Pharmacokinetic Data for Breakpoint Analysis

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Pharmacokinetic Data for Breakpoint Analysis

- For the interested (if any), this paper gave the original description of using Monte Carlo Simulation for breakpoint determination and, after expectation, dose choice

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2001, p. 13–22 Vol. 45, No. 1
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.1.13–22.2001

Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

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Pharmacokinetic Data for Breakpoint Analysis

- So, why go to all the trouble of generating breakpoint estimates mathematically (population modeling, Monte Carlo simulation, etc)?
- The reason is that we can clearly see the impact of the important factors influencing whatever endpoint is deemed important (clinical outcome, microbiological outcome, resistance suppression, etc)

Pharmacokinetic Data for Breakpoint Analysis

- What data are required and why?
  1) First and foremost, an exposure target (free drug)
  2) Drug exposure data and its VARIABILITY for a population of patients/subjects
  3) MIC variability for organisms of clinical interest
- These data lead to the ability to perform a target attainment analysis which is the decision support (NOT A DECISION IN ITSELF) for a breakpoint determination

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Exposure Target

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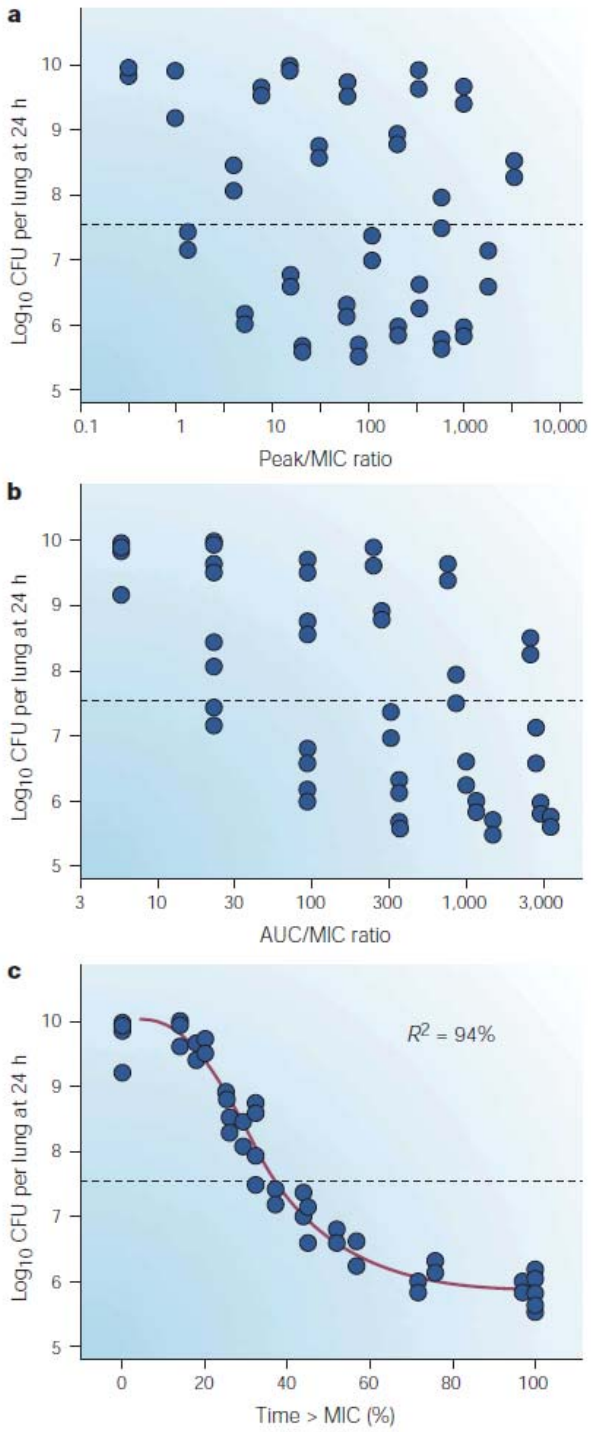
- The first issue for identifying an exposure target is to identify the exposure index linked to outcome



These are data from the Craig Lab, examining a cephalosporin against *Klebsiella pneumoniae* in a murine pneumonia model

It is obvious by inspection that Time > MIC explains more of the variability in bacterial kill than the other measures of drug exposure examined

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- The next issue is to determine the MAGNITUDE of the exposure required
- The magnitude is determined by BOTH a measure of drug, but also by the MIC value for the organism being treated

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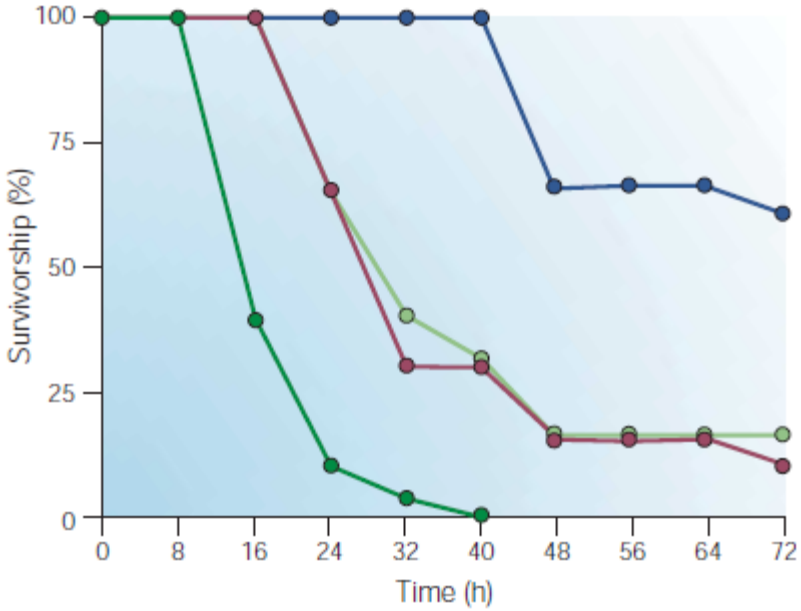
Strain	Fluoroquinolone MIC (mg L^{-1})	Daily dose (mg kg^{-1})
Parent	1.0	80
Daughter 1	4.0	80
Daughter 2	8.0	80
Parent	1.0	20



Drusano GL. Nature Reviews: Microbiology 2004;2:293-300

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- So, how do we determine the magnitude of the exposure required
- The answer, as always, is “It Depends”
- It depends on what data are available at the time that the process is ongoing
- One man’s opinion: Generally, actual outcome data from patients trumps all

