Bridging the Bench to Bedside Divide: Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

G.L. Drusano, M.D.

Professor and Director

Institute for Therapeutic Innovation

College of Medicine

University of Florida

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

Much of what is to be presented is supported by R01's AI079578 and AI090802

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

- PK/PD modeling is a valuable tool for pre-clinical/clinical bridging
- What is the critical question for drug development for anti-infectives?

-What is the Right Dose?

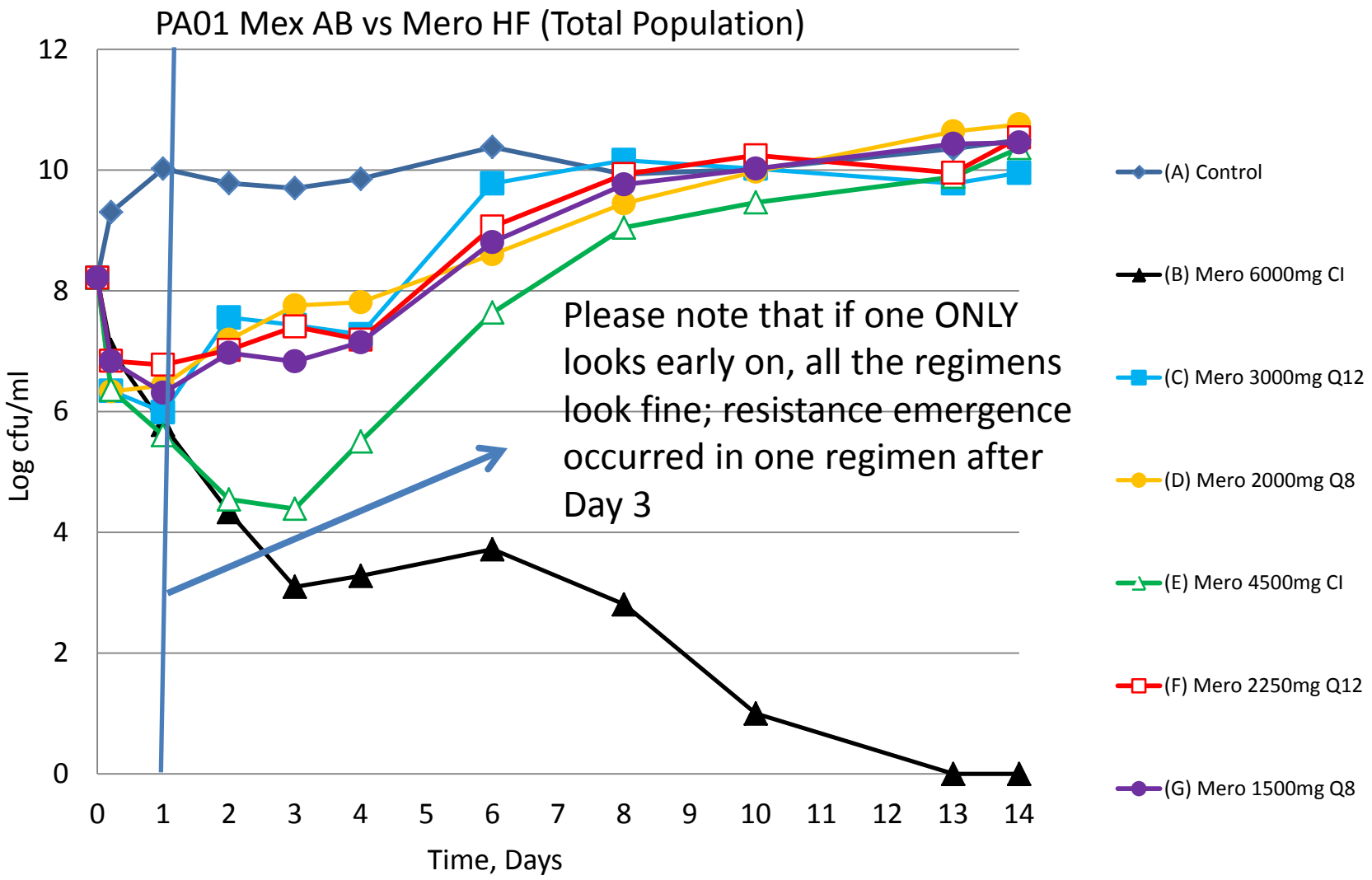
-An Ancillary Question is:

For What Purpose?

