Improving dosing regimens to minimise resistance

U. Theuretzbacher – Center for Anti-Infective Agents, Vienna, Austria

There is no conflict of interest to report in this presentation, because this presentation does not advocate or discourage the use of any commercial product, nor does it support or oppose change in any regulations that might enhance or deter the promotion or sale of any commercial product.

CENTER FOR ANTI-INFECTIVE AGENTS

Outline

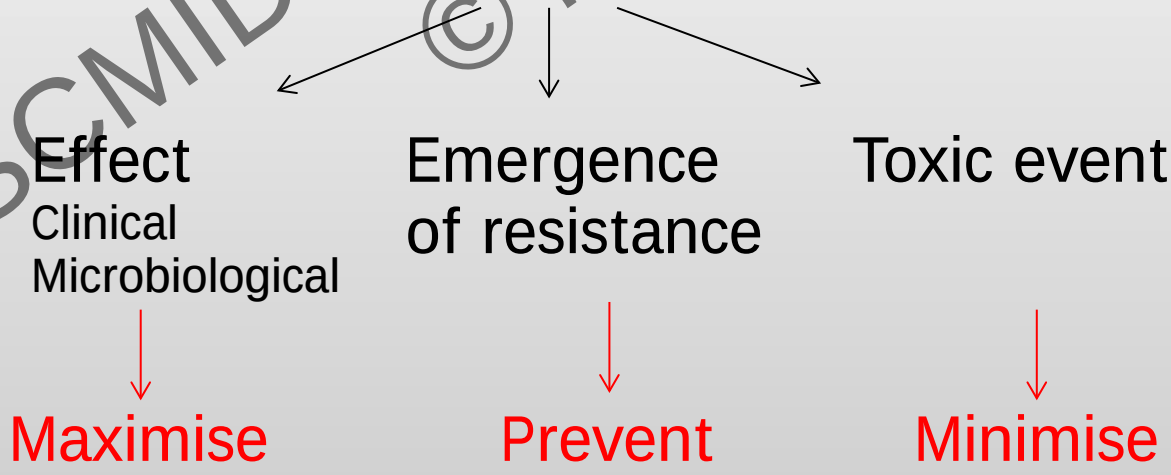
- Dosing regimen
  - dose, application, dosing schedule, duration of therapy

↓

- Antibacterial drug exposure (PK)
  Bacterial susceptibility (PD)

↓

- Exposure - outcome relationship (PK/PD)



Outline

- Dosing regimen
  - dose, application, dosing schedule, duration of therapy

↓

- Antibacterial drug exposure (PK)
  Bacterial susceptibility (PD)

↓

- Exposure - outcome relationship (PK/PD)