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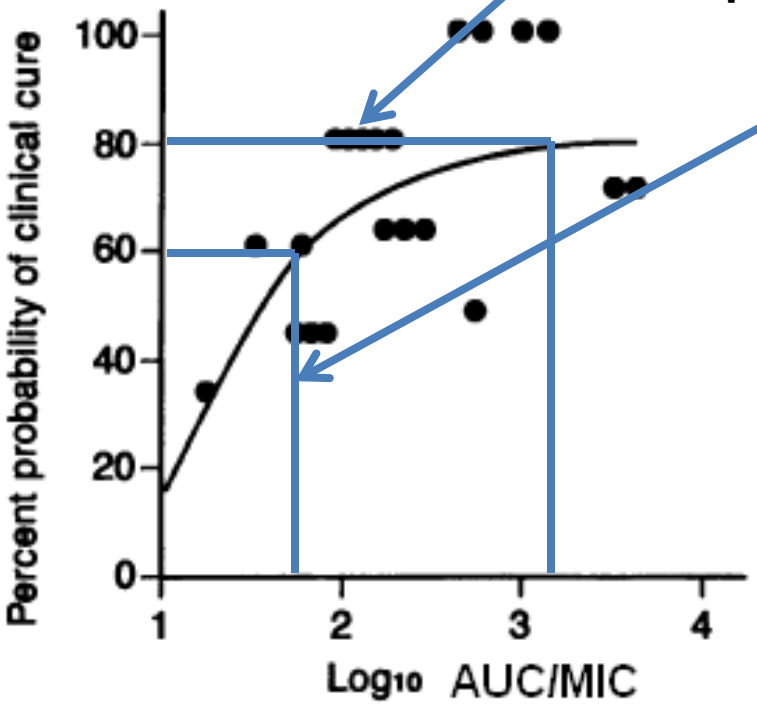
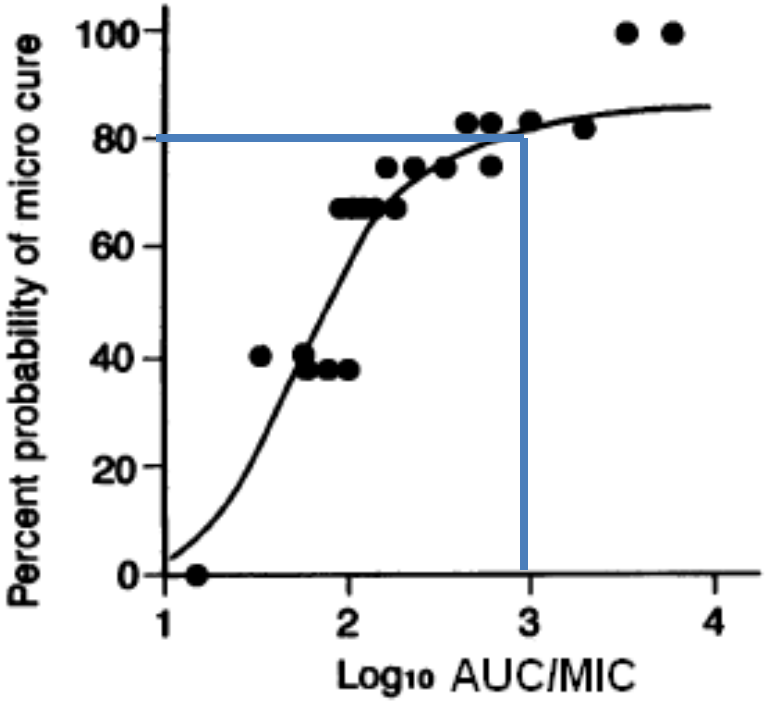
Ciprofloxacin Clinical Outcome **Ciprofloxacin Micro Outcome**

Exposure for Dear Old Mom

Exposure for Mother-In-Law





Forrest et al AAC 1993;37:1073-1081

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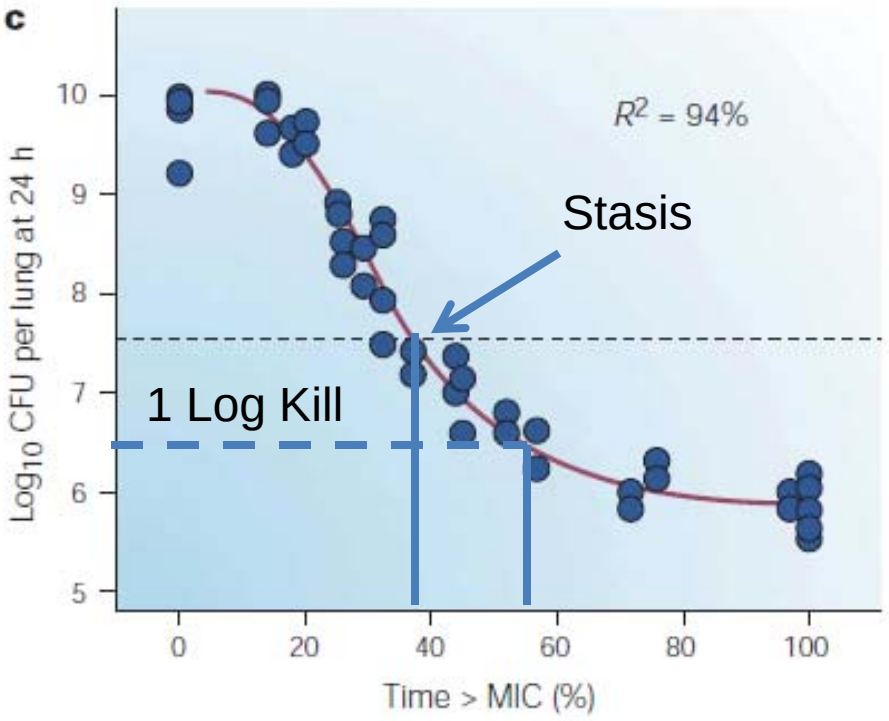
- Sometimes, we don't have clinical data and must rely on pre-clinical data
- We can then choose an amount of microbiological effect
- How much is enough?
- Here, we are guided by experience and a little theory



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- For instance, acute bacterial skin and skin structure infections generally require attainment of stasis or, at most 1 Log bacterial kill (see Ambrose et al “its just not for mice anymore CID paper)
- For HAP/VAP, requirements are much more stringent and a 2-3 Log bacterial kill is near optimal
- The size of the bacterial burden is critical, as granulocyte kill is saturable

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- So, now we can step up to the plate and perform the analysis
- Let us assume that the dynamically-linked index is AUC/MIC Ratio
- We know the exposure target we would prefer
- So, now we need pharmacokinetic information
  1) What are the PK parameter values?
  2) as or MORE importantly, what is the dispersion?

