Pharmakokinetik Beim Intensivpatienten: Brauchen Wir Individuelle Dosierungen?

Stephan Schmidt, Ph.D.

Center for Pharmacometrics and Systems Pharmacology (CPSP),
University of Florida, Orlando, USA

23. Jahrestagung der Pau-Ehrlich-Gesellschaft fuer Chemotherapie e.V.,
Dresden, 12. Oktober 2012

Need to Know

Pharmacokinetic

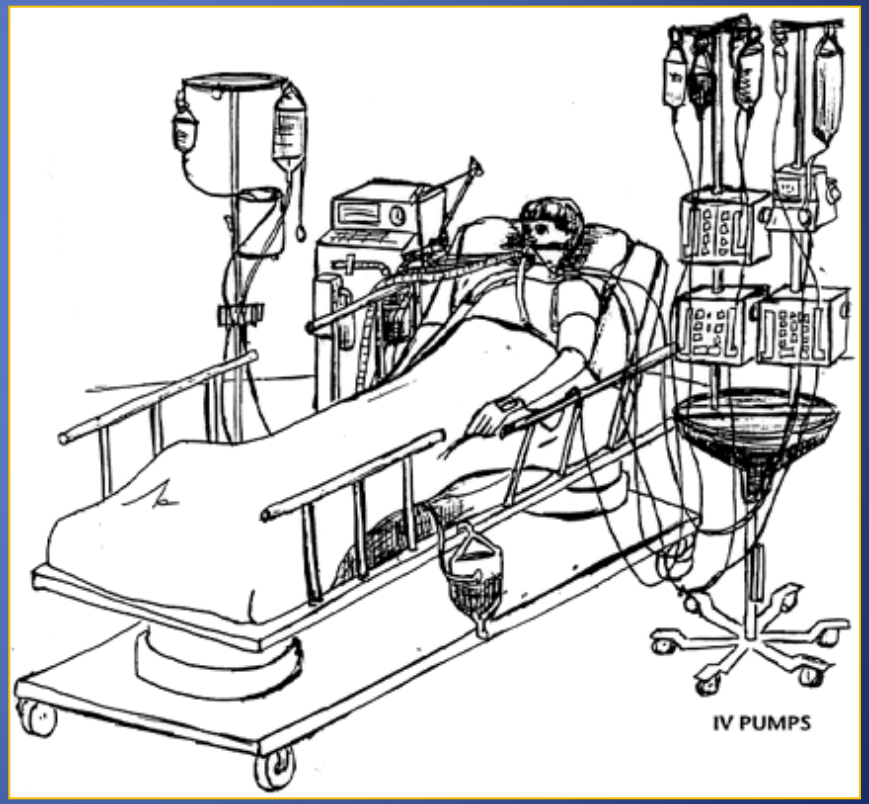
→ Determinants of Target Site Concentrations:

- (Absorption)
- Distribution
- Metabolism
- Elimination

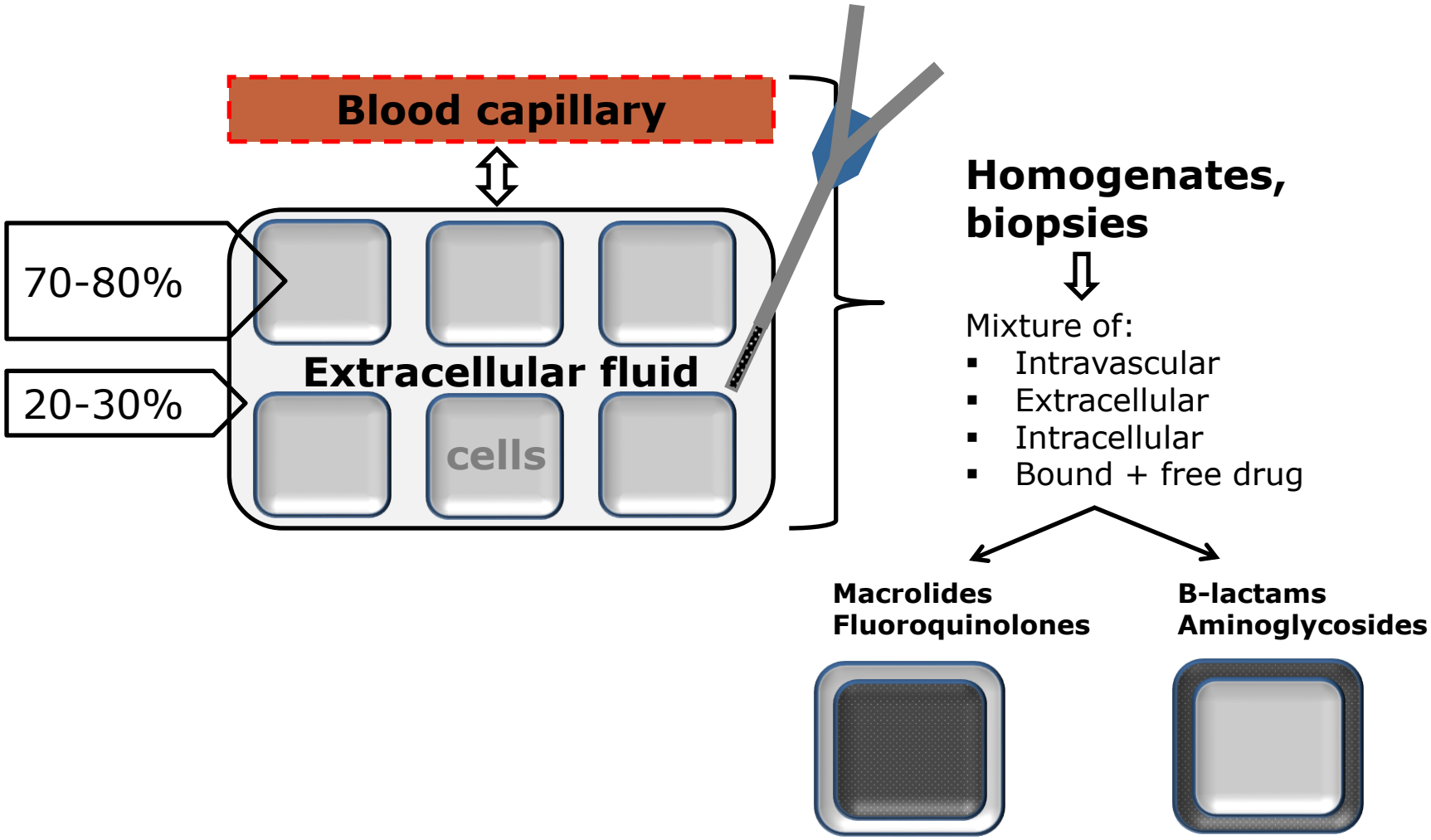
→ Free tissue concentrations

→ How different are they in critically ill patients?

Critically-ill patient

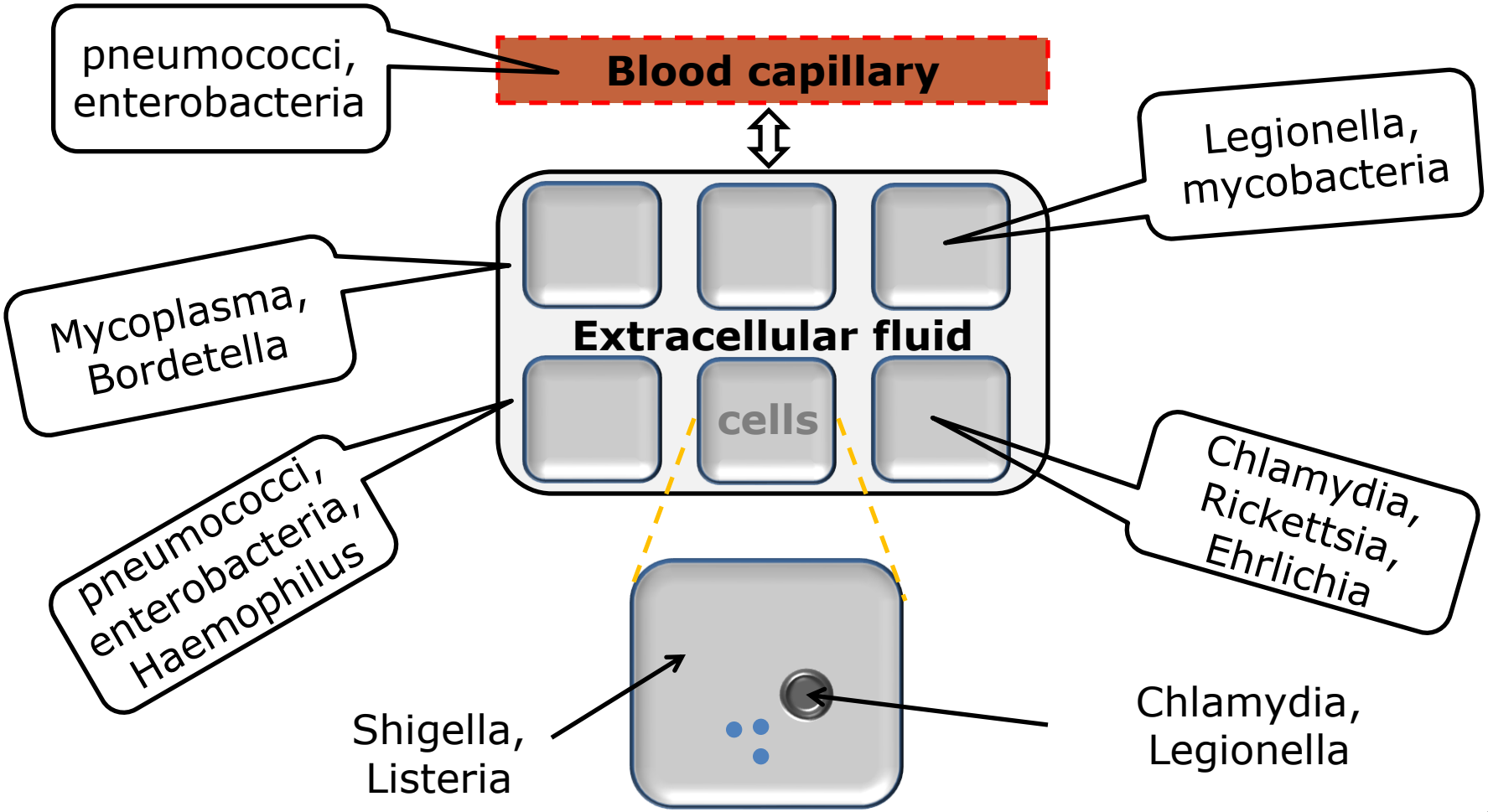


Distribution of Antibiotic in the Tissue



Modified from Theuretzbacher (2005) at ECC, Firenze.

