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**Advanced Concepts in Pediatric TB:
Pharmacotherapeutics of TB Drugs**





UF UNIVERSITY OF FLORIDA
The Foundation for The Better Nation
June 12, 2015

Charles A. Peloquin, Pharm. D.
Professor, and Director
Infectious Disease Pharmacokinetics Laboratory
College of Pharmacy and
The Emerging Pathogens Institute
University of Florida



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 antimycobacterial agents.
- Identify the uses of therapeutic drug monitoring.



Drugs FDA Approved for TB

Aminosalicylate sodium (PAS)	Isoniazid
Capreomycin	Pyrazinamide
Cycloserine	Rifampin
Ethionamide	Rifapentine
Ethambutol	Streptomycin



Drugs not FDA Approved for TB

Other Aminoglycosides:	Fluoroquinolones:
<u>Amikacin</u>	<u>Moxifloxacin</u>
Kanamycin	<u>Levofloxacin</u>

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

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Rifapentine (RPNT)
 Rifapentine Pharmacokinetics and Tolerability in Children and Adults
 Treated Once Weekly
 With Rifapentine and Isoniazid
 for Latent Tuberculosis Infection (Study 26)


UF UNIVERSITY of FLORIDA J Ped Infect Dis June 2014 3:2 132- 145. Southeastern National Tuberculosis Center

Rifapentine (RPNT)

- 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.


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Rifabutin (RBN)
role: instead of RIF for HIV + patients
action: DNA - dependent RNA polymerase
dosage: oral
dose: 300 mg (150 - 450 mg) QD //
 pediatric data lacking (est. 5 mg / kg)
cleared: liver >> kidneys
toxicity: neutropenia, thrombocytopenia, uveitis




Rifamycins


	CYP 3A4 induction	Unique features
Rifampin	1.00	flu - like syndrome
Rifabutin	0.40	uveitis, neutropenia
Rifapentine	≥ 1.00 (daily)	98% protein bound




Pyrazinamide (PZA)
role: primary drug, first 2 months
action: via metabolite pyrazinoic acid
dosage: oral
dose: 25 - 30 mg / Kg QD // 35 mg / Kg for 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: 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 - 20* mg / Kg for kids
cleared: kidneys
toxicity: CNS effects, GI, tendonitis


 • Pharmacokinetics and Dosing of Levofloxacin in Children (manuscript in press)
 

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 - 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.



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.



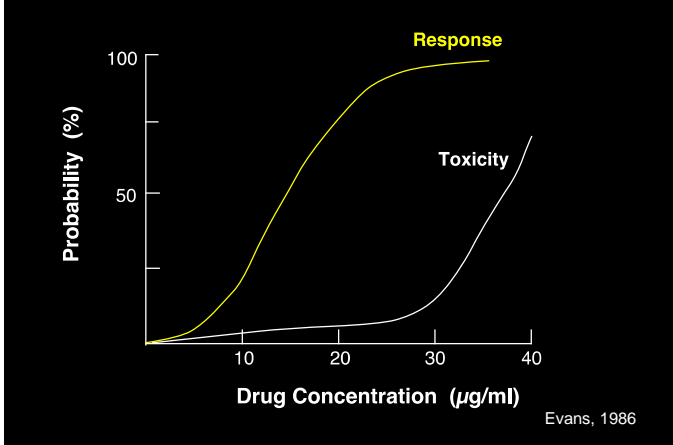
Pharmacodynamics (PD)