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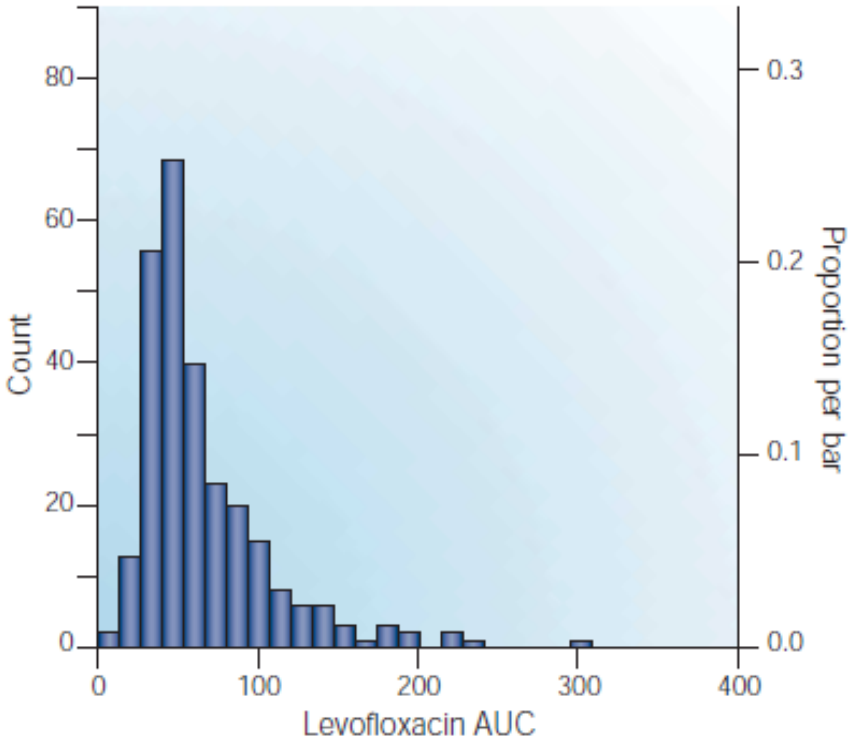
- These data come from our levofloxacin data set published in JAMA and represent the range of AUC values for a 500 mg dose seen in 252 patients with PK determinations
- IT IS A WIDE RANGE!
- The drug dose chosen needs to achieve the desired target for an acceptably large fraction of the population



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- We often speak of obtaining “POPULATION pharmacokinetic parameter values”
- Well there are a number of ways of doing this
- Some are fancier than others, but the “old fashioned way of studying some reasonable number of patients/subjects and obtaining a measure of central tendency (mean/median) and dispersion (standard deviation) is acceptable

Pharmacokinetic Data for Breakpoint Analysis

- So, why do we get fancy with very mathematically intensive population analysis either parametrically or non-parametrically (in the distribution)?
- Generally, the fancier methods allow partitioning of the variability into different pots (due to fixed effects such as creatinine clearance, weight, etc or into true between-subject variability), between-occasion variability, residual variability
- Theoretically this provides the most accurate estimates of true between-patient variability

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How About Volunteer versus Patient Data?

Pharmacokinetic Data for Breakpoint Analysis

TABLE 1. Demographics of population analyzed[a]

Parameter	Age (yr)	Wt (kg)	Estimated CL_{CR} (ml/min)	Sex (M/F)	Race (C/B/H/O)	Patients/volunteers
Mean	34	75	106			
Median	30	75	109			
Range	18–65	49–99	7–169			
No. of subjects				115/35	127/10/10/3	39/111

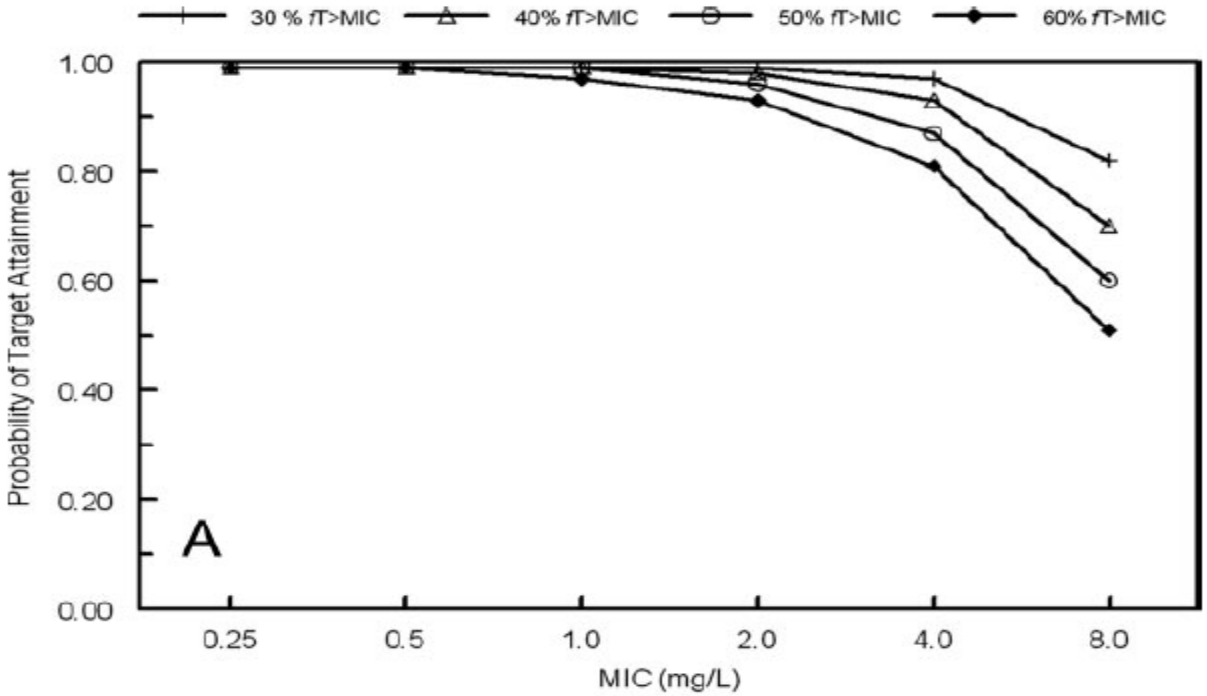
[a] M, male; F, female; C, Caucasian; B, black; H, Hispanic; O, other.

TABLE 2. Population pharmacokinetic parameter values for ceftobiprole[a]