Determine concentrations in response to a dose

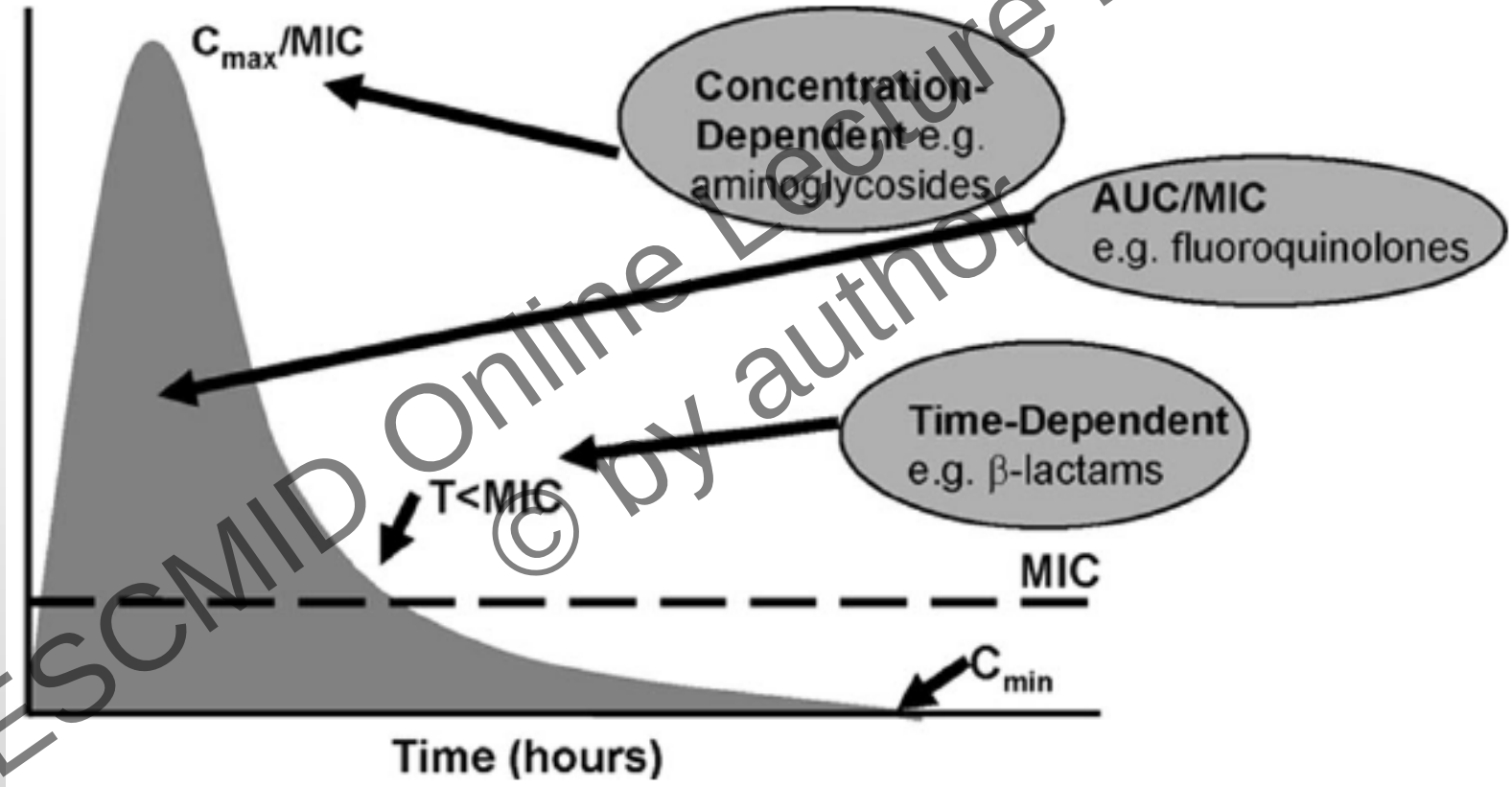
Determine MIC

Determine optimal PK/PD relationship in vitro, in vivo

Effect	Emergence of resistance	Toxic event
Clinical Microbiological		
↓	↓	↓
Maximise	**Prevent**	**Minimise**

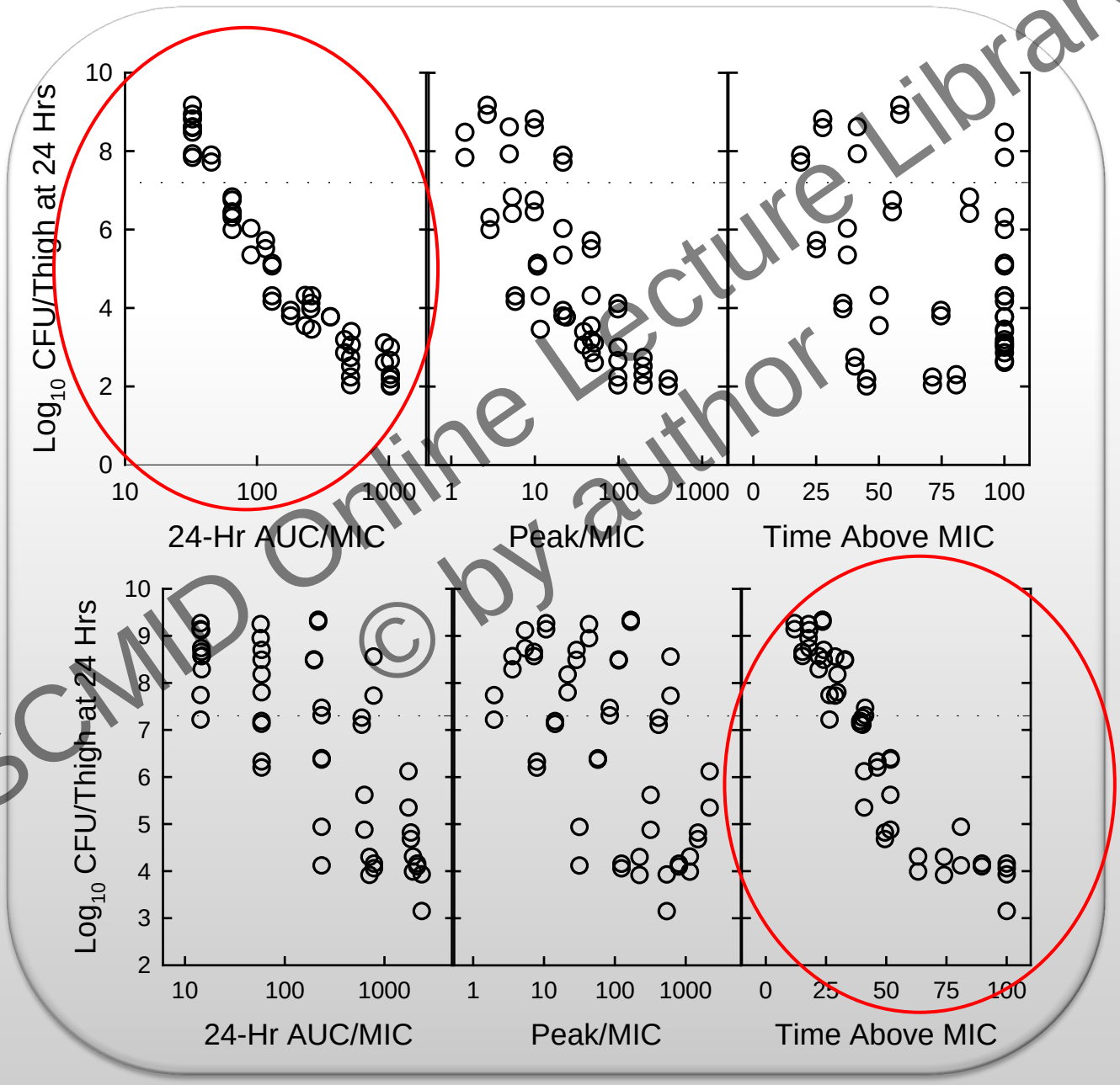
PK/PD index – Correlation with outcome

Free concentrations!