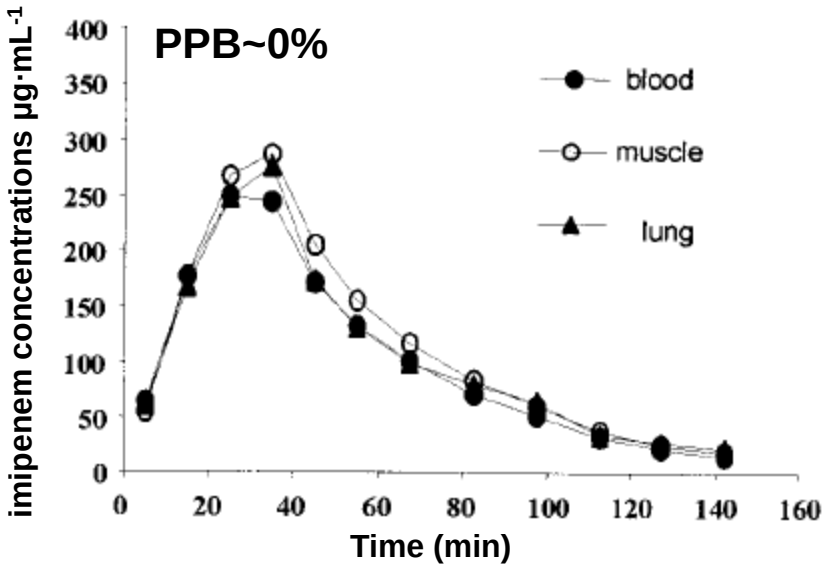
Why is the Location of the Antibiotic in the Tissue Important?

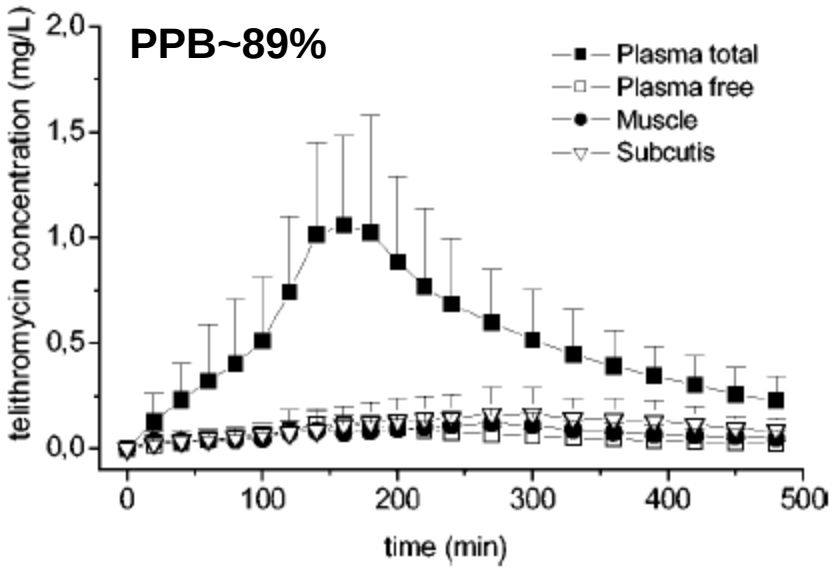


Modified from Theuretzbacher (2005) at ECC, Firenze.

Volume of Distribution as a Surrogate for Tissue Concentrations

$$V_d = V_p + \frac{f_{u,p}}{f_{u,T}} \cdot V_T$$





*Marchand et al. (2005) Antimicrob Agents Chemother **49**: 2356-61.*

*Gattringer et al. (2004) Antimicrob Agents Chemother. **48**:4650-3.*

However, at Steady-State…

***Free, active* average steady-state concentrations:**

$$C_{ss}(free) = \frac{f_u \cdot F \cdot D}{CL \cdot \tau}$$

→ At steady-state distribution is finished

→ Dependent on PPB, clearance & route of administration

For intensive care patients:

$$C_{ss}(free) = \frac{f_u \cdot D}{CL \cdot \tau}$$

Steady-State Concentrations in Critically ill Patients

	f_{uP}	$V_{d(total)}$	$CL_{(total)}$	$t_{1/2}$	$\overline{C}_{ss(total)}$	$C_{max,ss(total)}$	$C_{min,ss(total)}$	$\overline{C}_{ss(free)}$	$C_{max,ss(free)}$	$C_{min,ss(free)}$	F^a
Parenteral administration											
Low E^b–low V_d	↑	↔	↑	↓	↓	↓	↓	↔	↑	↓	—
	↓	↔	↓	↑	↑	↑	↑	↔	↓	↑	—
Low E^b–high V_d	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	—
	↓	↓	↓	↔	↑	↑	↑	↔	↔	↔	—
High E–low V_d	↑	↔	↔	↔	↔	↔	↔	↑	↑	↑	—
	↓	↔	↔	↔	↔	↔	↔	↓	↓	↓	—
High E–high V_d	↑	↑	↔	↑	↔	↓	↑	↑	↑	↑	—
	↓	↓	↔	↓	↔	↑	↓	↓	↓	↓	—

→ Changes in plasma protein binding, due to disease are only important for highly bound (PPB>70%), high extraction drugs following parenteral administration

[b]same principles apply for renally eliminated drugs, glomerular filtration only