the study of the relationships between drug concentrations and responses

Methods

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

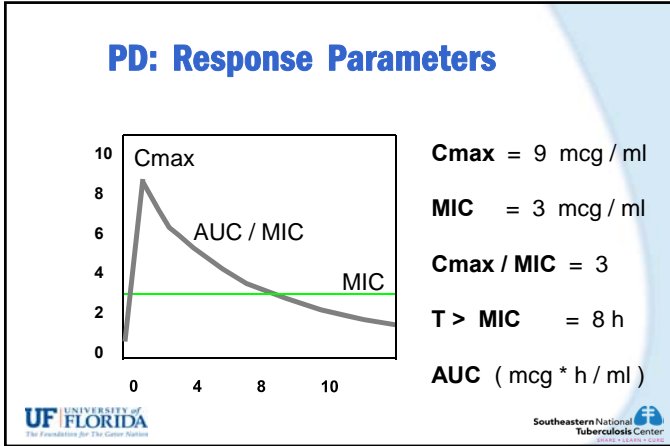




ID: Usual PK - PD Response Parameters

- Cmax / MIC
- AUC / MIC
- Time > MIC





PD: Response Parameters

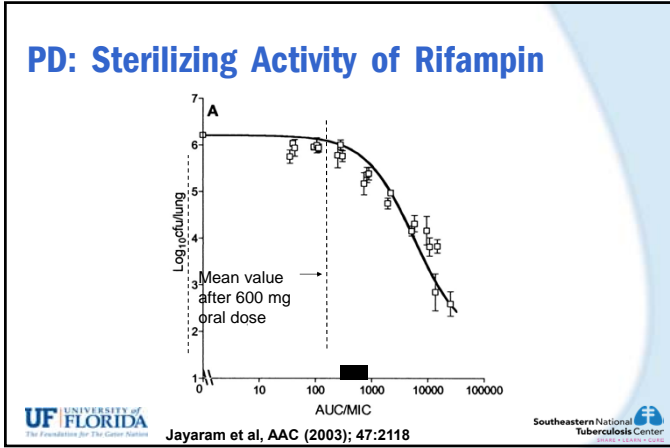
“Concentration - dependent” antimicrobials best given as large (daily) doses

- aminoglycosides, quinolones, RIFAMYCINS (based on *in vitro*, animal and human data)
- target a C_{max} / MIC of at least 10 - 12

PD: Sterilizing Activity of Rifampin

Week		5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg
Lung week 1	CFU	100,000,000	100,000,000	100,000,000	100,000,000
Lung week 10	CFU	10,000	100	10	0
% reduction		99.99000%	99.99990%	99.99999%	100.00000%

Verbist L. Acta Tuberculosa et Phneumolgia Belgica 1969; number 3 - 4: 397 - 412.



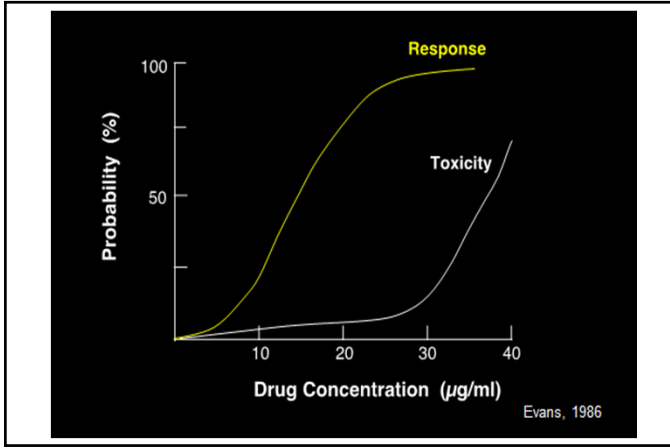
PD: Sterilizing Activity of Rifapentine

- 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.

* Am J Respir Crit Care Med. 2015; 191: 333 - 343

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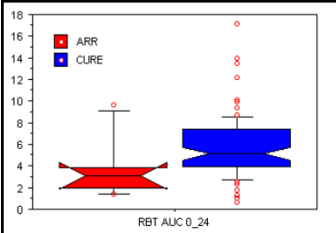
PD: Response Data

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

Weiner M, Benator D, Burman W, Peloquin CA, Khan A, Vernon A, Jones B S, Silva-Trigo C, Zhao Z, Hodge T and the Tuberculosis Trials Consortium

University of Florida Clinical Infectious Diseases 2005; 40: 1481 - 1491. Southeastern National Tuberculosis Center

Example : Lower rifabutin AUC with Acquired Rifamycin Resistance (ARR) versus cure



Group	No.	Dose mg/kg Med (IQC)	AUC _{0,24} Med (IQC)	P-Value*
ARR	6	4.6 (3.5 - 5.7)	3.1 (2.0 - 3.8)	
CURE	82	4.8 (4.2 - 6.2)	5.1 (4.0 - 7.4)	0.04

* P for RBT AUC ARR vs. cure, Mann-Whitney
 * ARR Odds ratio for RBN AUC = 23
 * ARR Odds ratio for CD4 count = 1.04

Clinical Infectious Diseases 2005; 40: 1481 - 1491.