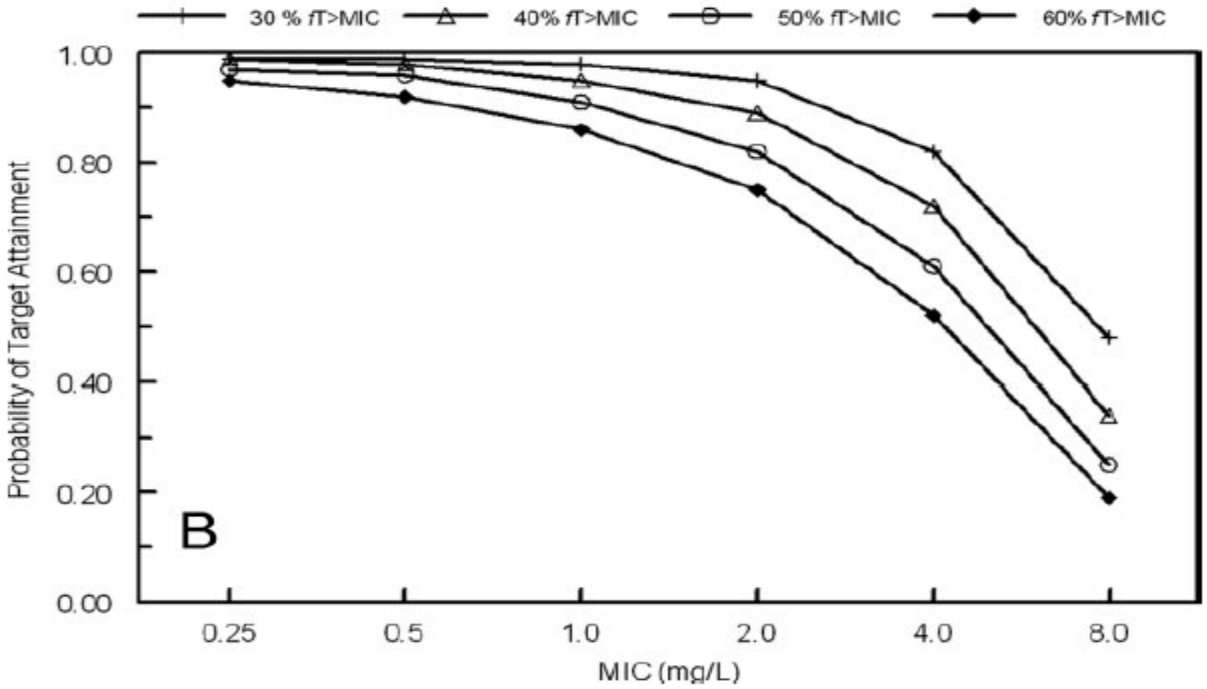
Parameter	k_h (h^{-1})	V_c (liters)	k_{23} (h^{-1})	k_{32} (h^{-1})	CL_{sl} (liters/h)	CL_{int} (liters/h)
Mean	51.8	7.65	3.05	1.10	0.510	2.35
Median	59.9	7.05	1.20	0.960	0.484	2.46
SD	17.5	3.89	5.14	0.951	0.318	1.98

[a] k_h, first-order hydrolysis rate constant; V_c, volume of the central compartment; k_{23} and k_{32}, first-order intercompartmental transfer rate constants; CL_{sl}, slope constant relating the estimated CR_{CL} to ceftobiprole clearance; CL_{int}, clearance intercept.

AAC 2007;51:2378-2387



Ceftobiprole 500 mg Q8h, 2 hr infusion



Ceftobiprole 500 mg Q12h, 1 hr infusion

Pharmacokinetic Data for Breakpoint Analysis

TABLE 5. Overall PTAs for *Staphylococcus aureus*, both methicillin resistant and sensitive, for targets maintaining 30% (stasis), 40%, and 50% (nearly maximal effect) *fT* > MIC

Treatment and organism	PTA (%) for:		
	30% *fT* > MIC	40% *fT* > MIC	50% *fT* > MIC
Ceftobiprole 500 mg i.v. q12h (1-h infusion)			
MRSA (n = 170)	98.4	96.0	92.6
MSSA (n = 291)	99.5	98.5	96.9
Ceftobiprole 500 mg i.v. q8h (2-h infusion)			
MRSA (n = 170)	99.9	99.6	98.8
MSSA (n = 291)	99.9	99.9	99.9

TABLE 6. Overall PTAs for gram-negative bacilli for a ceftobiprole regimen of 500 mg q8h as a 2-h infusion for targets maintaining 40% (stasis), 50%, and 60% (nearly maximal effect) *fT* > MIC

Organism	PTA (%)		
	40% *fT* > MIC	50% *fT* > MIC	60% *fT* > MIC
AmpC-producing gram-negative bacilli (n = 166)	89.8	88.9	87.8
Non-AmpC-producing gram-negative bacilli (n = 206)	95.2	94.8	94.1
Pseudomonas aeruginosa (n = 407)	71.1	66.4	62.0

Pharmacokinetic Data for Breakpoint Analysis

TABLE 1. Parameter estimates and correlation matrix obtained after population modelling[a]

Parameter	Parameter estimate (mean ± SD)	Correlation matrix		
		Volume (liter)	CL (liter/h)	K_{cp} (h^{-1})
Volume (liter)	10.386 ± 2.013	1		
CL (liter/h)	5.111 ± 0.518	0.07657	1	
K_{cp} (h^{-1})	0.542 ± 0.237	−0.61920	0.42430	1
K_{pc} (h^{-1})	0.883 ± 0.335	−0.09290	0.25250	0.73700

[a] Abbreviations: CL, clearance; K_{cp} and K_{pc}, equilibrium constants from central to peripheral compartment and from peripheral to central compartment, respectively.

AAC 2004;48:1713-1718

TABLE 2. Population pharmacokinetic parameter values for ceftobiprole[a]

Parameter	k_h (h^{-1})	V_c (liters)	k_{23} (h^{-1})	k_{32} (h^{-1})	CL_{sl} (liters/h)	CL_{int} (liters/h)
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Median	59.9	7.05	1.20	0.960	0.484	2.46
SD	17.5	3.89	5.14	0.951	0.318	1.98

[a] k_h, first-order hydrolysis rate constant; V_c, volume of the central compartment; k_{23} and k_{32}, first-order intercompartmental transfer rate constants; CL_{sl}, slope constant relating the estimated CR_{CL} to ceftobiprole clearance; CL_{int}, clearance intercept.

AAC 2007;51:2378-2387

2.5 Percentile-97.5 Percentile of Clearance (L/hr) From a 9,999 Subject Monte Carlo Simulation

2.5%tle	97.5%tle	Mean	SD
4.16	6.20	5.11	0.518

2.5 Percentile-97.5 Percentile of Clearance (L/hr) From a 9,999 Subject Monte Carlo Simulation

2.5%tle	97.5%tle	Mean	SD
1.98	12.46	5.53	2.78

Pharmacokinetic Data for Breakpoint Analysis

AAC 2004;48:1713-1718 **AAC 2007;51:2378-2387**

Target Attainment for a 500 mg Q8h, 0.5 hr Infusion Regimen of Ceftobiprole

MIC (mg/L)	Target (% of Dosing Interval)				Target (% of Dosing Interval)			
	30%	40%	50%	60%	30%	40%	50%	60%
1.0	1.0	1.0	1.0	1.0	0.99	0.98	0.96	0.94
2.0	1.0	1.0	1.0	0.72	0.98	0.95	0.92	0.87

Pharmacokinetic Data for Breakpoint Analysis

- So, strangely, volunteer data is NOT always the most conservative estimate of a drug's target attainment performance
- The variability of the estimates plays a major role in the outcome of the target attainment analyses by Monte Carlo simulation
- The TYPE of infection and the sickness of the patient also has a major influence

Meropenem in VAP

Population Pharmacokinetic Parameters for Intubated Patients with Hospital-Acquired Pneumonia (n=39).