JA Roberts et al, Crit Care Med 2008;36,8:2433

PK/PD index – Correlation with outcome



levofloxacin

ceftazidime

Andes IJAA 2002

CENTER FOR ANTI-INFECTIVE AGENTS

PK/PD - It's not just for mice anymore

Disease	Drug	Human Value	Mice Value
HAP	Quinolones	AUC/MIC **62-75**	AUC/MIC **70-90**
CAP	Quinolones	AUC/MIC **34**	AUC/MIC **25-34**
	ß-Lactams	T>MIC **40%**	T>MIC **30-40%**
SSTI	Linezolid	AUC/MIC **110**	AUC/MIC **83**
	Tigecycline	AUC/MIC **18**	AUC/MIC **15-20**

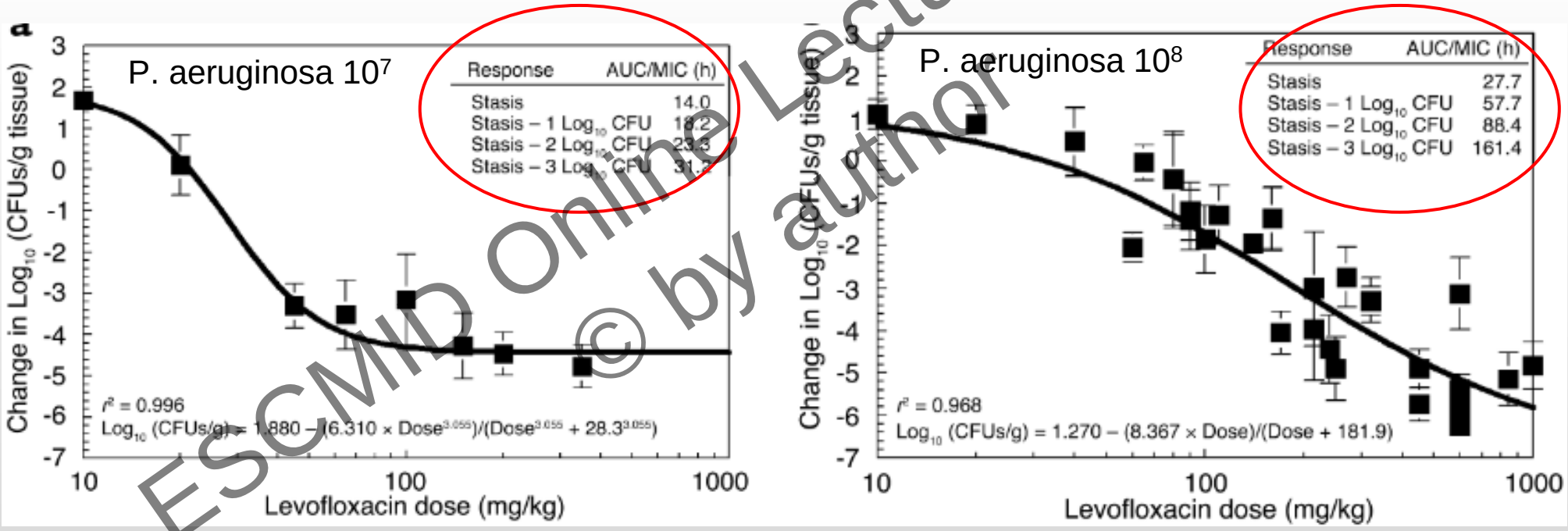
P Ambrose et al: Clin Infect Dis. 2007;44:79-86

CENTER FOR ANTI-INFECTIVE AGENTS

PK/PD Index Value

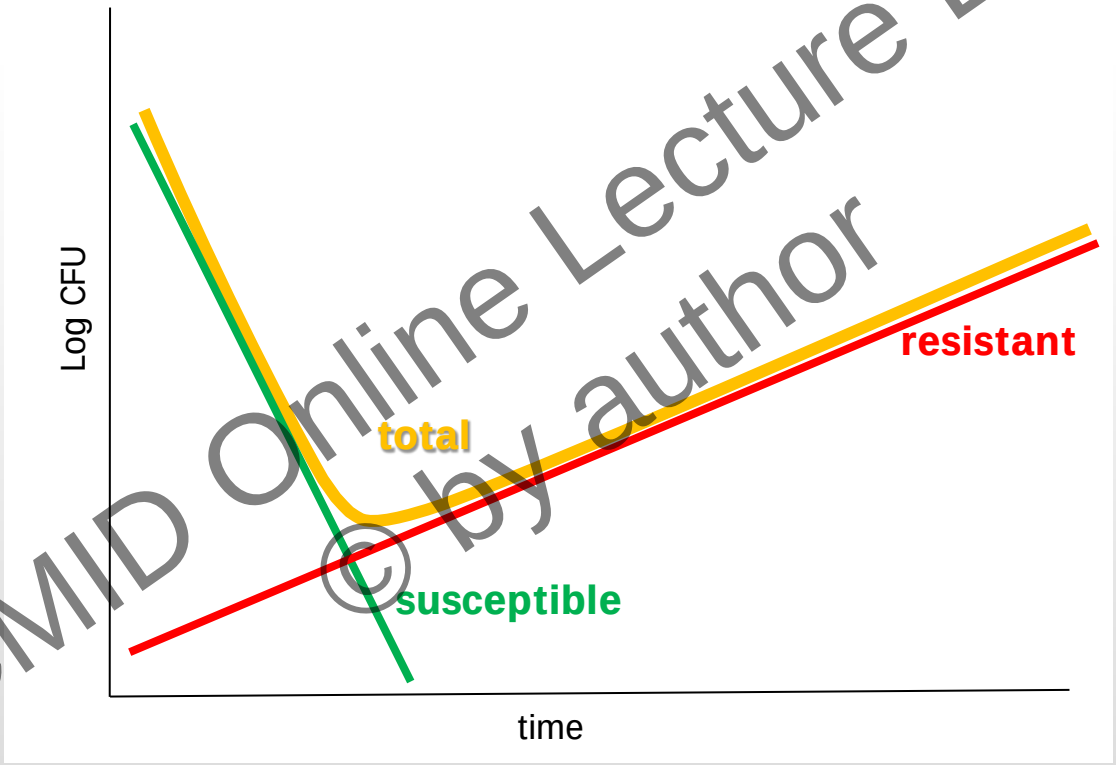
AUC/MIC exposures needed to attain similar log10 killing for the inocula tested