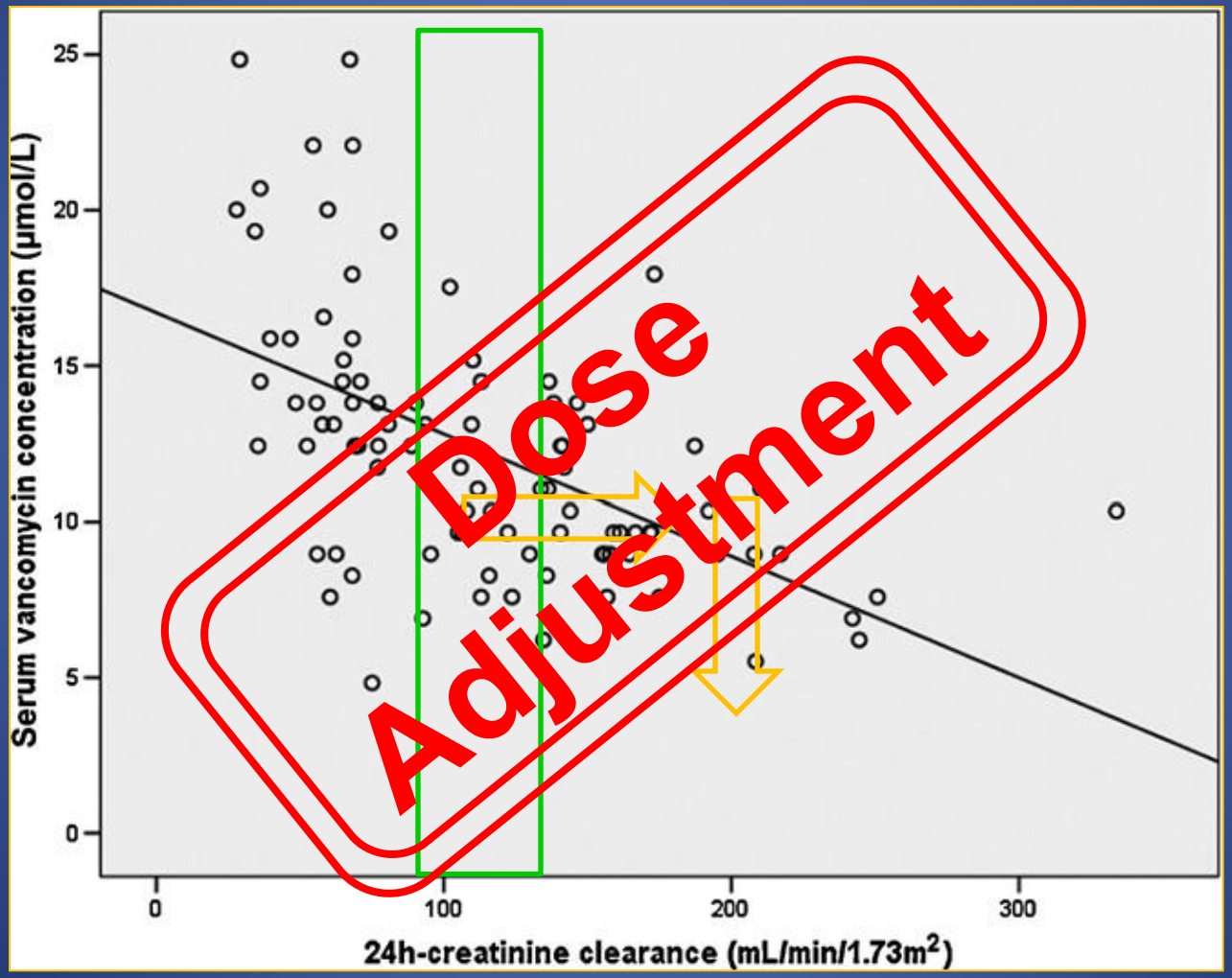
Schmidt et al. (2010) J Pharm Sci. ***99****: 1107-22.*

	Protein binding (%)	*CL (ml/min · kg)*
Alfentanil*	92	10.6§
Amitriptyline†‡	95	11.5§
Buprenorphine*†	96	13.3§
Butorphanol*†	80	22§
Chlorpromazine*‡	95	8.6§
Cocaine*	91	32§
Diltiazem*‡	78	11.4§
Diphenhydramine*‡	78	6.2§
Doxorubicin*	76	16.2§
Erythromycin*‡	84	8.0§
Fentanyl*	84	12.3§
Gold sodium thiomalate (INN, sodium aurothiomalate)†	95	4.8¶
Haloperidol†‡	92	11.8§
Idarubicin*‡	97	29§
Itraconazole*‡	99	12.7§
Lidocaine*	70	9.2§
Methylprednisolone*†‡	78	6.2§
Midazolam*†‡	98	6.6§
Milrinone*	70	5.2¶
Nicardipine*‡	99	10.4§
Pentamidine*	70	16§
Propofol*	98	27§
Propranolol*‡	87	18§
Remifentanil*	92	40-60#
Sufentanil*	93	12§
Verapamil*‡	90	15§