Parameter	**V_C**	**CL**
Units	**L**	**L/h**
Mean	12.6	15.2
Median	6.7	13.5
S.D.	13.3	9.7
CV% (Mean)	105.6%	63.8%
CV% (Median)	198.5%	71.8%

V_c = Volume central compartment; CL = Meropenem Plasma Clearance; S.D. = Standard Deviation

In Review AAC

The fit of the model to the data was quite acceptable. For plasma, Observed = 0.998 x Predicted + 0.919; r^2 = 0.962. For ELF, Observed = 1.0014 x Predicted – 0.0024; r^2 = 0.999.

Levofloxacin in HAP

Table 1. Population pharmacokinetic parameter values derived from 58 patients with nosocomial pneumonia who were receiving levofloxacin (750 mg intravenous) as a 1.5-h constant-rate infusion.

Unit	Vol, L	Kcp, h^{-1}	Kpc, h^{-1}	CL, L/h
Mean	34.4	7.65	6.07	7.24
Median	23.3	2.66	0.924	6.24
SD	33.5	9.59	12.0	4.36

NOTE. CL, total clearance of levofloxacin; Kcp and Kpc, the first-order intercompartmental transfer rate constants connecting the central and peripheral compartments; Vol, volume of the central compartment.

Parameter	Vc (L)	CL (L/hr)
Mean	34.4	7.24
Median	23.3	6.24
SD	33.5	4.36
CV% Mean	**97.4**	**60.2**
CV% Median	**144**	**69.9**

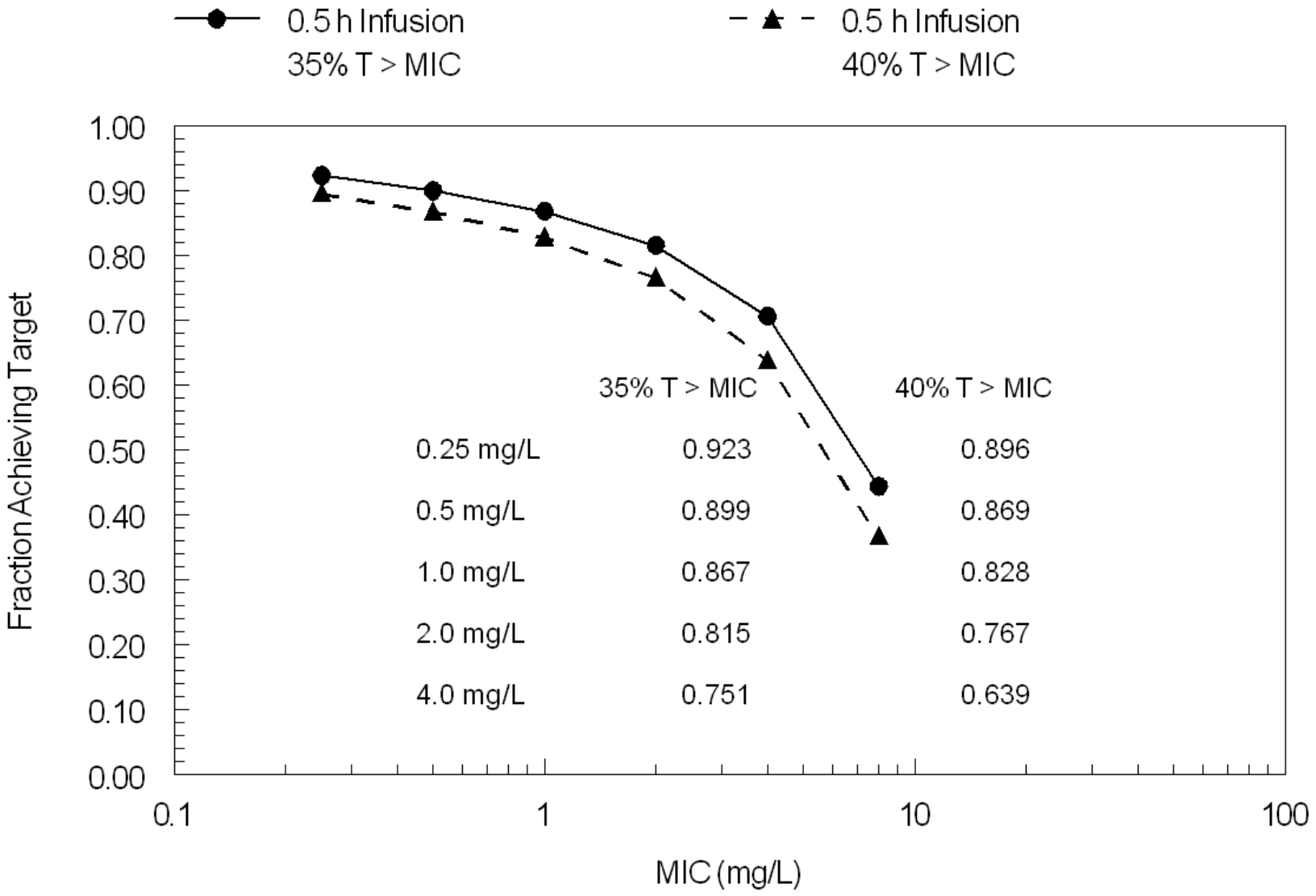
JID 2004;189:1590-1597

Pharmacokinetic Data for Breakpoint Analysis

- Not ALL volunteer studies are as tight as the ceftobiprole one with respect to CV% for clearance (circa 10% - it was done in Switzerland)
- What is clear is that patient studies have broader ranges of clearance identified
  Ceftobiprole Skin
  volunteers circa 10%; patients plus volunteers 62%
  HAP and VAP 60-70% for meropenem and levofloxacin
- The variability has an impact on target attainment

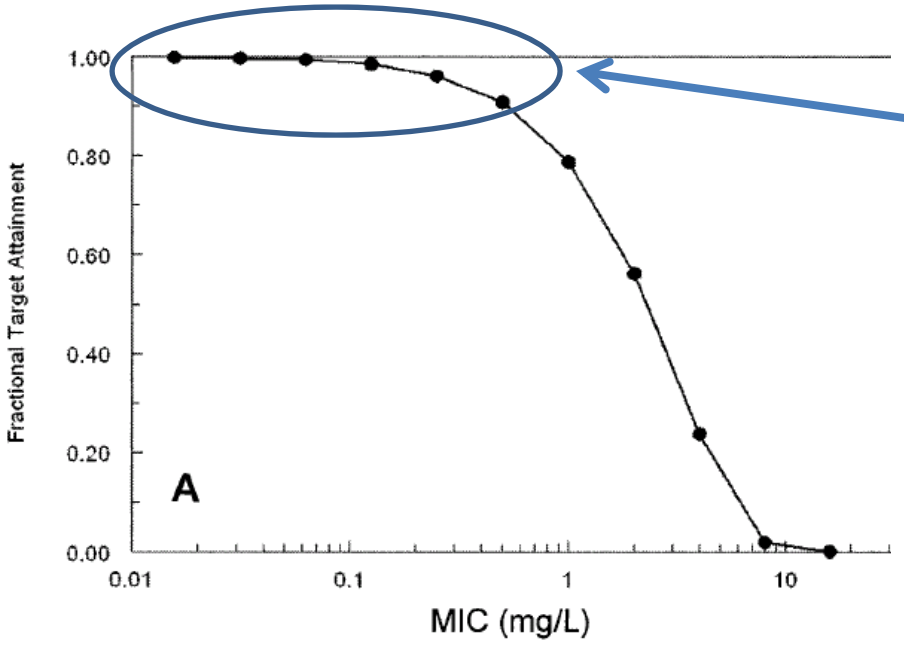
Meropenem 1.0 gm Q 8 h, Half Hour Infusion