Non-neutropenic mouse model



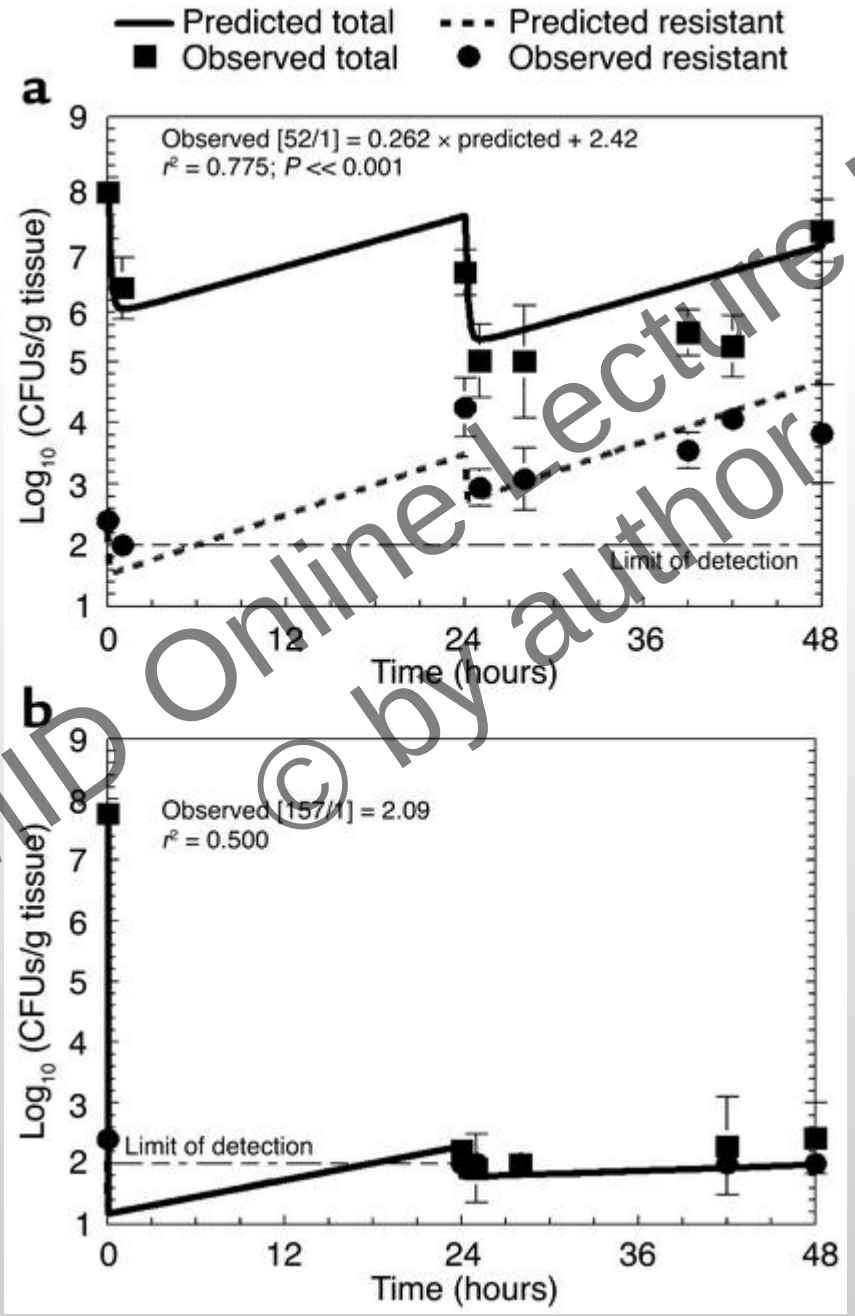
N Jumbe et al: J Clin Invest 2003;112:275

