Therapeutic Drug Monitoring Of Newer Compounds

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

Disclaimer

Dr. Peloquin does not have any conflicts of interest.

He directs a not – for – profit clinical lab that provides TDM.

The lab does not pay is salary, and he does not work on commission.

Outline

What is TDM ?

General PK PD principles

Specific TB drugs by WHO grouping

Conclusions

What is TDM ?

Therapeutic drug monitoring (TDM) is the use of serum or plasma concentration data in the clinical setting to achieve the desired drug exposures in a given patient.

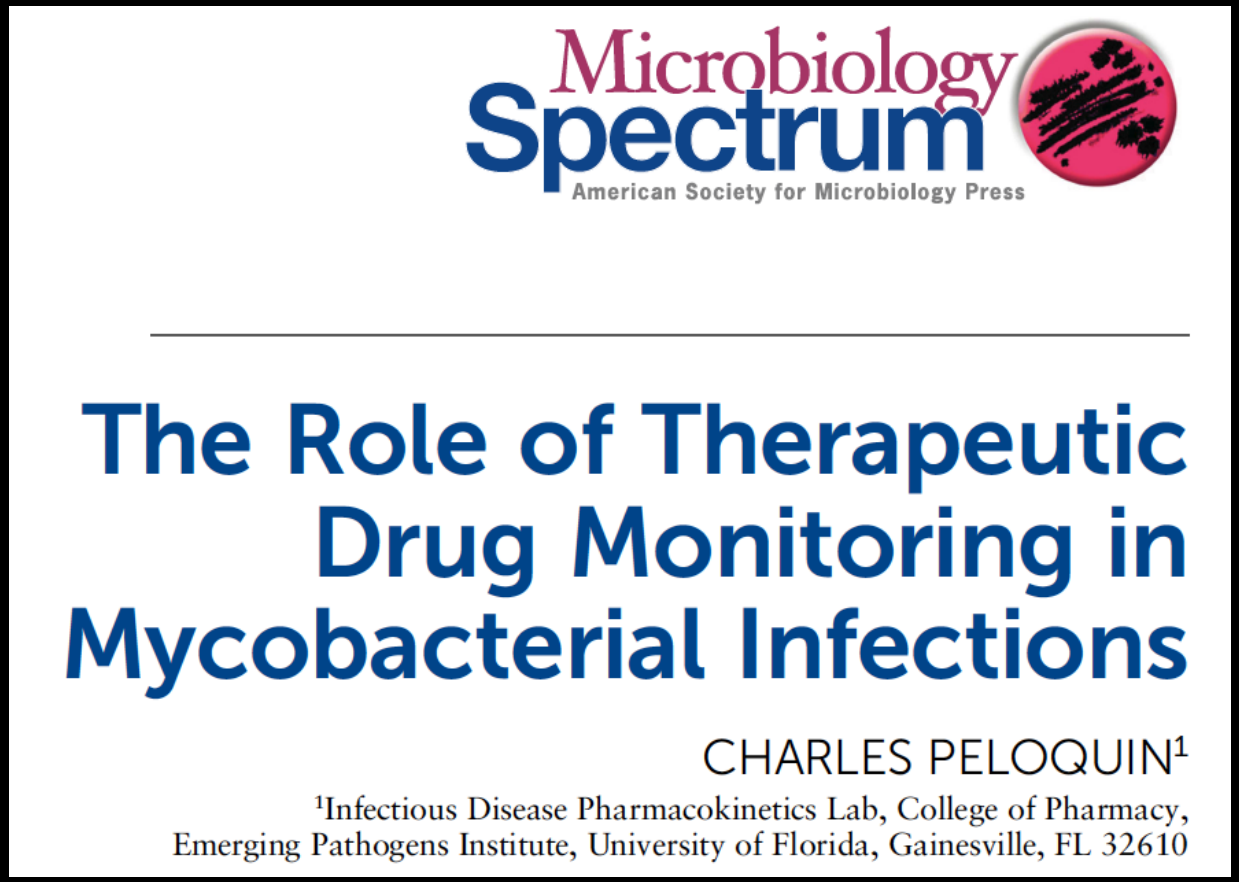
Key references on TDM

Jelliffe R.