Fractional Target Attainment



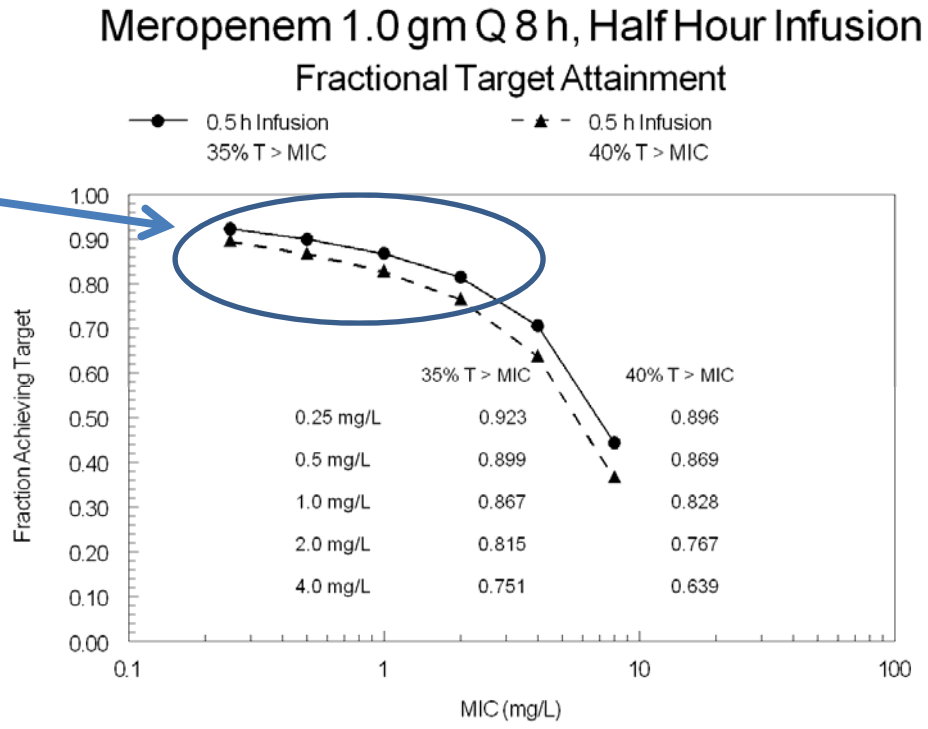
Pharmacokinetic Data for Breakpoint Analysis

Meropenem 1 g 0.5 hr infusion Q8h – Volunteers – 40% Time > MIC



AAC 2005;47:1881-1889

Meropenem 1 g 0.5 hr infusion Q8h – VAP patients



AAC In Review

Pharmacokinetic Data for Breakpoint Analysis

- The volunteers had a higher clearance but were less variable relative to the VAP patients
- This resulted in considerably lower target attainments, especially at lower MIC values

	Volunteers		VAP Patients	
	Mean	SD	Mean	SD
Vc	12.4	3.51	12.6	13.3
CL	16.3	3.08	15.2	9.7

Pharmacokinetic Data for Breakpoint Analysis

- Generally, we do breakpoint analysis on the basis of plasma concentration-time data
- More recently, we have started to look at target site attainment
- For meropenem, we have ELF penetration data taken from VAP Patients
- We also derived ELF targets for cell kill and resistance suppression in a murine pneumonia model
- The variability in ELF penetration was awful!

Resistance Suppression in *Pseudomonas aeruginosa*

Observed-Predicted Regression Equations for the System Outputs After the Bayesian Estimation Step for the Murine Model

Plasma

Observed = 0.980 * Predicted + 0.164; $r^2 = 0.995$

ELF

Observed = 0.960 * Predicted + 0.025; $r^2 = 0.997$

Total Bacterial Population

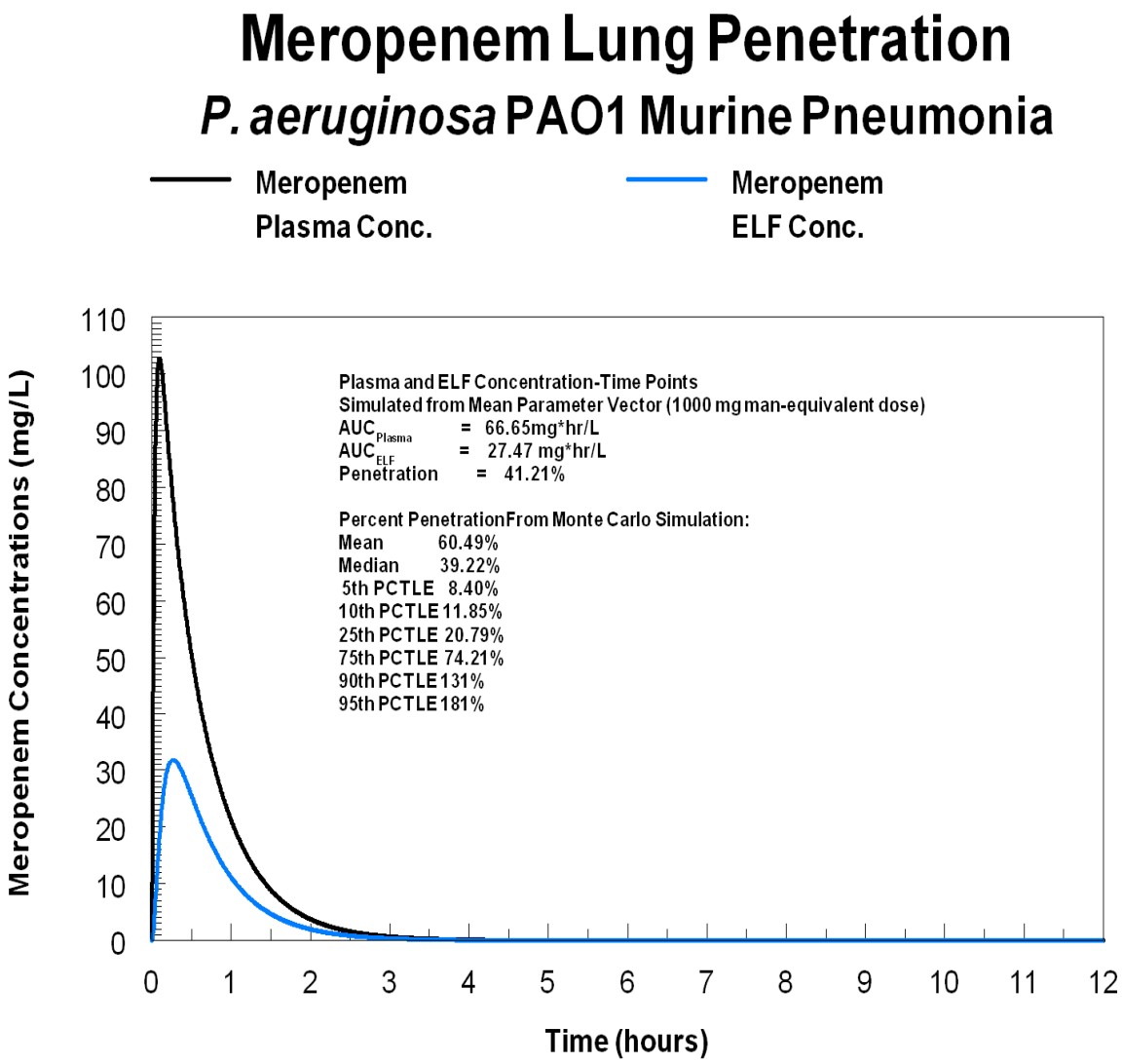
Observed = 0.883 * Predicted + 0.638; $r^2 = 0.914$