Bacterial Population Analysis



G Drusano: Nat Rev Microbiol 2004;2:289–300

PK/PD – resistance suppression



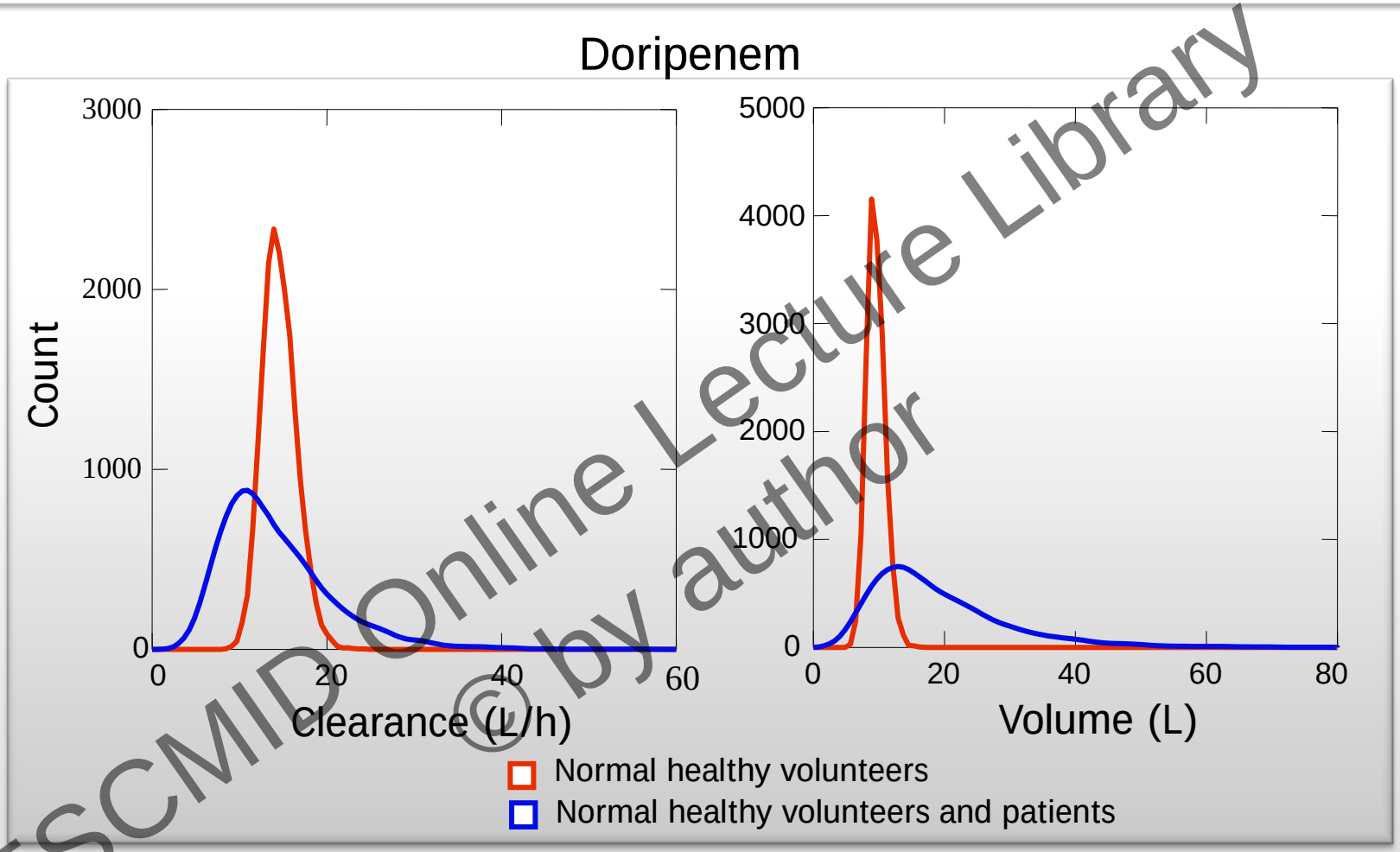
AUC/MIC 52

AUC/MIC 157

N Jumbe et al: J Clin Invest 2003;112:275
G Drusano et al: J Infect Dis. 2004;189:590

CENTER FOR ANTI-INFECTIVE AGENTS

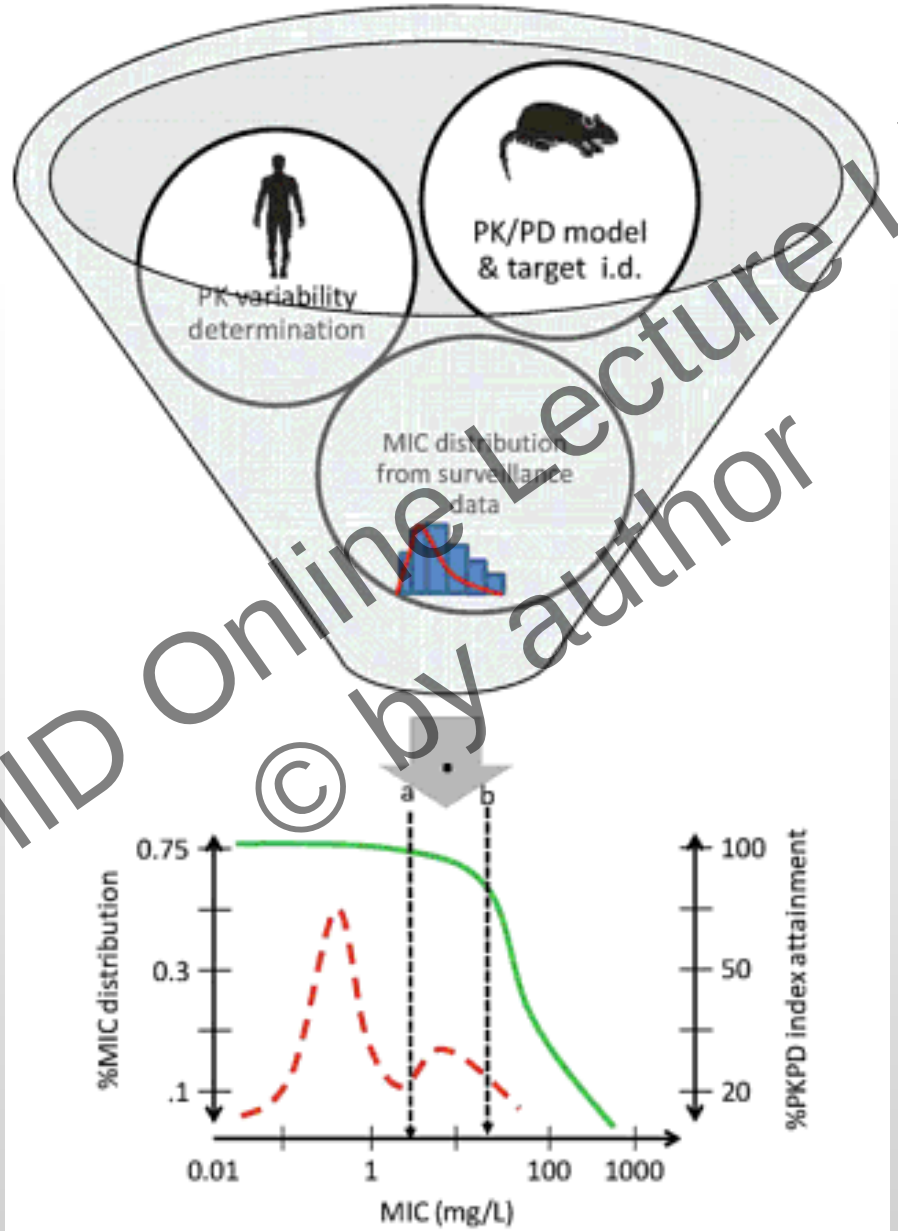
PK Variability



Parameter	Phase 1 population		Phase 1 and 2 populations	
	Population Mean Estimate	Interindividual Variability (% CV)	Population Mean Estimate	Interindividual Variability (% CV)
CL (L/hr)	14.5	13.2%	12.9	42.9%
Vc (L)	9.43	14.4%	16.7	53.4%

