetics

<table>
<thead>
<tr>
<th>Two Sample Conc</th>
<th>Infusion Hrs post dose</th>
<th>Ln Conc</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.30</td>
<td>2.00</td>
<td>3.27</td>
</tr>
<tr>
<td>9.40</td>
<td>6.00</td>
<td>2.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>ke</th>
<th>t 1/2</th>
<th>Cmax</th>
<th>Cmax intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.26</td>
<td>3.78</td>
<td>0.257</td>
<td>2.69</td>
<td>43.99</td>
<td>43.99</td>
</tr>
</tbody>
</table>
Pharmacokinetics (PK)

Approaches:
Non-compartmental analysis (NCA):

Provides a general description of drug behavior, typically using Cmax, Tmax, and AUC.

Assuming that the terminal slope is log-linear, NCA provides an estimate of Kel and t1/2.
Pharmacokinetics (PK)

Approaches:
Compartmental analysis:

Provides a good description of drug behavior using a structural (compartmental) model

Typically needs many data points in order to get precise PK parameter estimates
Pharmacokinetics (PK)

Approaches:
Compartmental analysis:

Allows for simulation of future scenarios
“What if…?”

Remember –
“All models are wrong…
but some models are useful”
Pharmacokinetics (PK)

Approaches:
Population PK analysis:

Provides a good description of drug behavior using a structural (compartmental) model

Often requires fewer data points per subject than typical a compartmental analysis
Pharmacodynamics (PD)

the study of the relationships between drug concentrations and responses

Methods

• in vitro models
• animal models
• human clinical trials with dose escalation
ID: Usual PK - PD Response Parameters

- Cmax / MIC
- Time > MIC
- AUC > MIC
**PD: Response Parameters**

- **Cmax** = 9 mcg/ml
- **MIC** = 3 mcg/ml
- **Cmax / MIC** = 3
- **T > MIC** = 8 h
- **AUC** (mcg * h / ml)

Graph showing:
- **Cmax** = 9 mcg/ml
- **MIC** = 3 mcg/ml
- **AUC > MIC**
- **T > MIC** = 8 h
ETHIONAMIDE

![Graph showing the concentration over time for ETHIONAMIDE with a peak at 'eta' and a horizontal line indicating MIC at 1.0.](image)
"Concentration-dependent" antimicrobials best given as large (daily) doses

- aminoglycosides, quinolones, RIFAMYCINS (based on *in vitro*, animal and human data)

- target a $\frac{C_{\text{max}}}{MIC}$ of at least 10 - 12
### PD: Sterilizing Activity of Rifampin

<table>
<thead>
<tr>
<th>Week</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
<th>20 mg/kg</th>
<th>40 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung week 1</td>
<td>100,000,000 CFU</td>
<td>100,000,000 CFU</td>
<td>100,000,000 CFU</td>
<td>100,000,000 CFU</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>10,000 CFU</td>
<td>100</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>% reduction</td>
<td>99.990000%</td>
<td>99.99990%</td>
<td>99.99999%</td>
<td>100.000000%</td>
</tr>
</tbody>
</table>

PD: Sterilizing Activity of Rifampin

Mean value after 600 mg oral dose

Jayaram et al, AAC (2003); 47:2118
Drug Concentration (µg/ml)

Evans, 1986
**Rifampin 600 mg in Humans**

Cumulative percentage culture negative

<table>
<thead>
<tr>
<th>month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRZS</td>
<td>38</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>HRZE</td>
<td>35</td>
<td>77</td>
<td>99</td>
</tr>
</tbody>
</table>

H 300 mg, S 750 mg, Z 35 mg / Kg, E 25 mg / Kg


Average patient weight about 48 Kg
Rifampin 1200 mg in Humans

Cumulative percentage culture negative

<table>
<thead>
<tr>
<th>month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS QD</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>HRS QOD</td>
<td>70</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

H 900 mg, S 1000 mg QD both regimens
## Rifampin 600 mg vs. 1200 mg

<table>
<thead>
<tr>
<th>Month</th>
<th>Cumulative percentage culture negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>HRZS QD</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>900 mg</td>
</tr>
<tr>
<td>R 600 mg, with Z</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
</tr>
<tr>
<td>HRS QD</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>900 mg</td>
</tr>
<tr>
<td>R 1200 mg, NO Z</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>900 mg</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
</tr>
</tbody>
</table>
Flu-like syndrome was NOT reported by Kreis et al (3 months of treatment).

Even with highly-intermittent RIF, syndrome usually appears after 3 to 6 months.

Association between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and TB [Study 23A].


