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PKPD drug principles of TB agents

Antimicrobial fundamentals

How antibiotics work.

- For any drug with a known mechanism of action: **Drug enters the organism, binds a target, and produces an inhibitory or lethal effect.**
- For every drug given parenterally or orally: **The bloodstream is the only way for the drug to reach the bug.**

We are playing the game of "Concentration Gradient."

- Building a strong drug concentration in blood gets drug to the bug. Blood concentration drives drug to interstitial fluid, which drives drug to host cells and lesions, which drives drug to the microbe.
- Drug loss occurs all along the way. **If you administer enough drug, the drug will reach the microbe.**

Mechanism of action determines the strategy.

- Time-dependent agent: "Siege the castle." **Give enough drug to maintain the target conc from dose to dose**
  - Cell wall active drugs (penicillins, cephalosporins, carbapenem).
- Concentration-dependent agent: "Storm the castle". **"Give as much drug as possible.**
  - Intracellular poisons (aminoglycosides, rifamycins, fluoroquinalones).

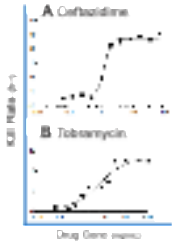
Recommended Resources
CH Nightingale, PG Ambrose, GL Drusano, T Murakawa, Eds. *Antimicrobial Pharmacodynamics in Theory and Clinical Practice, 2nd edition*.CRC Press; 2007.
JC Rotschafer, DR Andes, KA Rodvold, Eds. *Antibiotic Pharmacodynamics*. Humana Press; 2016.

General pharmacodynamic concepts

Multiple interrelated factors determine treatment outcome.

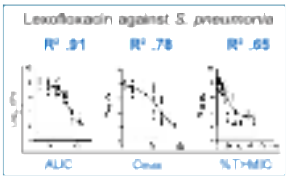
- Considerations include the bug, the drug, and the patient.

Antimicrobial killing patterns (Ceftazidime vs Tobramycin against P aeruginosa).



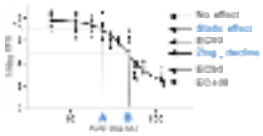
- Time-dependent **(A)**.
  - **More drug does not increase killing** above a certain concentration.
  - Curve resembles a step-function within the clinically useful range.
- Concentration-dependent **(B)**.
  - **More drug increases killing** across the clinically useful range.
  - Killing plateaus at very high concentrations (all targets saturated).

Sigmoid Emax model describes the relationship between PD parameters and efficacy (levofloxacin against *S. pneumonia*).



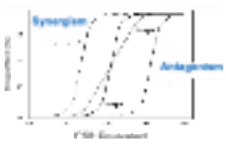
- Best fit model describes the driver of efficacy (AUC > Cmax > %T>MIC).
  - **AUC is always a safe guess.** Usually ranks first (conc-dep) or second (time-dep), depending on the mechanism of action.
  - **PD indices are correlated** when giving a fixed dose at a fixed interval.

Variable slope describes the progression from no effect to 100% Emax (as drug exposure increases).



- PD targets correspond to measures of effect. Drug concentration needed to achieve static effect (A) or 2$\log_{10}$ decline in CFU (B).
- **TB studies often use 2$\log_{10}$ decline in CFU.**

Two-drug interactions.



- Synergism. The drug combination produces an effect that the single drugs cannot produce (Left shift).
- Antagonism. Efficacy is lost by administering the two drugs together (Right shift).

Tuberculosis drugs

Sources of PKPD data.

- 1950s to 1970s. Gordon Ellard, Gianni Acocella, Ludo Verbist, and others generated considerable PK data.
- 1980s to 2000s. Recommended resources:

Peer-Reviewed Articles	Books
Holdiness MR. Clinical pharmacokinetics of the anti-tuberculosis drugs. Clin Pharmacokinet. 1984;9(6):511-44.	K Bartmann, ed. Antituberculosis Drugs. Springer-Verlag; 1988. **Translates several non-English papers.**
Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169-2183. **Current opinion – updated in 2014.**	Peloquin CA. Antituberculosis Drugs: Pharmacokinetics. In: Heifets L, ed. Drug Susceptibility in the Chemotherapy of Mycobacterial Infections. CRC Press; 1991:59-88.
Nueremberger E, Grosset J. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. Eur J Clin Mirobiol Infect Dis. 2004;23:243-55.	Global TB Alliance. Handbook of anti-tuberculosis agents. Tuberculosis. 2008;88(2):1-169. **TB drug database with a few pages on each drug.**
Budha NR, Lee RE, Meibohm B. Biopharmaceutics, pharmacokinetics and pharmacodynamics of antituberculosis drugs. Current Medicinal Chemistry. 2008;15:809-825. **Great tables with PKPD parameters.**	

Rifamycin studies indicate substantial interindividual variation and concentration-dependent killing.

- Dose-ranging trial of rifampin (Boeree MJ et al, 2011 and 2015).
  - **High interindividual variability** in Cmax and AUC within any given dose.
  - **Concentration-dependent killing.** Highest AUC achieved largest reduction in sputum Mtb CFU.
- Daily rifapentine for treatment of pulmonary TB (Dorman SE et al, 2015).
  - **No clear trend in efficacy across study arms.** Highest % culture-negative in the RPT20 arm.
  - **Antimicrobial activity strongly associated with RPT exposures.**
  - **PKPD evaluations provide important insights.**
- High-dose rifampin.
  - PubMed search on Oct 25, 2024, yielded 631 articles (many are relevant). Recommended resources:

Peer-Reviewed Articles	Books
Svensson EM et al. Potential treatment shortening with higher rifampicin doses: relating drug exposure to treatment response in patients with pulmonary tuberculosis. CID. 2018;67(1):34-41.	R Jelliffe and M Neely, eds. Individualized Drug Therapy for Patients: Basic Foundations, Relevant Software, and Clinical Applications. Academic Press; 2016.
Alkabab Y et al. Therapeutic drug monitoring and TB treatment outcomes in patients with diabetes mellitus. Int J Tuberc Lung Dis. 2023;27(2):135-139. **TDM hastened microbiological cure in a programmatic setting).**	
Alffenaar JWC, Stocker SL, Davies Forsman L, et al. Clinical standards for the dosing and management of TB. Int J Tuberc Lung Dis. 2022;26(6):483-499. **First consensus-based clinical standards.**	

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