Goal - oriented, model - based drug regimens: setting individualized goals for each patient.

Ther Drug Monit **2000**; 22: 325 – 329.

Key references on TDM



Microbiol Spectrum 5(1):TNMI7-0029-2016. doi:10.1128/microbiolspec.TNMI7-0029-2016.

National Jewish ID Team, Circa 1997

How Do Antibiotics Work ?

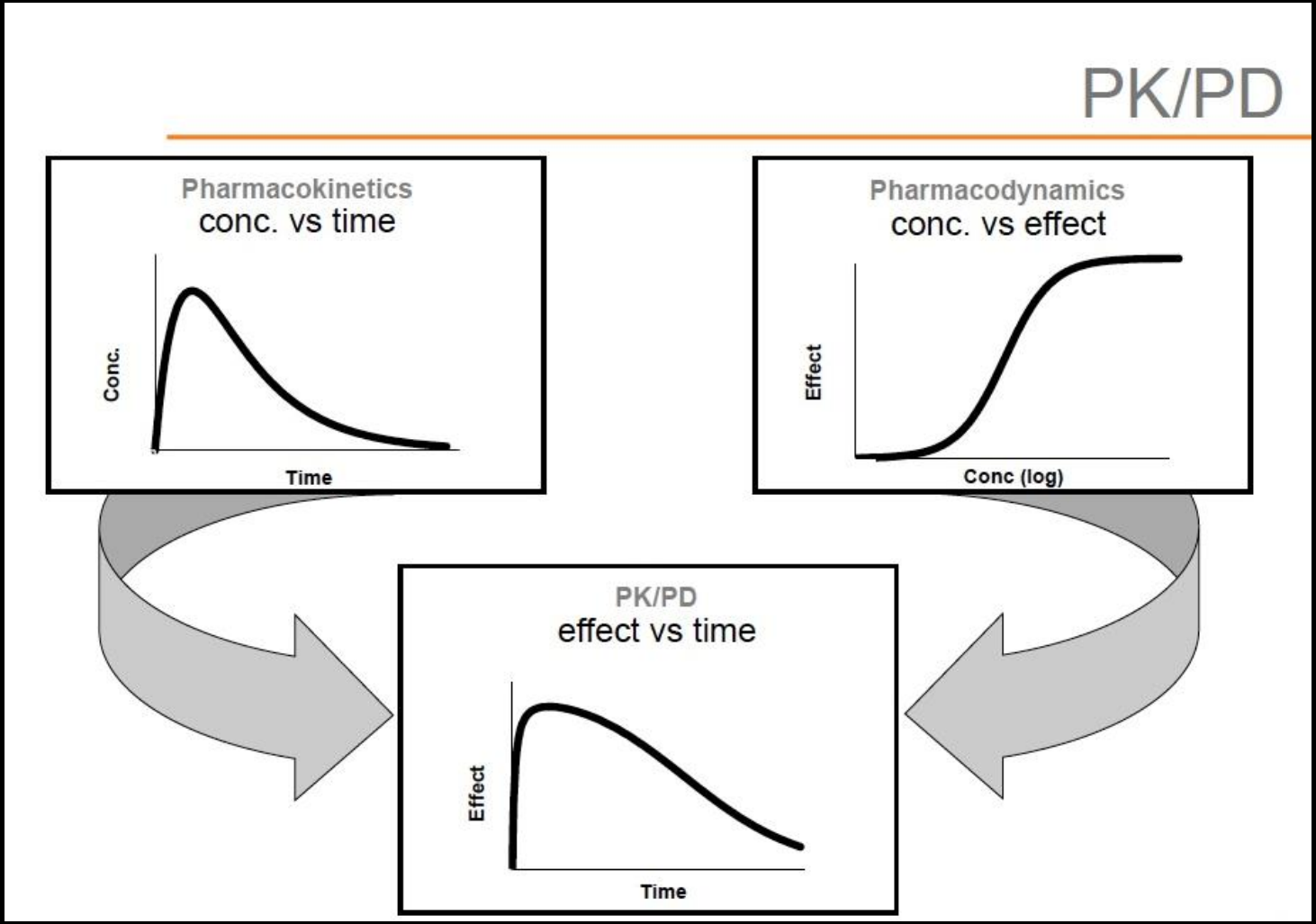
A drug must enter the organism,

bind to a specific target,

and produce an inhibitory or lethal effect.

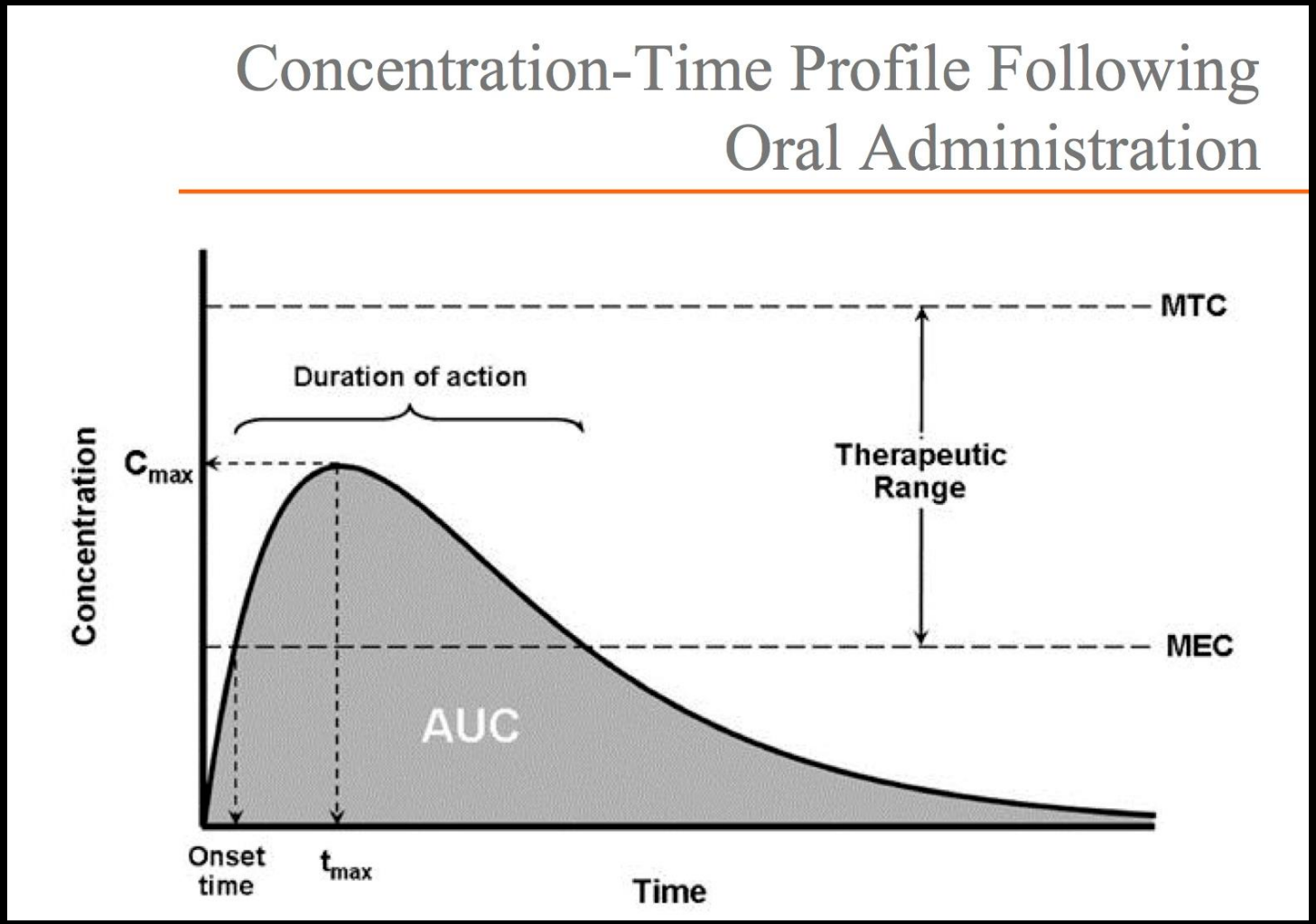
Unless the drug is delivered to the site of infection (PK), nothing happens (PD).