Dose Adjustment

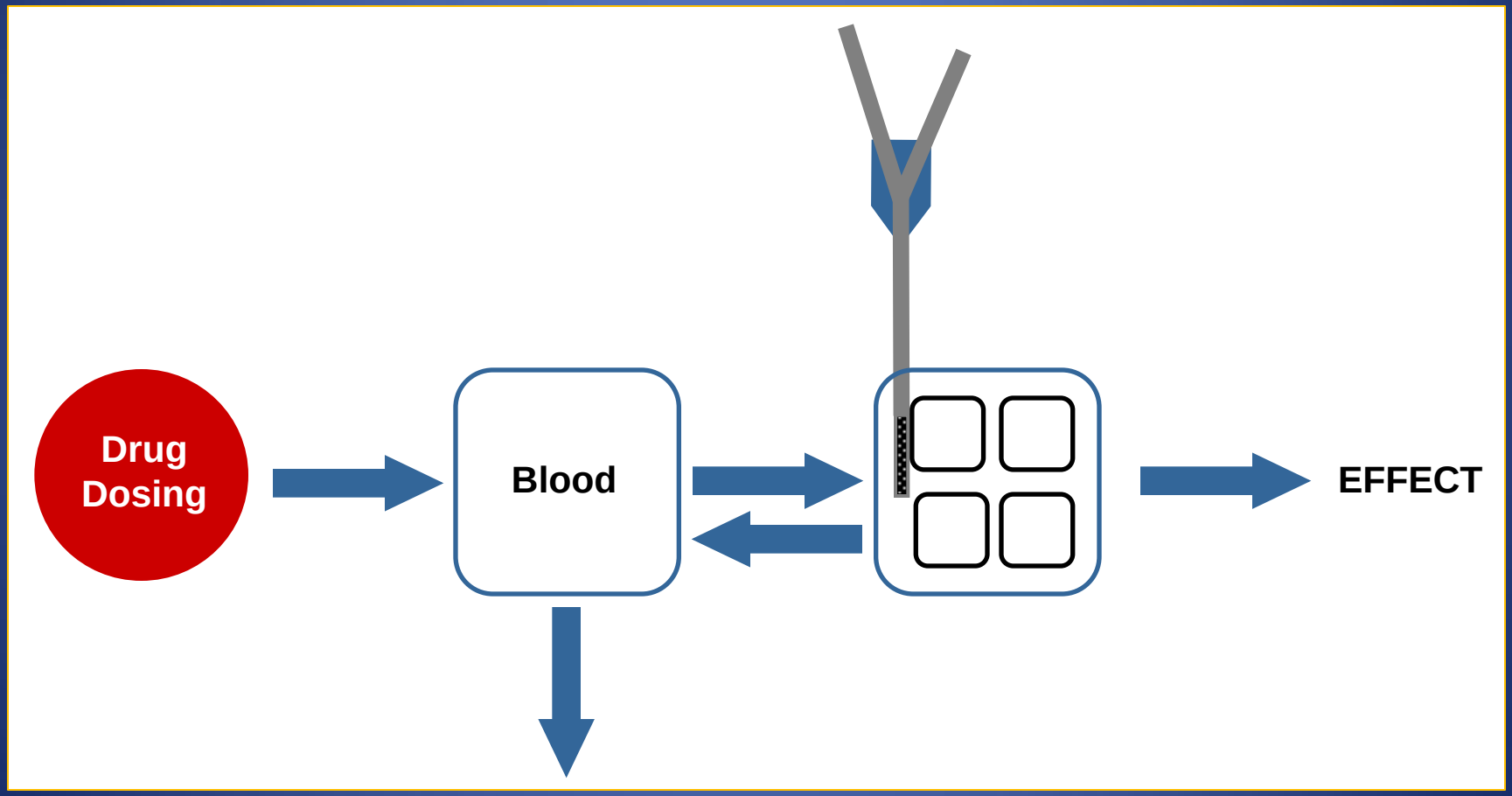
Benet and Hoener. (2002) Clin Pharmacol Ther. ***71****: 115-21.*

Impact of Changes in Clearance



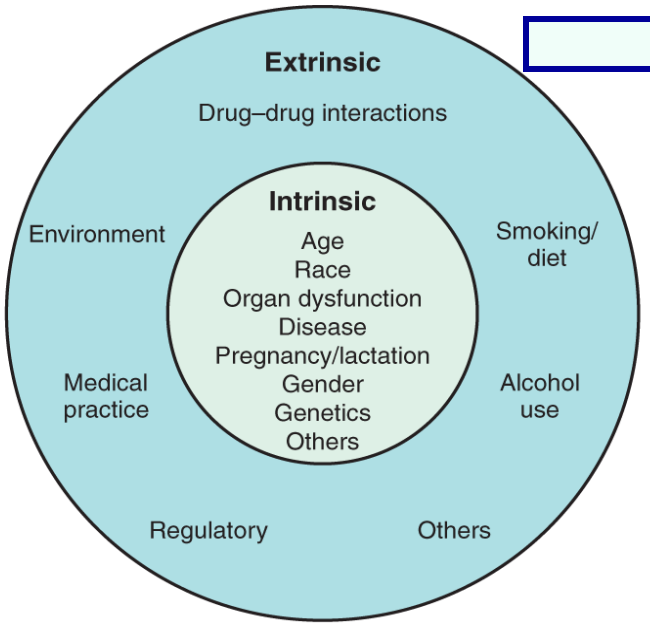
*Baptista et al. (2012) Int J Antimicrob Agents **39**: 420-3.*

Pharmacokinetic Measures



Physiology-Based Modeling

Intrinsic/extrinsic Factors



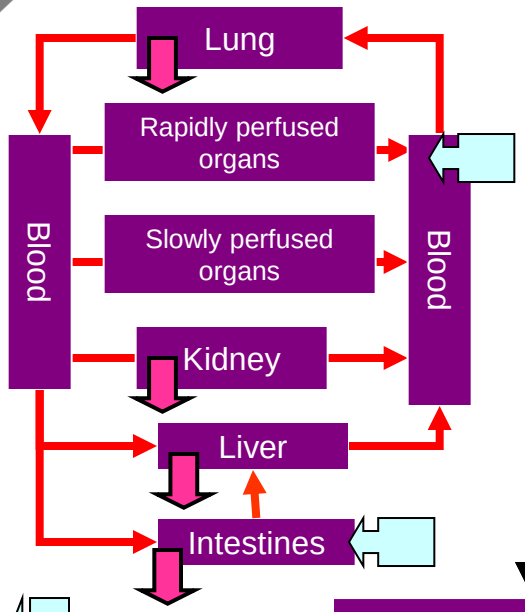
Huang and Temple, 2008

Individual or combined effects on human physiology

PBPK Model components

System component (drug-independent)