S. Bhavnani

PK/PD: in vitro, in vivo, clinical



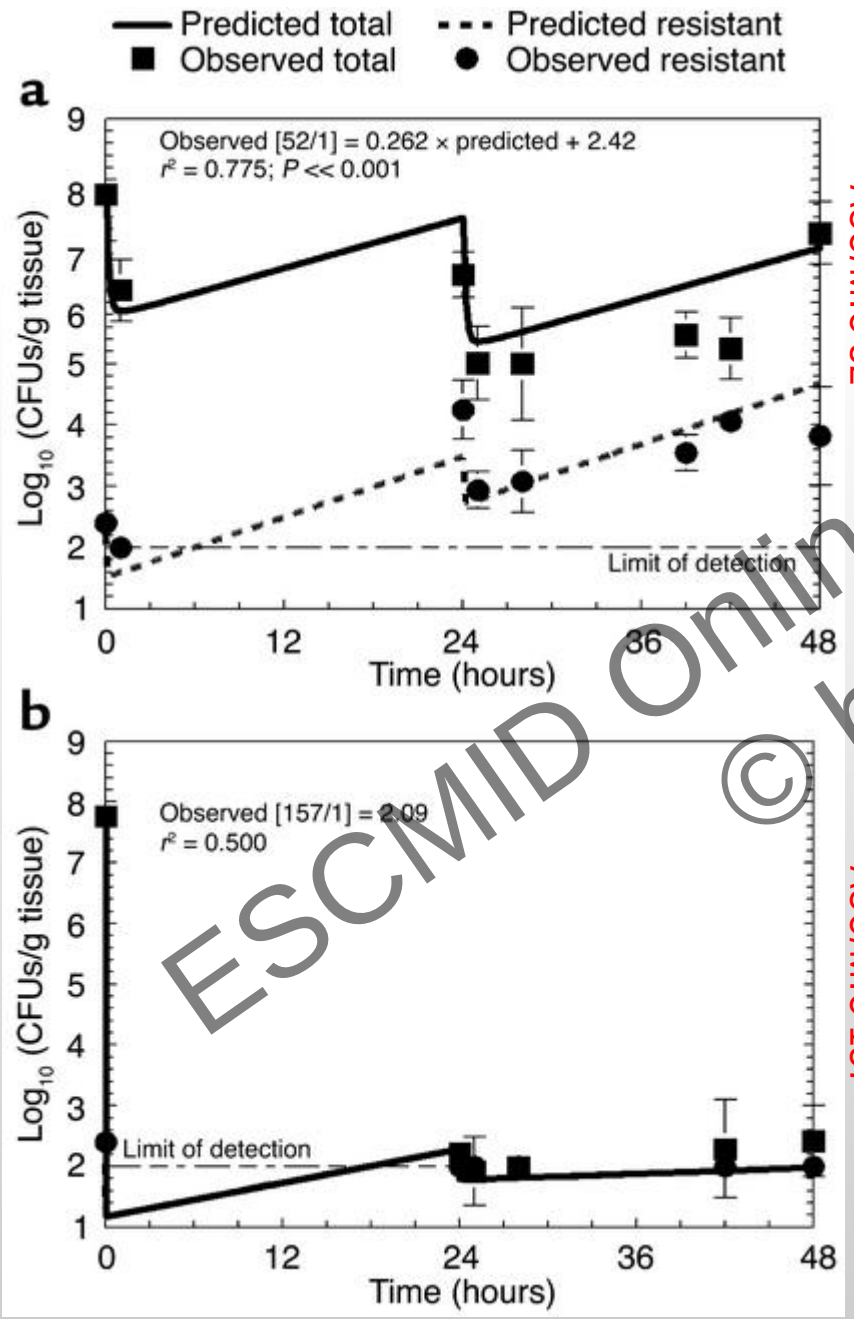
Jumbe NL, Drusano GL. 2011. *In Kimko HHC, Peck* CC (ed), Clinical trial simulations: applications and trends. Springer, NY.

PTAs in severely ill patients

Antibacterial class	PK/PD index predictive for outcome	Required magnitude of the PK/PD index to optimize activity	PTA (%) in severely ill cancer/ICU patients (selected examples)	Dosing strategy
Beta-lactam antibiotics	% *f*t>MIC	% *f*t>MIC: 40-70%, 80-100% in immunocompromised patients	**53 %** with imipenem 500mg q4h at MIC 1 mg/L (100 ml/min GFR)	I.v.: Prolonged infusion, continuous infusion; Oral: More frequent dosing per day
Aminoglycosides	AUC_{0-24}/MIC and C_{max}/MIC	AUC_{0--24}/MIC: >150	**55 %** with tobramycin 5mg/kg at MIC 1 mg/L	Once daily administration, duration of therapy not longer than 5-7 days, TDM
Glycopeptides: vancomycin	*f*AUC_{0-24}/MIC	AUC_{0-24}/MIC: >400 (total drug, protein binding 50%)	**50 %** with vancomycin 2g/day at MIC 2 mg/L (Cl_{ren} 60-120 mL/min)	Dosing according to TDM
Lipopeptides: Daptomycin	*f*AUC_{0-24}/MIC and *f*C_{max}/MIC	AUC_{0-24}/MIC: >800 (total drug, protein binding 90%)	**77 %** with daptomycin 6mg/kg/day at MIC 1 mg/L	High once daily dosing, TDM would be beneficial, not enough clinical data
Oxazolidinones: Linezolid	% *f*t>MIC and *f*AUC_{0-24}/MIC	AUC_{0-24}/MIC: >100 and % t>MIC >85% (total drug, protein binding 30%)	**70 %** with linezolid 600mg q12 h at MIC 2mg/L	Dosing according to TDM to avoid treatment failure and dose-dependent toxicity
Quinolones	*f*AUC_{0-24}/MIC	*f*AUC_{0-24}/MIC: 70-90 and >250 for maximal effect	**77 %** with ciprofloxacin 400mg q8h at MIC 0.25mg/L	High dosages, TDM may be beneficial