PK and PD



Meibohm and Derendorf

Pharmacodynamics （PD）



Meibohm and Derendorf

How do we know TB Drug PD ?

Various *in vitro* methods, including hollow fiber systems (HFS), show the activity of each drug against *M. tuberculosis.*

Nearly all TB drugs except beta lactams, cycloserine, and linezolid show a clear relationship with AUC / MIC.

How do we know TB Drug PD ?

For the excepted drugs beta lactams, cycloserine, and linezolid, a clear relationship has been shown with Cmin / MIC. That is, the trough concentration (or time above MIC) is the PD – linked variable.

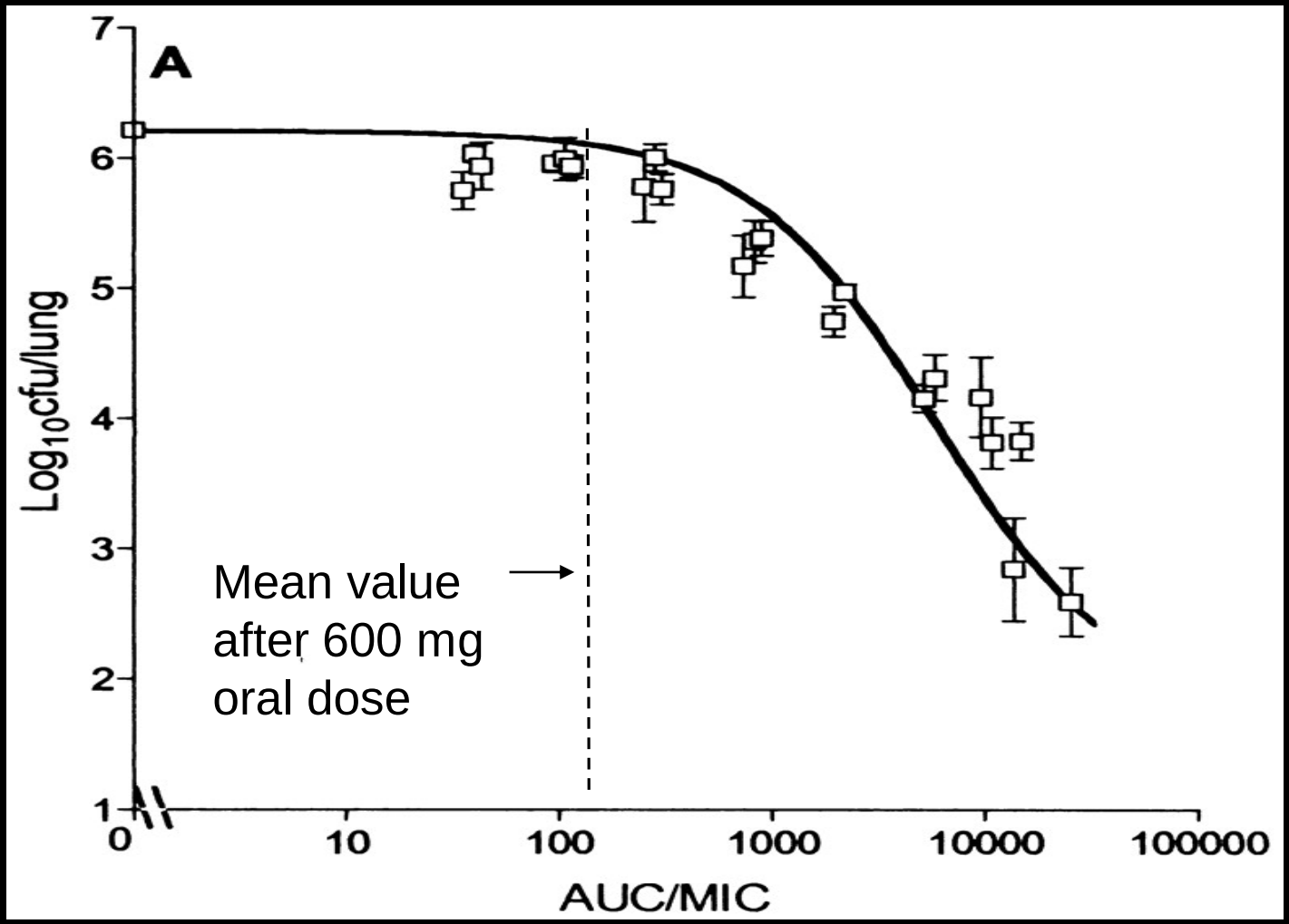
Cmin also is linked to linezolid bone marrow suppression.