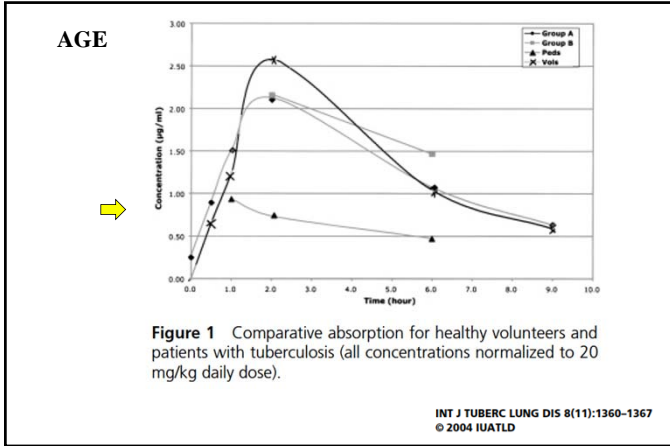
INT J TUBERC LUNG DIS 8(11):1360-1367 © 2004 IUATLD

Pharmacokinetics of ethambutol in children and adults with tuberculosis

M. Zhu,* W. J. Burman,* J. R. Starke,* J. J. Stambaugh,* P. Steiner,* A. E. Bulpitt,* D. Ashkin,* B. Auclair,* S. E. Berning,** R. W. Jelliffe,**†† G. S. Jaresko,**††† C. A. Peloquin,**§§§

Table 2 Median NPEM PK estimates of ethambutol in TB patients

	Adults		Children Group C (n = 14)	Volunteers (n = 16)	AGE
	Group A (n = 38)	Group B (n = 18)			
Ka (h ⁻¹)	0.68	0.68 fixed	0.68 fixed	0.37	
Kel (h ⁻¹)	0.22	0.23	0.33	0.38	
t ^{1/2} (h)	3.15	3.08	2.10	1.82	
V/F (L)	420	343	207	296	
V/F (L/kg)	6.02	6.03	13.21	3.77	
Cl/F (L/h)	86	75	60	99	
Cl/F (L/h/kg)	1.26	1.42	4.40	1.35	

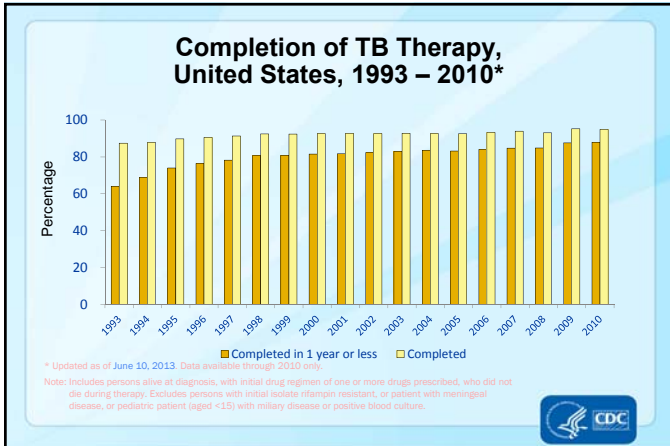


Issues with standard doses

- 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.


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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

Completion of therapy by month, 2010*

Treatment month	Completed therapy ≤1 year indicated**	% of those COT-eligible
COT within 6 months or less	1709	18.0%
COT by 7 months	4257	44.9%
COT by 8 months	5003	52.8%
COT by 9 months	5956	62.8%
COT by 10 months	7426	78.3%
COT by 11 months	7865	83.0%
COT by 12 months	8354	88.1%

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.



$18 / 6 = 3$

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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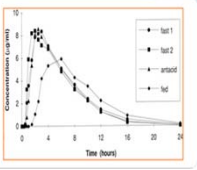
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Pharmacokinetics
Laboratory at
the University of Florida**



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