U Theuretzbacher: CID 2012;54(12):1785-92

PK/PD – resistance suppression

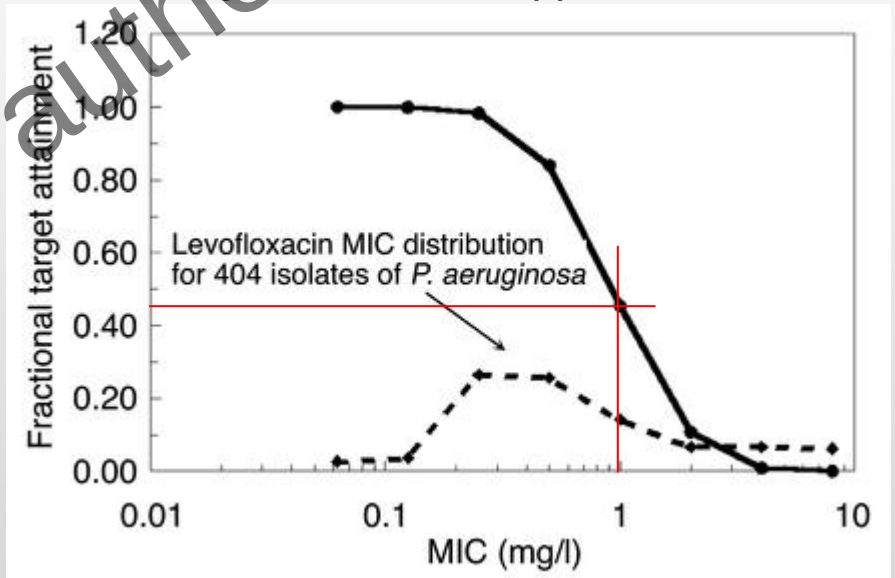


Patients - Monte Carlo Simulation

PK: patients treated with 750mg levofloxacin once daily for nosocomial pneumonia

PK/PD target microbiological outcome: >87
PTA: 72% at MIC 1 mg/L

PK/PD target resistance suppression: >157



N Jumbe et al: J Clin Invest 2003;112:275
G Drusano et al: J Infect Dis. 2004;189:590

CENTER FOR ANTI-INFECTIVE AGENTS

Probability of Target Attainment

- Monte Carlo Simulation, P. aeruginosa, target AUC/MIC 157:
  (G. Drusano, 2012)
  - Ciprofloxacin 400mg iv q8h:
    PTA 62%, emergence of resistance 38%
  - Ciprofloxacin 200mg iv q12h:
    PTA 25%, emergence of resistance 75%

- Clinical studies:
  - Ciprofloxacin 400mg iv q8h:
    Emergence of resistance 33%
  - Ciprofloxacin 200mg iv q12h in nosocomial pneumonia
    Emergence of resistance 70-77%

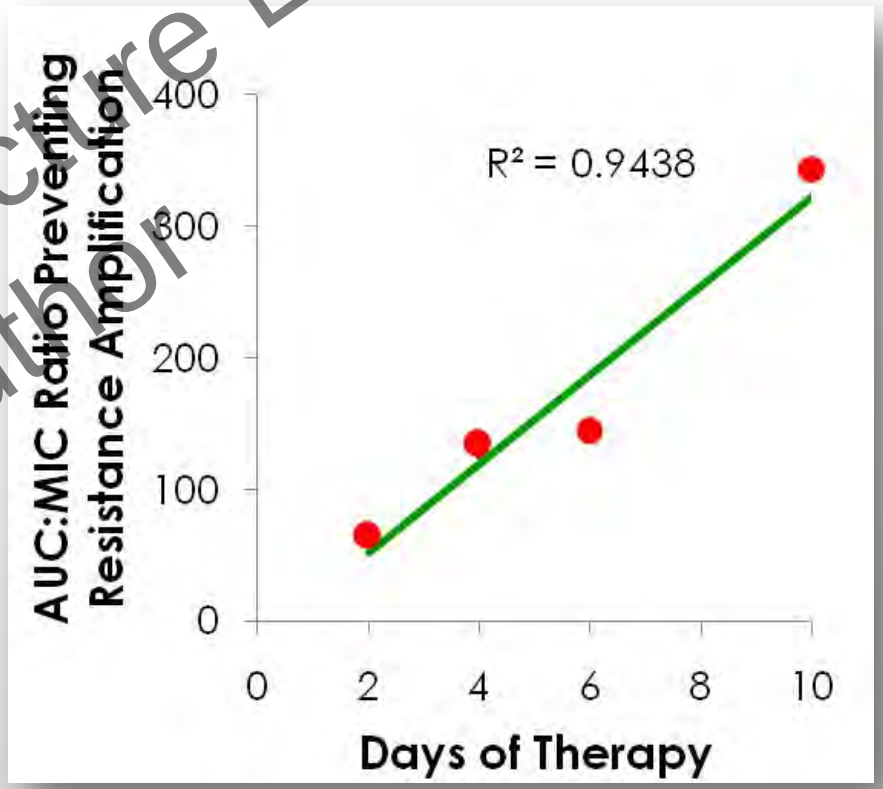
C Peloquin et al: Arch Intern Med. 1989;149:2269-73
M Fink et al: AAC 1994 ; 38:547-557