How do we know TB Drug PD ?

Next, animal model data from mice, rabbits, and macaques provides mammalian system data. The results have been very consistent with the hollow fiber system data.

In both types of models, the timing of the infection and the timing of the drug therapy are strictly controlled.

PD: Sterilizing Activity of Rifampin



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

How do we know TB Drug PD ?

Finally, we have clinical trial data. These data are the most complex data, and very few variables can be controlled effectively. Patients are heterogeneous.

We do not know when the infection occurred nor when the disease process actually started. Clinical manifestations vary (location and extent of cavities, etc.)

We cannot fully control or eliminate concurrent illnesses.

How do we know TB Drug PD ?

Despite these major limitations, recent studies clearly show concentration – response relationships.

This has been most clearly demonstrated with **high dose rifampin and high dose rifapentine.**

Daily Rifapentine for Treatment of Pulmonary Tuberculosis

RPNT doses per se did not predict the clearance of *Mtb* from the sputum.

High RPNT exposures (AUC) were associated with high levels of sputum sterilization at the completion of 8 weeks of treatment (end of intensive phase)

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

Summary of PD Data

Housing, nutrition and supportive care are important, but are not the primary means of treatment.

Surgery is seldom used as a primary modality.

Summary of PD Data

If you use drug susceptibility testing for clinical decision making, you are accepting PK PD principles (even if you don't know it).

Susceptible only applies to achievable concentrations in humans. If you do not achieve those concentrations, the organism is resistant.

Summary of PD Data

TB therapy is based upon drug therapy.

All of the drugs have exposure – response relationships.

If you do not control exposure, you cannot control the drug therapy.

Summary of PD Data

Adherence to therapy is essential, because a missed dose produces an AUC of zero.

The goal of adherence is not to produce “any” AUC. The goal is to produce an effective AUC.

Summary of PD Data

Humans are outbred and very diverse.

Giving all patients the same dose simply cannot produce an effective AUC in all of them.

Again, if you do not control exposure,
you cannot control the drug therapy.

Second - Line TB Drugs

The WHO rapid communication August 2018

Group A: Medicines to be prioritized:
levofloxacin / moxifloxacin, bedaquiline and linezolid

Group B: Medicines to be added next:
clofazimine, cycloserine / terizidone

Group C: Medicines to complete the regimens:
ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide / prothionamide, p-aminosalicylic acid

Group A TB Drugs

Fluoroquinolones (levofloxacin and moxifloxacin) are bactericidal and potentially sterilizing.

They clearly have shown concentration - dependent activity (AUC / MIC).

2 & 6 hour post dose serum concentrations do a good job at describing exposure.

Levofloxacin

Levofloxacin pharmacokinetics and pharmacodynamics and outcome in MDR-TB patients.

