Objectives

- Describe general principles of antimicrobial use including:
  - Pharmacokinetic principles of absorption, distribution, metabolism, half-life, clearance and elimination.
  - Monitoring for toxicity/efficacy.
- Describe the spectrum of activity, mechanism of action, routes of administration, adverse effects, common drug interactions of antmycobacterial agents.
- Identify the uses of therapeutic drug monitoring.

Drugs FDA Approved for TB

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>API Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylate sodium (PAS)</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Rifapentine</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Streptomycin</td>
</tr>
</tbody>
</table>
**Drugs not FDA Approved for TB**

**Other Aminoglycosides:**  
Amikacin  
Kanamycin

**Fluroquinolones:**  
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

**Pediatric Considerations**

**Maturation**
Small children cannot swallow adult dosage forms.

Extemporaneous dosage forms (example: crushed tablets mixed with food) may have variable oral absorption, and may not be stable for storage.
Pediatric Considerations

Maturation
Total body water is highest in infants, and decreases over the first few years of life.

Drugs that distribute into water may have lower plasma concentrations in young children. (aminoglycosides, ethambutol, cycloserine and isoniazid are examples)

Pediatric Considerations

Maturation
Renal function is below that of adults at birth, and increases over the first 6-12 months of life.

Renally cleared drugs may need adjustment. (aminoglycosides, ethambutol, cycloserine are examples)

Pediatric Considerations

Maturation
Total clearance (renal plus hepatic) often is faster in children than in adults.

Equivalent doses (mg per kg) will often produce lower plasma concentrations in children.
Pediatric Considerations

**Maturation**
Combined, the previously listed factors typically mean that children need higher mg per kg doses than adults after the first 6 – 12 months of life.

---

**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 - 15 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
Rifapentine (RPNT)

**Role:** Primary drug, along with INH

**Action:** DNA-dependent RNA polymerase

**Dosage:** Oral

**Dose:** 1200 mg QD* // (20 mg/Kg for kids)

**Cleared:** Liver >> kidneys

**Toxicity:** Hepatotoxicity, flu-like syndrome

---

Rifapentine Pharmacokinetics and Tolerability in Children and Adults

Treated Once Weekly

With Rifapentine and Isoniazid

for Latent Tuberculosis Infection (Study 26)

---

**Conclusions.** A 2-fold greater rifapentine dose for all children resulted in a 1.3-fold higher AUC compared to adults administered a standard dose.

**Use of higher weight-adjusted rifapentine doses for young children are warranted to achieve systemic exposures that are associated with successful treatment of latent tuberculosis infection in adults.
### Rifabutin (RBN)

<table>
<thead>
<tr>
<th>Role</th>
<th>instead of RIF for HIV+ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>DNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Dosage</td>
<td>oral</td>
</tr>
<tr>
<td>Dose</td>
<td>300 mg (150 - 450 mg) QD //</td>
</tr>
<tr>
<td></td>
<td>Pediatric data lacking (est. 5 mg/kg)</td>
</tr>
<tr>
<td>Cleared</td>
<td>Liver &gt;&gt; kidneys</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Neutropenia, thrombocytopenia, uveitis</td>
</tr>
</tbody>
</table>

### Rifamycins

<table>
<thead>
<tr>
<th>CYP 3A4 Induction</th>
<th>Unique Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>1.00</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.40</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>≥1.00 (daily)</td>
</tr>
</tbody>
</table>

- Rifampin: flu-like syndrome
- Rifabutin: uveitis, neutropenia
- Rifapentine: 98% protein bound

### Pyrazinamide (PZA)

<table>
<thead>
<tr>
<th>Role</th>
<th>Primary drug, first 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Via metabolite pyrazinoic acid</td>
</tr>
<tr>
<td>Dosage</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose</td>
<td>25 - 30 mg/Kg QD // 35 mg/Kg for kids</td>
</tr>
<tr>
<td>Cleared</td>
<td>Liver, then metabolites via kidneys</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Hepatotoxicity, elevated uric acid</td>
</tr>
</tbody>
</table>
**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:** Formerly a “fourth drug” in case of resistance  
**action:** inhibits protein synthesis  
**dosage:** I.M., I.V.  
**dose:** 15 - 30 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 // 15 – 20mg/Kg for kids
cleared: kidneys
toxicity: CNS effects, GI, tendonitis

Moxifloxacin (Moxi)
role: drug resistant TB
action: inhibits DNA gyrase
dosage: oral, i.V.
dose: 400 mg QD // pediatric data lacking
cleared: kidneys and liver
toxicity: CNS effects, GI, tendonitis, QTc prolongation (rare)

Ethionamide (ETA)
role: drug resistant TB
action: inhibits cell wall synthesis
dosage: oral
dose: 250 - 500 mg BID // 15 - 20mg/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.

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.
Pharmacodynamics (PD)

- the study of the relationships between drug concentrations and responses

Methods
- in vitro models
- animal models
- human clinical trials with dose escalation

Pharmacodynamics (PD)

Evans, 1986

ID: Usual PK-PD Response Parameters

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

“Concentration-dependent” antimicrobials best given as large (daily) doses

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

- target a \( \frac{C_{\text{max}}}{\text{MIC}} \) 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>CFU</td>
<td>100,000,000</td>
<td>100,000,000</td>
<td>100,000,000</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>CFU</td>
<td>10,000</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>% reduction</td>
<td>%</td>
<td>99.99900%</td>
<td>99.99990%</td>
<td>99.99999%</td>
</tr>
</tbody>
</table>

**PD: Sterilizing Activity of Rifampin**

- Mean value after 600 mg oral dose

Jayaram et al, AAC (2003); 47:2118

---

**PD: Sterilizing Activity of Rifapentine**

- Study 29X Conclusions: Daily rifapentine was well tolerated and safe. High rifapentine exposures were associated with high levels of sputum sterilization at completion of intensive phase.
PD: Response Data

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.
Issues with standard doses

- 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 low drug exposure.

Completion of TB Therapy, United States, 1993 – 2010

* Updated as of June 10, 2013. Data includes January through December only.

Note: Includes persons with a diagnosis of TB, regardless of age or race. Includes persons with a new or previously treated infection. Excludes persons with a history of TB, as well as persons who received TB treatment in another country or who were treated in the United States by local health departments, private physicians, or nurse practitioners.
**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>
So what?

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.

Dosing Drugs

It is not possible to give drugs for the explicit purpose of avoiding toxicity.

To guarantee no toxicity, do not give the drug.

Dosing Drugs

If you give the drug, you must accept some probability of toxicity.

The best way to avoid toxicity is to give the most effective doses for the shortest possible time.
Therapeutic Drug Monitoring (TDM)

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

Therapeutic Drug Monitoring

Доверяй, но проверяй (doveryai, no proveryai)

(Trust but Verify)

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http://idpl.pharmacy.ufl.edu/