Meropenem-Resistant Bacterial Population

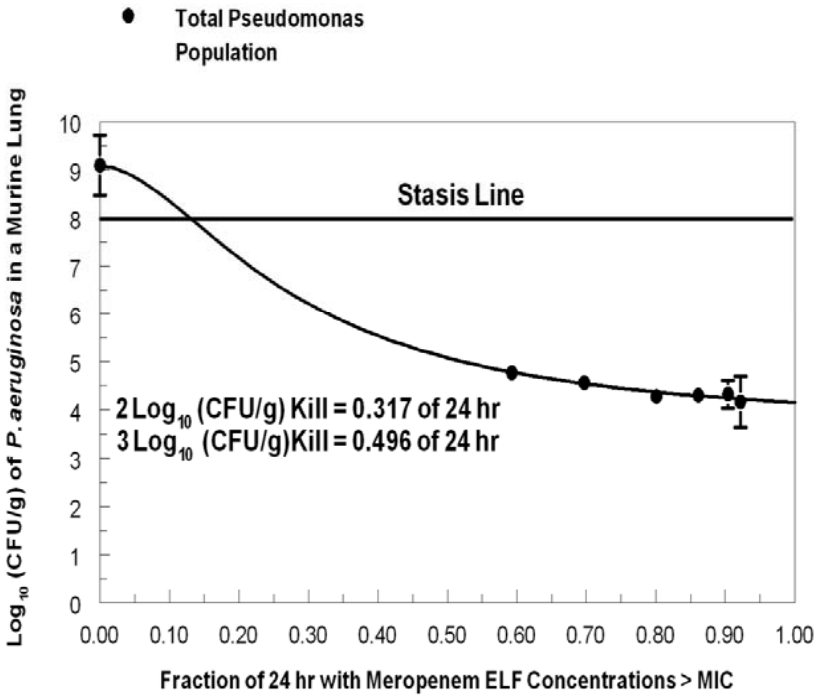
Observed = 0.776 * Predicted + 0.464; $r^2 = 0.801$

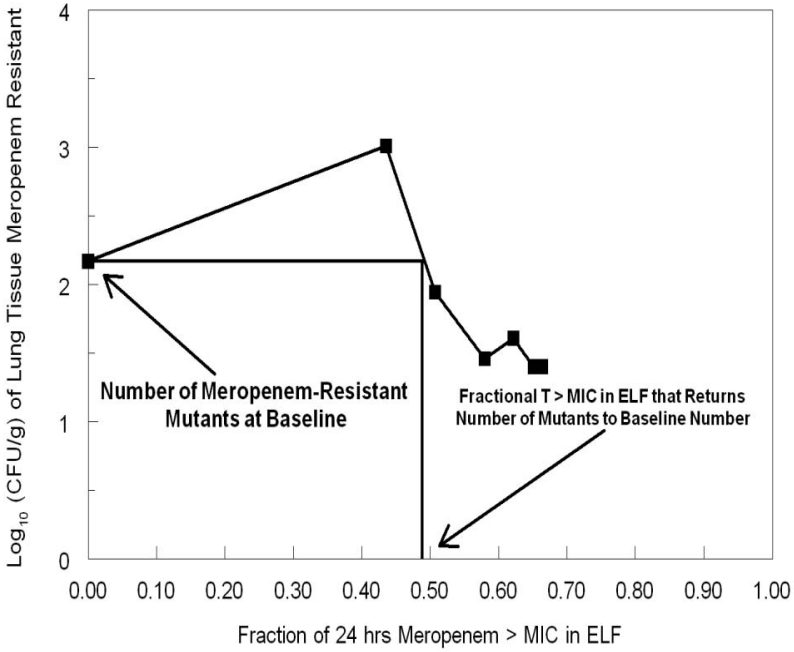
Data generation supported from RO1 AI079578 to our laboratory

Resistance Suppression in *Pseudomonas aeruginosa*



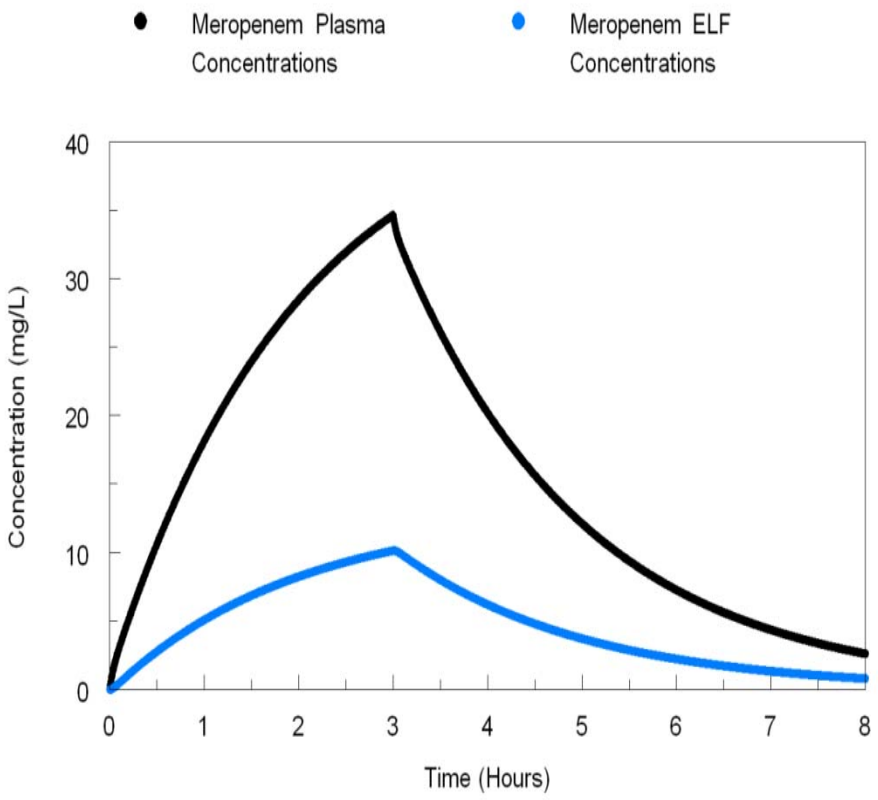
Resistance Suppression in *Pseudomonas aeruginosa*