Ghimire S, Maharjan B, Jongedijk EM, et al.

Eur Respir J. 2019 Jan 17. pii: 1802107.
PMID: 30655280

Levofloxacin

Levofloxacin Pharmacokinetics / Pharmacodynamics, Dosing, Susceptibility Breakpoints, and Artificial Intelligence in the Treatment of Multidrug - resistant Tuberculosis.

Deshpande D, Pasipanodya JG, Mpagama SG, et al.

Clin Infect Dis. 2018 Nov 28; 67 (suppl_3):S293-S302. PMID: 30496461

Levofloxacin

Increased Doses Lead to Higher Drug Exposures of Levofloxacin for Treatment of Tuberculosis.

Peloquin CA, Phillips PPJ, Mitnick CD, et al.

Antimicrob Agents Chemother. 2018 Sep 24; 62 (10). pii: e00770-18. Print 2018 Oct.
PMID: 30012767

Moxifloxacin

Effect of Moxifloxacin plus Pretomanid against *Mycobacterium tuberculosis* in Log Phase, Acid Phase, and Nonreplicating - Persister Phase in an *In Vitro* Assay.

de Miranda Silva C, Hajihosseini A, Myrick J, et al.

Antimicrob Agents Chemother. 2018 Dec 21;63(1). pii: e01695-18. PMID: 30397058

Moxifloxacin

Dose optimization of moxifloxacin and linezolid against tuberculosis using mathematical modeling and simulation.

Heinrichs MT, Drusano GL, Brown DL, et al.

Int J Antimicrob Agents. 2018 Oct 29.
pii: S0924-8579(18)30304-2.
PMID: 30385322

Fluoroquinolones

The Role of Fluoroquinolones in the Treatment of Tuberculosis in 2019.

Pranger AD, van der Werf TS, Kosterink JGW, et al.

Drugs. 2019 Feb; 79 (2): 161-171.
PMID: 30617959

Group A TB Drugs

Linezolid is bactericidal and sterilizing.

It clearly has shown **time - dependent activity (Cmin / MIC or Time > MIC).**

2 & 6 hour post dose serum concentrations do a good job at describing exposure. A trough value would provide further information.

Linezolid

Effect of Linezolid plus Bedaquiline against Mycobacterium tuberculosis in Log Phase, Acid Phase, and Nonreplicating – Persister Phase in an In Vitro Assay.

de Miranda Silva C, Hajihosseini A, Myrick J, et al.

Antimicrob Agents Chemother. 2018 Jul 27;62(8). pii: e00856-18.
PMID: 29866874

Linezolid

Linezolid - based Regimens for Multidrug - resistant Tuberculosis (TB): A Systematic Review to Establish or Revise the Current Recommended Dose for TB Treatment.

Bolhuis MS, Akkerman OW, Sturkenboom MGG, et al.

Clin Infect Dis. 2018 Nov 28; 67(suppl_3): S327-S335. PMID: 30496467

Group A TB Drugs

Bedaquiline is bactericidal and sterilizing.

It clearly has shown **concentration - dependent activity (Cmax / MIC and AUC / MIC).**

6 hour post dose and trough serum concentrations do a good job at describing exposure.

Bedaquiline

Population Pharmacokinetics of Bedaquiline and Metabolite M2 in Patients With Drug - Resistant Tuberculosis: The Effect of Time – Varying Weight and Albumin.

Svensson EM, Dosne AG, Karlsson MO.

CPT Pharmacometrics Syst Pharmacol. 2016 Dec; 5(12): 682-691.
PMID: 27863179

Bedaquiline

Modelling of mycobacterial load reveals bedaquiline's exposure - response relationship in patients with drug - resistant TB.

Svensson EM, Karlsson MO.

J Antimicrob Chemother. 2017 Dec 1; 72(12): 3398-3405. PMID: 28961790

Group B TB Drugs

Cycloserine is potentially bactericidal.