Resistance Development – Treatment Duration

Staph. aureus - Garenoxacin
*f*AUC/MIC 100

4 doses: susceptible population dominant, resistant subpopulation amplifying

>4 doses: resistant population exceeded the susceptible population at the end of therapy



G. Drusano et al. JID 2009, 199: 219
VH Tam et al: J Infect Dis 2007, 195:1818-27

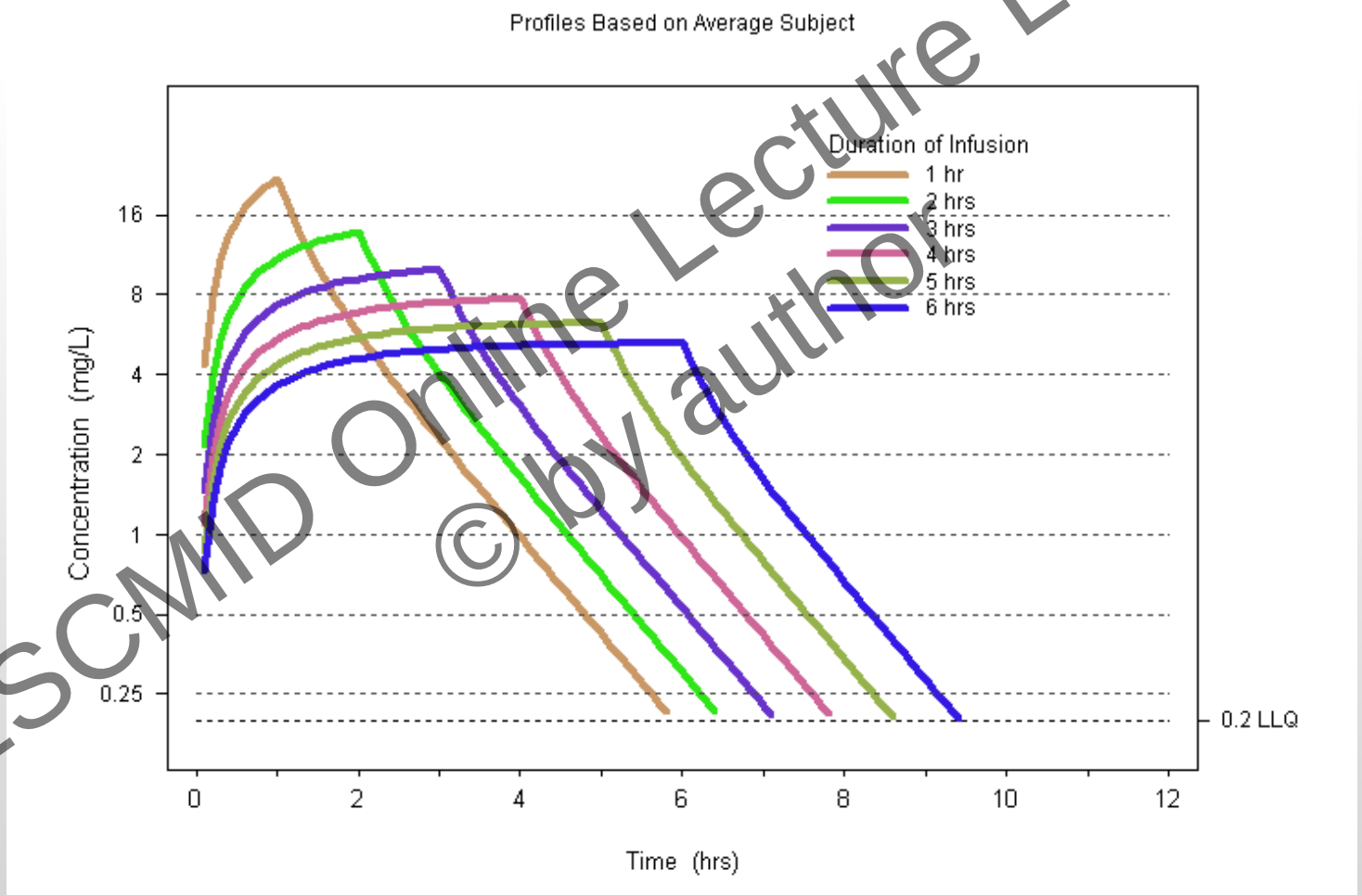
CENTER FOR ANTI-INFECTIVE AGENTS

Dose Optimisation

- Critically ill patients with potentially decreased drug exposure
- Elevated MIC or risk for decreased susceptibility
- High bacterial burden
- Neutropenia

Dose optimisation

Optimizing Doripenem % T>MIC with prolonged infusion



Bhavnani SM et al: AAC 2005; 49:3944-3947

CENTER FOR ANTI-INFECTIVE AGENTS

Dose Optimisation

- Beta-lactam antibiotics
  - High dose, infusion time (2-3 hours), continuous infusion?
  - Short dosing intervall
- Quinolones
  - Increased daily dosage
- Aminoglycosides
  - Increased dosage once daily, TDM, short duration of therapy
- Linezolid
  - Dosing according to TDM (AUC_{0-24}/MIC: >100 and %t>MIC >85%)
- Vancomycin
  - Dosing according to TDM (target trough levels of 15–20 mg/L)

Duration of therapy as short as possible!

Combination therapy!

International Society of Anti-Infective Pharmacology
Founded in 1991

www.isap.org

EPASG
ESCMID PK/PD OF ANTI-INFECTIVES STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

www.escmid.org/epasg

Preserving old antibiotics for the future
www.aida-project.eu

Supported by the EU 7th Framework Program