Drug-dependent component



ADME, PK, PD and MOA

Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

Dosing

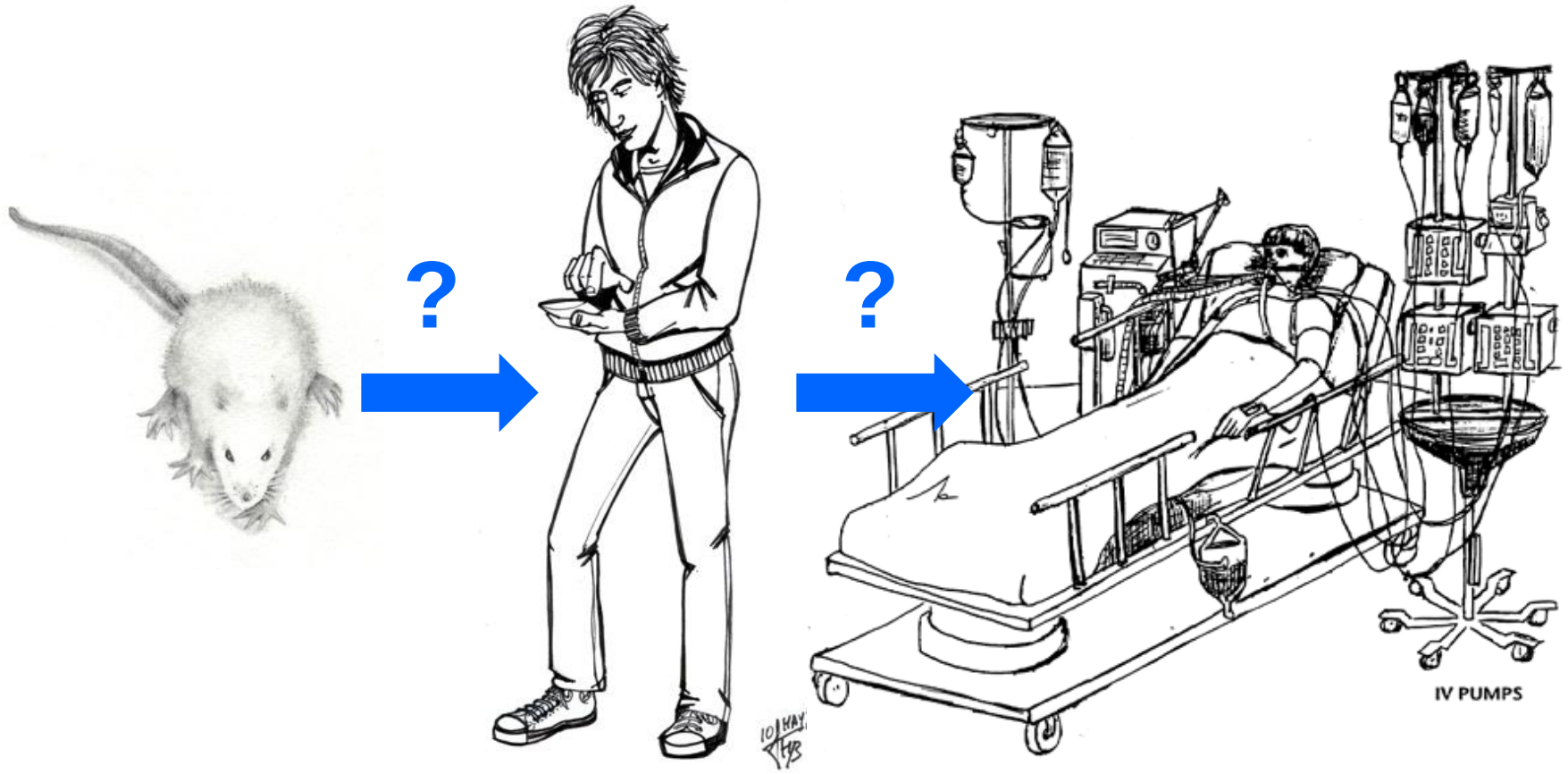
Elimination

PBPK Model