It clearly has shown time - dependent activity (Cmin / MIC or Time > MIC).

2 & 6 hour post dose serum concentrations do a good job at describing exposure. A trough value would provide further information.

Cycloserine

d - Cycloserine Pharmacokinetics / Pharmacodynamics, Susceptibility, and Dosing Implications in Multidrug resistant Tuberculosis: A Faustian Deal.

Deshpande D, Alffenaar JC, Köser CU, et al.

Clin Infect Dis. 2018 Nov 28; 67 (suppl_3): S308-S316. PMID: 30496460

Cycloserine

Pharmacokinetic-Pharmacodynamic Target Attainment Analysis of Cycloserine in TB Patients

Wael A Alghamdi[1], Abdullah Alsultan[2], Mohammad H Al-Shaer[1], Guohua An[3], Amirhossein Hajihosseini[4], Farzaneh Maleki[4], Carolina De Miranda Silva[4], Yosra Alkabab[5], Sayera Banu[6], Maia Kipiani[7], George Drusano[8], Stephan Schmidt[4], Scott K Heysell[5], Russell R Kempker[9], Peter Cegielski[10], Charles A Peloquin[1]

Poster session Friday 1 pm

Group C TB Drugs

Injectables (especially amikacin) are bactericidal.

They clearly have shown concentration - dependent activity (Cmax / MIC and AUC / MIC).

2 & 6 hour post dose serum concentrations

do a good job at describing exposure.

Example: Amikacin Kinetics

Two Sample Infusion

Conc	Hrs post dose	Ln Conc
26.30	2.00	3.27
9.40	6.00	2.24

Slope	Intercept	ke	t 1/2	Cmax	Cmax intercept
-0.26	3.78	0.257	2.69	43.99	43.99

Amikacin

Amikacin Dosing for MDR Tuberculosis: A Systematic Review to Establish or Revise the Current Recommended Dose for Tuberculosis Treatment.

Sturkenboom MGG, Simbar N, Akkerman OW, et al.

Clin Infect Dis. 2018 Nov 28; 67 (suppl_3): S303-S307.
PMID: 30496466

Amikacin

Treatment correlates of successful outcomes in pulmonary multidrug - resistant tuberculosis: an individual patient data meta - analysis.

Collaborative Group for the Meta - Analysis of Individual Patient Data in MDR - TB treatment – 2017, Ahmad N, Ahuja SD, Akkerman OW, et. al.

Lancet. 2018 Sep 8; 392 (10150): 821-834.
PMID: 30215381

What are specimen collection requirements ?

Same as a chemistry panel : plain red top tube.

Time the observed dose.

Time the blood draw (s).

Record the information on the form.

Process the sample promptly.

Where is testing done ?

Several labs offer some testing.

Two labs offer most testing.

One lab includes PK consultations with each sample for each patient at no extra charge.

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.

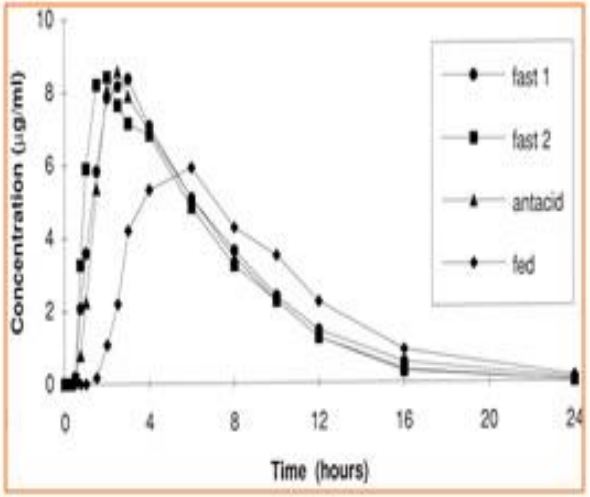
Thanks

- **The IDP Lab Team:**

  TJ Zagurski, Kyung Mee Kim, Emily Graham, Stacy Stoneberger, Wael Alghamdi, Mohammad Alshaer, Gena Burch