Clinical Infectious Diseases 2005; 40: 1481 - 1491.
Lesser INH AUC in Study 23A ARR versus 23A cure versus 22PK cure and HIV-seronegative

<table>
<thead>
<tr>
<th>Group</th>
<th>Study (N)</th>
<th>Outcome</th>
<th>AUC$_{0-12}$ Med (IQC)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23 (6)</td>
<td>ARR HIV (+)</td>
<td>20.6 (11.4 - 23.6)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>23 (79)</td>
<td>Cure HIV (+)</td>
<td>28.0 (16.4 - 44.8)</td>
<td>0.26 A vs B</td>
</tr>
<tr>
<td>C</td>
<td>22 (39)</td>
<td>Cure HIV (-)</td>
<td>52.9 (32.2 - 67.8)</td>
<td>0.0001 B vs C</td>
</tr>
</tbody>
</table>

P = 0.0002, Kruskal-Wallis

Isoniazid dose 15 mg/kg to 900 mg, prospective PK

* P-Value by Mann-Whitney
Lesser rifabutin AUC with ARR versus cure

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Dose mg/kg Med (IQC)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; Med (IQC)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>6</td>
<td>4.6 (3.5 - 5.7)</td>
<td>3.1 (2.0 - 3.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>CURE</td>
<td>82</td>
<td>4.8 (4.2 – 6.2)</td>
<td>5.1 (4.0 - 7.4)</td>
<td></td>
</tr>
</tbody>
</table>

* P for RBT AUC ARR vs. cure, Mann-Whitney
Where Does TB Drug PK Data Come From?

Data were compiled from all available sources (both healthy volunteers and TB patients) by:

Mack Holdiness Clin Pharmacokinet. 1984; 9 (6) : 511 - 44

Charles Peloquin (1991 and later)

Global Alliance for TB Drug Development

Handbook of Anti-Tuberculosis Agents 2008

among others …
CHAPTER 2
ANTITUBERCULOSIS DRUGS: PHARMACOKINETICS
Charles A. Peloquin, Pharm.D.


191 references
Therapeutic Drug Monitoring (TDM)

aims to promote optimum drug treatment by maintaining serum drug concentrations within a "normal range," or preferably a "therapeutic range"
Malabsorption, or lack of blood flow to the site of infection, lead to treatment failures and to the selection of resistance.

The question: Standardized treatment for everyone, and if they don’t respond, continue the same tx,

Or

See why this is happening, adapt, and overcome.
Role for Therapeutic drug monitoring

Slow responses to TB treatment are common, as shown on the next slide.

While many of these slow responses are due to treatment interruptions (adverse drug reactions, patients leaving treatment programs, etc.), in our experience, a substantial portion of these are due to poor drug absorption.
Completion of TB Therapy, United States, 1993 – 2010*

* Updated as of June 10, 2013. Data available through 2010 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy. Excludes persons with initial isolate rifampin resistant, or patient with meningeal disease, or pediatric patient (aged <15) with miliary disease or positive blood culture.
Completion of TB Therapy, United States, 1993 – 2010*

• Updated as of June 10, 2013.
• Data available through 2010 only.

Note: **Includes** persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy.  
**Excludes:** rifampin resistant TB, meningeal disease, or pediatric patients (aged <15) with miliary disease or positive blood culture.
TB Treatment Is Guideline-Driven

The standard claim is that TB can be treated with a 6-month regimen that has roughly 98% success, followed by about 3% relapses, for about a 95% overall cure.
Completion of TB Therapy, United States, 1993 – 2010*

• So, what percentage of US TB patients complete the 6-month regimen in 6 months?
# Length of Treatment in the US

<table>
<thead>
<tr>
<th>Treatment month</th>
<th>Completed therapy ≤1 year indicated**</th>
<th>% of those COT-eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>COT within 6 months or less</td>
<td>1709</td>
<td>18.0%</td>
</tr>
<tr>
<td>COT by 7 months</td>
<td>4257</td>
<td>44.9%</td>
</tr>
<tr>
<td>COT by 8 months</td>
<td>5003</td>
<td>52.8%</td>
</tr>
<tr>
<td>COT by 9 months</td>
<td>5956</td>
<td>62.8%</td>
</tr>
<tr>
<td>COT by 10 months</td>
<td>7426</td>
<td>78.3%</td>
</tr>
<tr>
<td>COT by 11 months</td>
<td>7865</td>
<td>83.0%</td>
</tr>
<tr>
<td>COT by 12 months</td>
<td>8354</td>
<td>88.1%</td>
</tr>
</tbody>
</table>
Remember, this is supposed to be a 6-month “short-course” therapy.

If it takes 12 to 18 months, it is no longer “short-course” therapy.

\[
18 / 6 = 3
\]
In theory, there is no difference between theory and practice. In practice, there is.

Yogi Berra
PD: Sterilizing Activity of Rifampin

A

Log$_{10}$ cfu/lung

Mean value after 600 mg oral dose

AUC/MIC

Jayaram et al, AAC (2003); 47:2118
most useful when there is a direct relationship between serum concentrations and therapeutic response, and when serum concentrations serve as a surrogate for drug concentrations at the site of action
TDM

most important when there is a narrow range of concentrations that are effective and safe, and when toxicity or lack of effectiveness puts the patient at great risk
in conjunction with other clinical data, allows for an assessment of the patient's status, and for timely therapeutic interventions
The decision to use TDM is the same as the decision to check a CBC with diff., or the decision to get a CT or MRI.

None of these guarantee the outcome of Tx.

However, all of these inform the clinician prior to making clinical decisions.