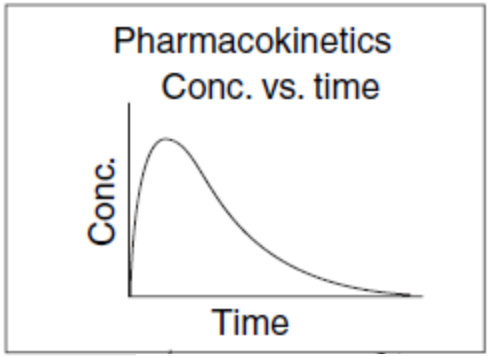
Predict, Learn, Confirm, Apply

Zhao P, et al Clin Pharmacol Ther 2011

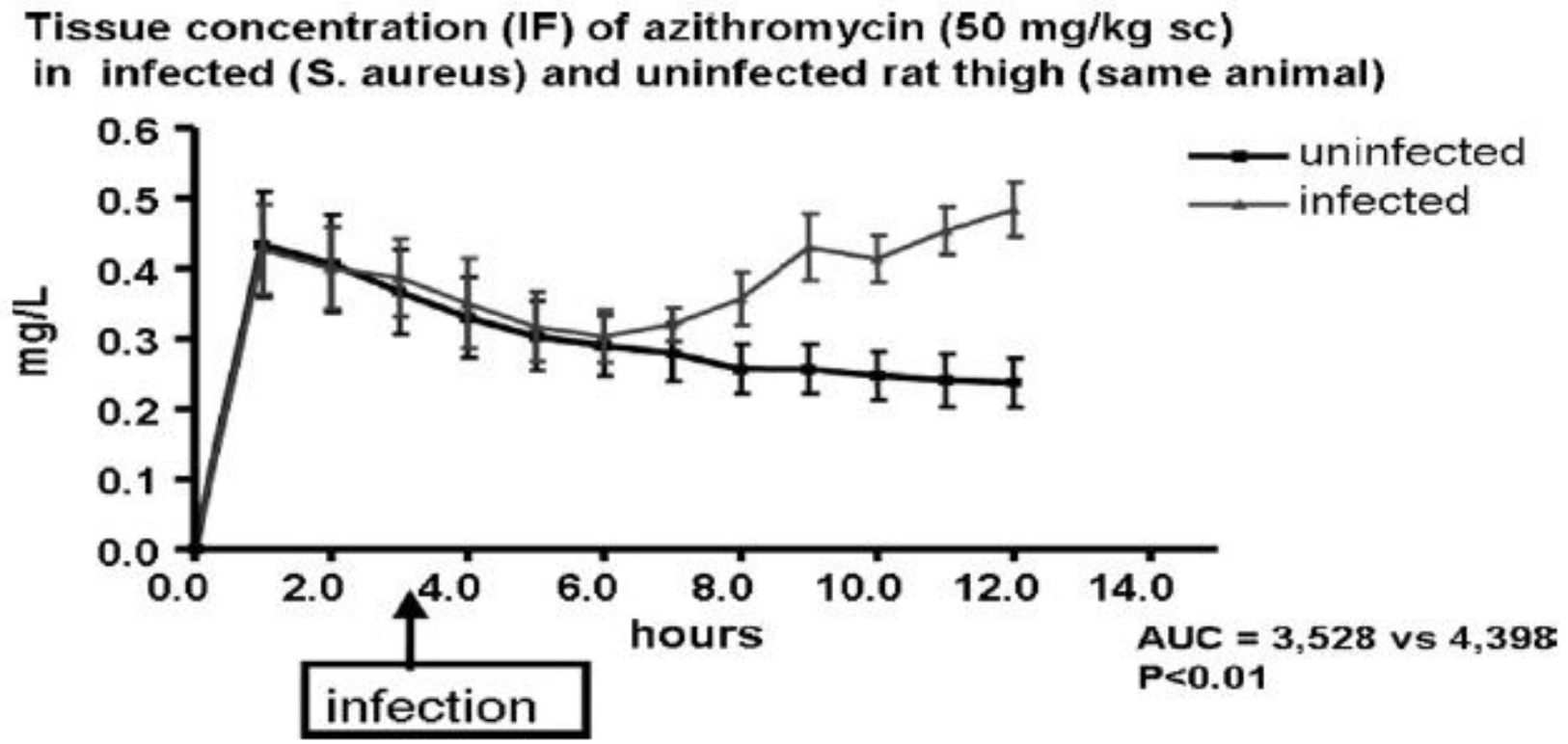
Extrapolation (Scaling) of PK/PD by Function Rather Than Size