http://idpl.pharmacy.ufl.edu

Infectious Disease Pharmacokinetics Laboratory at the University of Florida



http://idpl.cop.ufl.edu/

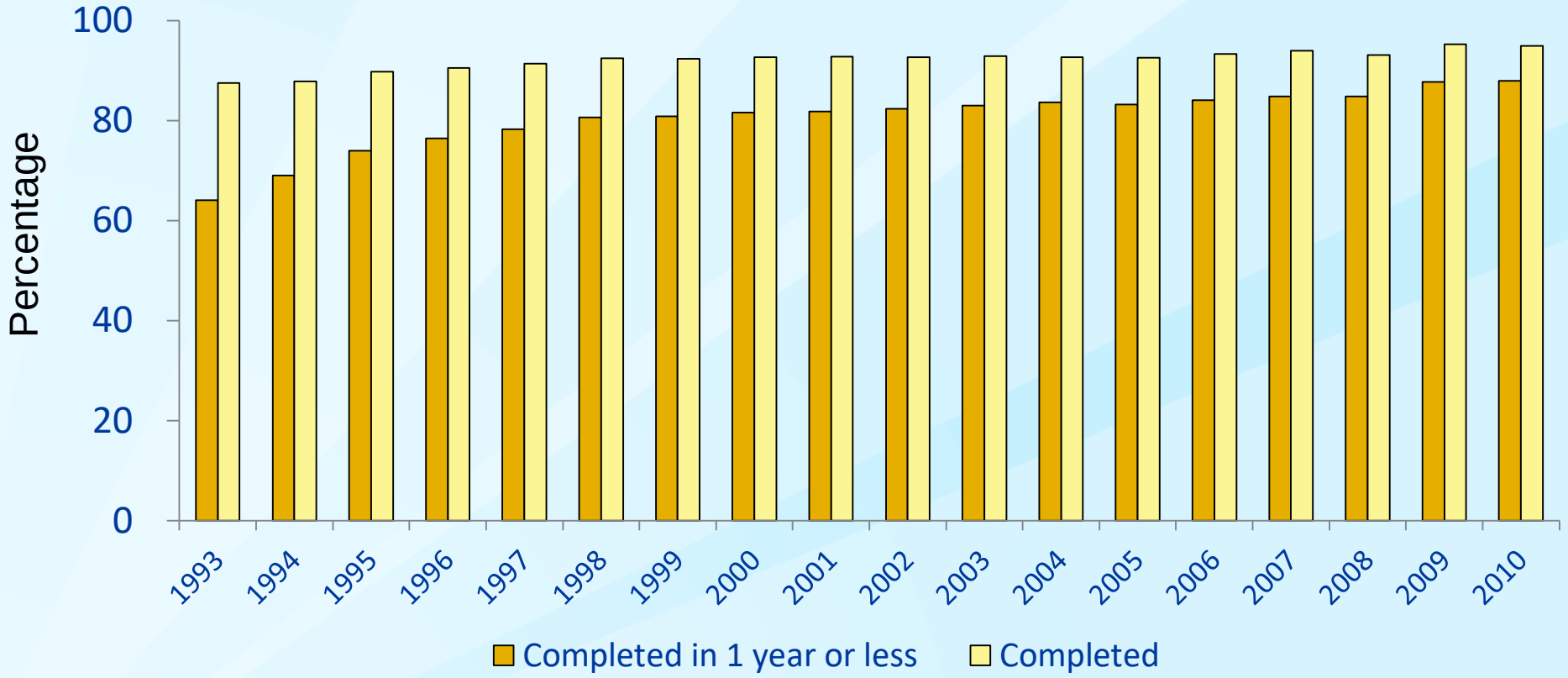
How much does TDM cost ?

In our lab, a single test is $80.

A pair of tests (i.e., 2 and 6 hour samples) per drug are $70 each ($20 discount).

Shipping costs vary.

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.

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%