These are the exposure targets in ELF for cell kill and resistance suppression, as derived from the model

Penetration of Meropenem into Epithelial Lining Fluid (ELF) in 39 Patients with Ventilator-Associated Pneumonia. All Patients had their Pathogen Recovered in a Broncho-Alveolar Lavage at Baseline with more than 10^4 CFU/ml. A 9,999 Subject Monte Carlo Simulation was Performed to Examine Variability in Penetration



Observed-Predicted Regressions After the Bayesian Step

Plasma

Observed = 0.998 * Predicted +0.919

$r^2 = 0.962$; $p << 0.001$

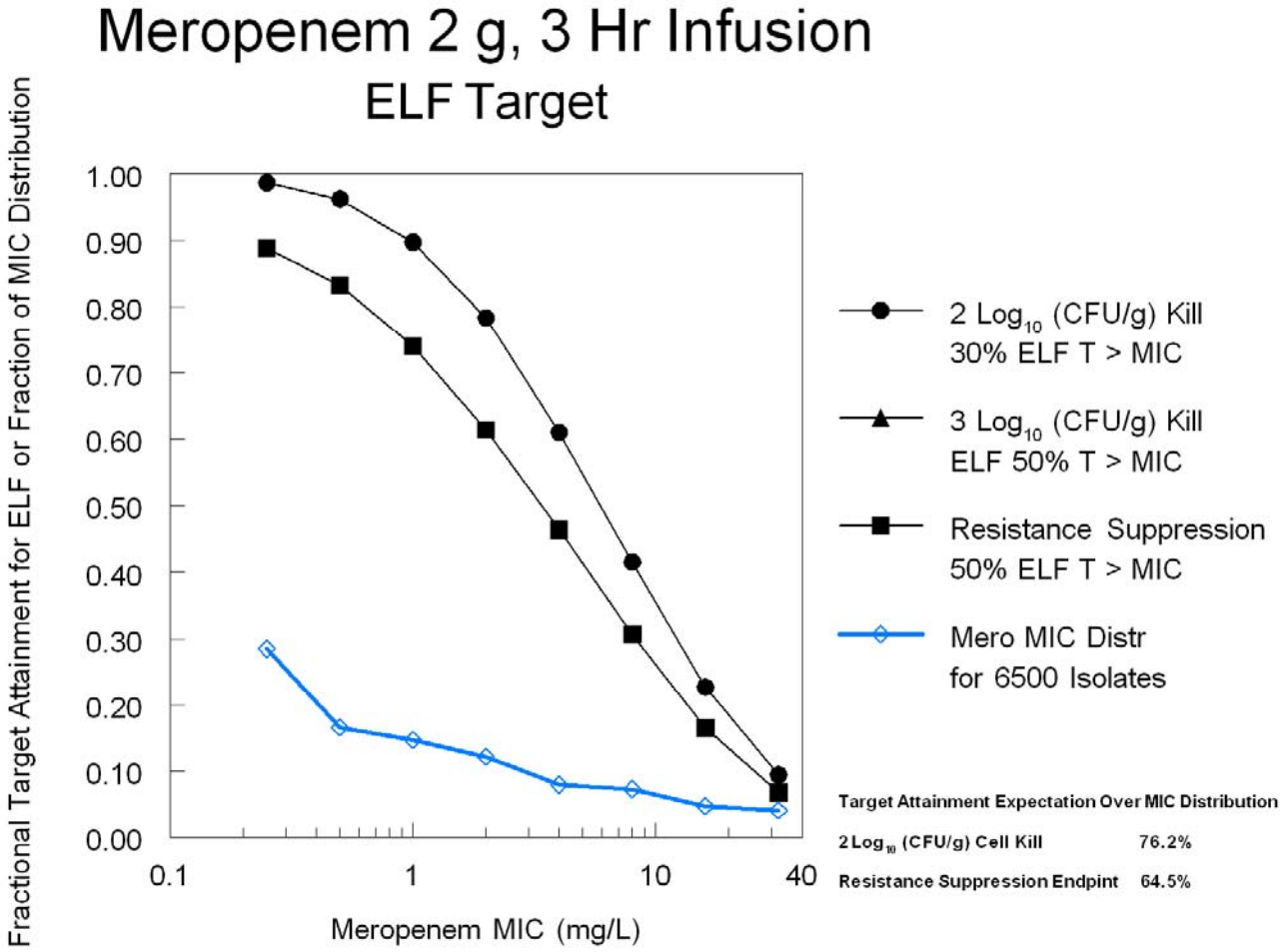
ELF

Observed = 1.0014 * Predicted – 0.0024

$r^2 = 0.999$; $p << 0.001$

	AUC_{PL} (mg*h/L)	AUC_{ELF} (mg*h/L)	PENETRATION Fraction
Mean	150.8	82.3	0.816
Median	130.9	35.0	0.254
5^{th} Pctle	51.6	2.75	0.021
10^{th} Pctle	63.9	4.76	0.037
25^{th} Pctle	90.1	12.5	0.090
75^{th} Pctle	189.3	92.1	0.701
90^{th} Pctle	262.1	204.7	1.779
95^{th} Pctle	315.7	315.3	3.153

Target Attainment of a 2000 mg Meropenem Dose Administered as a 3-hour infusion for Both Cell Kill Targets and Resistance-Suppression Targets



Resistance Suppression in *Pseudomonas aeruginosa*

- Meropenem is an excellent single agent and may be the best β-lactam against *P. aeruginosa* (Dori is also excellent, but the comparison must be dose dependent and, truthfully, we are just about to get Dori ELF penetration data)
- The intense variability in ELF penetration does not allow target attainment for either 2 Log_{10}(CFU/g) kill or resistance suppression to rise to an acceptable level, particularly when MIC values are > 1.0 mg/L
- It looks GREAT in combination with either an aminoglycoside or a fluoroquinolone

Pharmacokinetic Data for Breakpoint Analysis-Conclusions

- We use population PK modeling techniques to get accurate estimates of true between subject/patient variability in the important parameters
- While many feel that volunteer data is the most "conservative", this may not be true in all cases, because real patients frequently have greater variability in their PK parameters
- This may translate into lower target attainments because a larger fraction of the population will have HIGHER clearances because of the greater RANGE of the parameter values