PK/PD Relationships

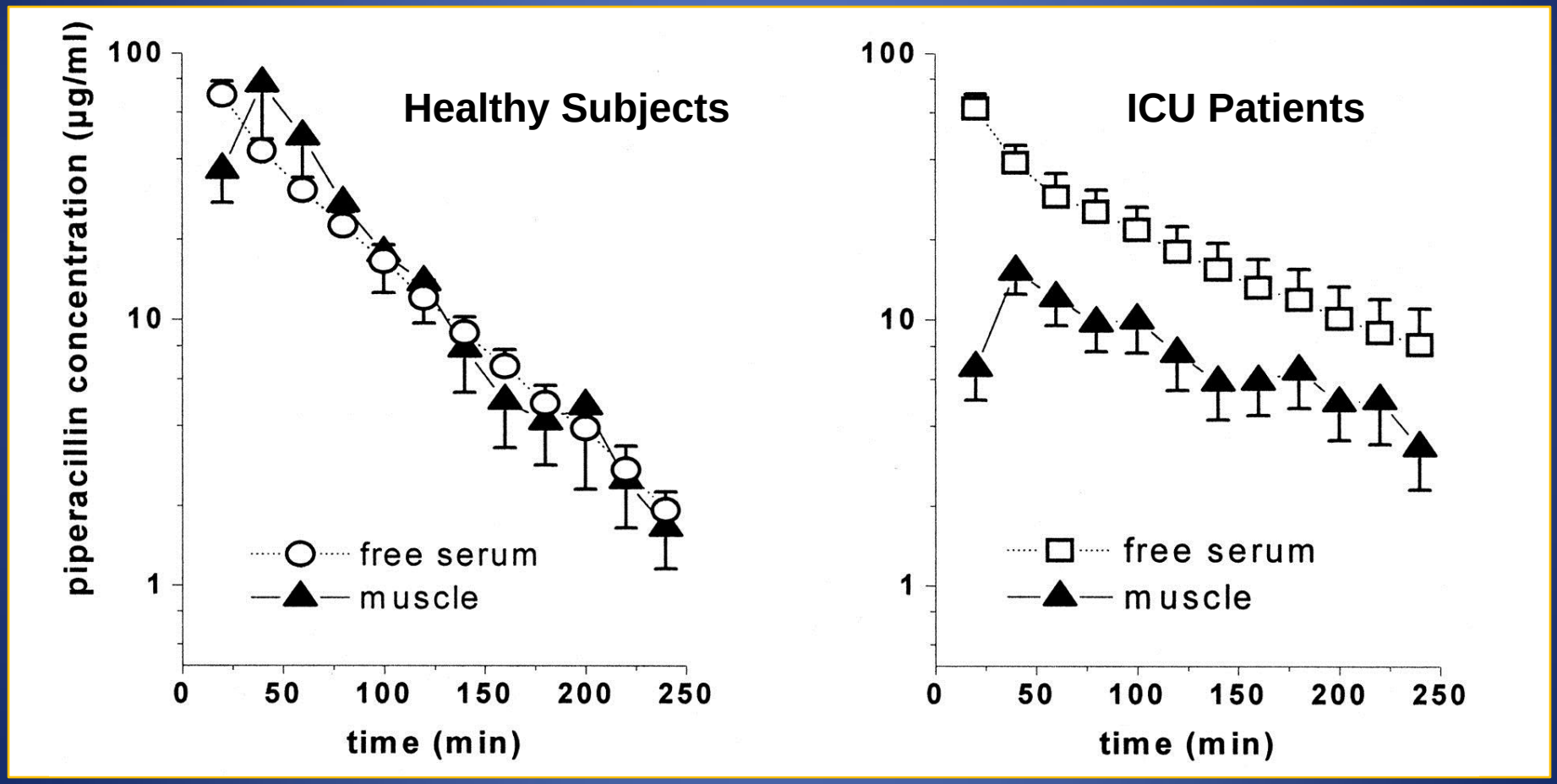


Impact of Disease on Tissue Distribution



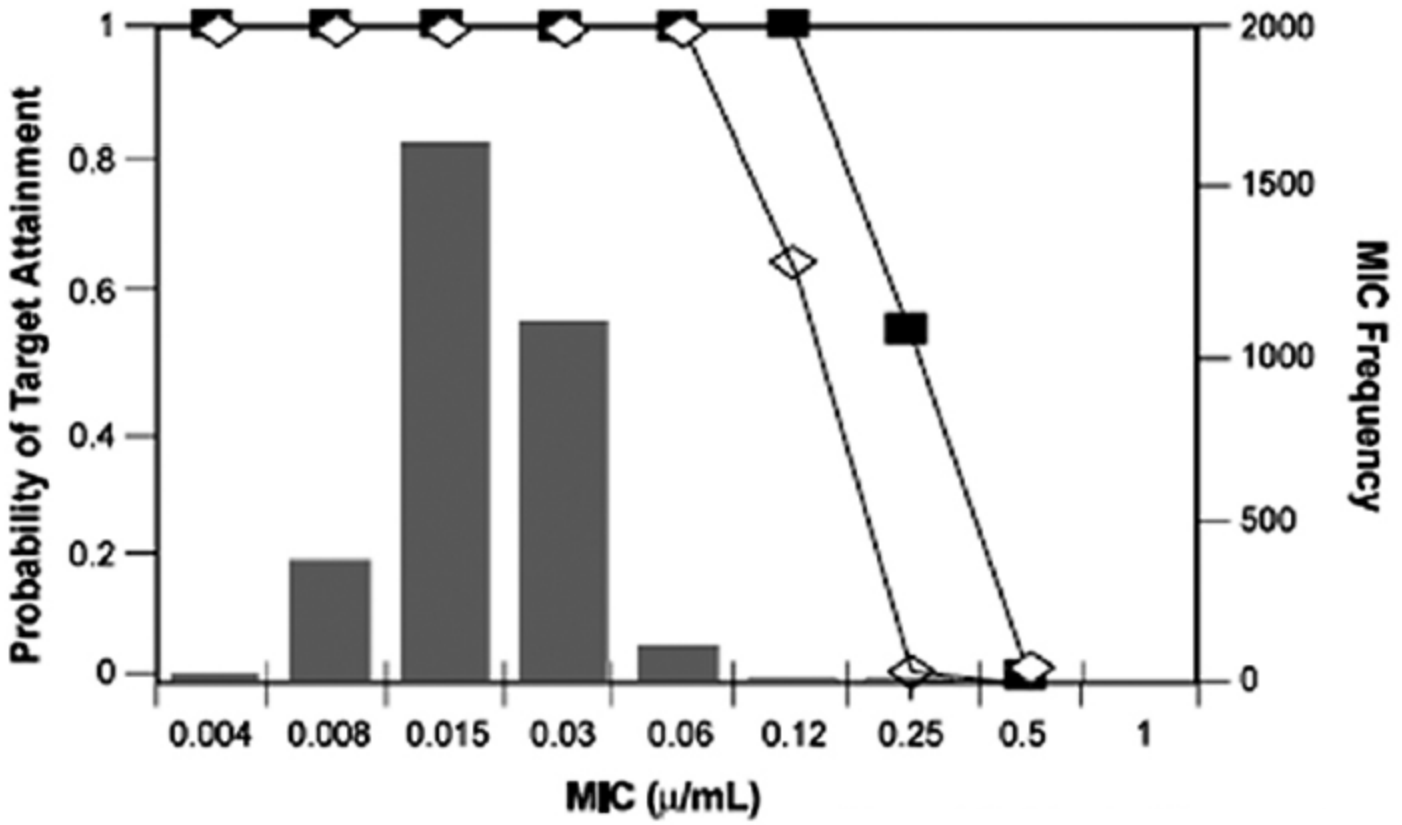
Lucini et al. (2006) Poster at ICAAC (abstract A-335).

Healthy Subjects vs. Patients



Brunner et al. (2000) Crit Care Med. ***28****: 1754-9.*

Linking PK & PD



Owens et al. (2005) Diagn Microbiol Infect Dis ***51****: 45-49.*


FLORIDA