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

- We examined meropenem in two pre-clinical models:
  *Hollow Fiber Infection Model with *P. aeruginosa*
  *Murine pneumonia model with *P. aeruginosa*
- In both systems, virtually any resistance mechanism can be studied
- We tend to employ isogenic sets

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens



Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

- One needs a LOT of meropenem to shut off resistance amplification in the hollow fiber system, because of the complete lack of an immune system
- Regimen failure was because of resistance
- We developed a neutropenic murine pneumonia model to examine this issue in the Epithelial Lining Fluid (ELF)
- We developed a very large mathematical model to simultaneously examine plasma and ELF meropenem concentrations and the effect on the total population and resistant subpopulation

TABLE 2. Parameter estimates from the population pharmacokinetic/dynamic analysis from the murine pneumonia model with *Pseudomonas aeruginosa* PAO1 as the infecting pathogen

Parameter[a]	Mean	Median	SD
V_c/F (liters)	0.00879	0.00880	0.00266
CL/F (liters/h)	0.0198	0.0179	0.00549
K_{12} (h^{-1})	1.13	0.992	0.443
K_{21} (h^{-1})	5.10	5.35	1.46
V_{ELF} (liters)	0.00508	0.00541	0.00268
K_a (h^{-1})	19.5	18.1	7.92
$K_{gmax\text{-}s}$ (h^{-1})	0.952	0.711	0.478
$K_{killmax\text{-}s}$ (h^{-1})	1.86	1.70	0.745
$C_{50k\text{-}s}$ (mg/liter)	2.08	1.65	1.25
$H_{k\text{-}s}$	17.7	19.0	4.50
POPMAX (CFU/g)	1.96×10^9	2.21×10^9	1.30×10^9
$K_{gmax\text{-}r}$ (h^{-1})	0.307	0.309	0.179
$K_{killmax\text{-}r}$ (h^{-1})	0.498	0.605	0.252
$C_{50k\text{-}r}$ (mg/liter)	5.38	5.57	2.75
$H_{k\text{-}r}$	20.9	20.4	5.52
IC_4 (CFU/g)	3.46×10^8	4.27×10^8	1.59×10^8
IC_5 (CFU/g)	131	244	98

[a] V_c/F, volume of the central compartment; CL/F, plasma clearance; K_{12}, K_{21}, first order intercompartmental transfer rate constants; V_{ELF}, volume of the ELF compartment; K_a, first order absorption rate constant; $K_{gmax\text{-}s}$ and $K_{gmax\text{-}r}$, first order growth rate constants for the susceptible and resistant subpopulations; $K_{killmax\text{-}s}$ and $K_{killmax\text{-}r}$, first order kill rate constants for the susceptible and resistant subpopulations; $C_{50k\text{-}s}$ and $C_{50k\text{-}r}$, drug concentration at which the kill rate is half maximal; $H_{k\text{-}s}$ and $H_{k\text{-}r}$, Hill's constants for the susceptible and resistant subpopulations; POPMAX, maximal population density; IC_4 and IC_5, initial densities of total pathogens and resistant pathogens.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3406–3412 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01559-10

Meropenem Penetration into Epithelial Lining Fluid in Mice and Humans and Delineation of Exposure Targets[▽]

G. L. Drusano,[1]* T. P. Lodise,[1,2] D. Melnick,[3] W. Liu,[1] A. Oliver,[4] A. Mena,[4] B. VanScoy,[1] and A. Louie[1]

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

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

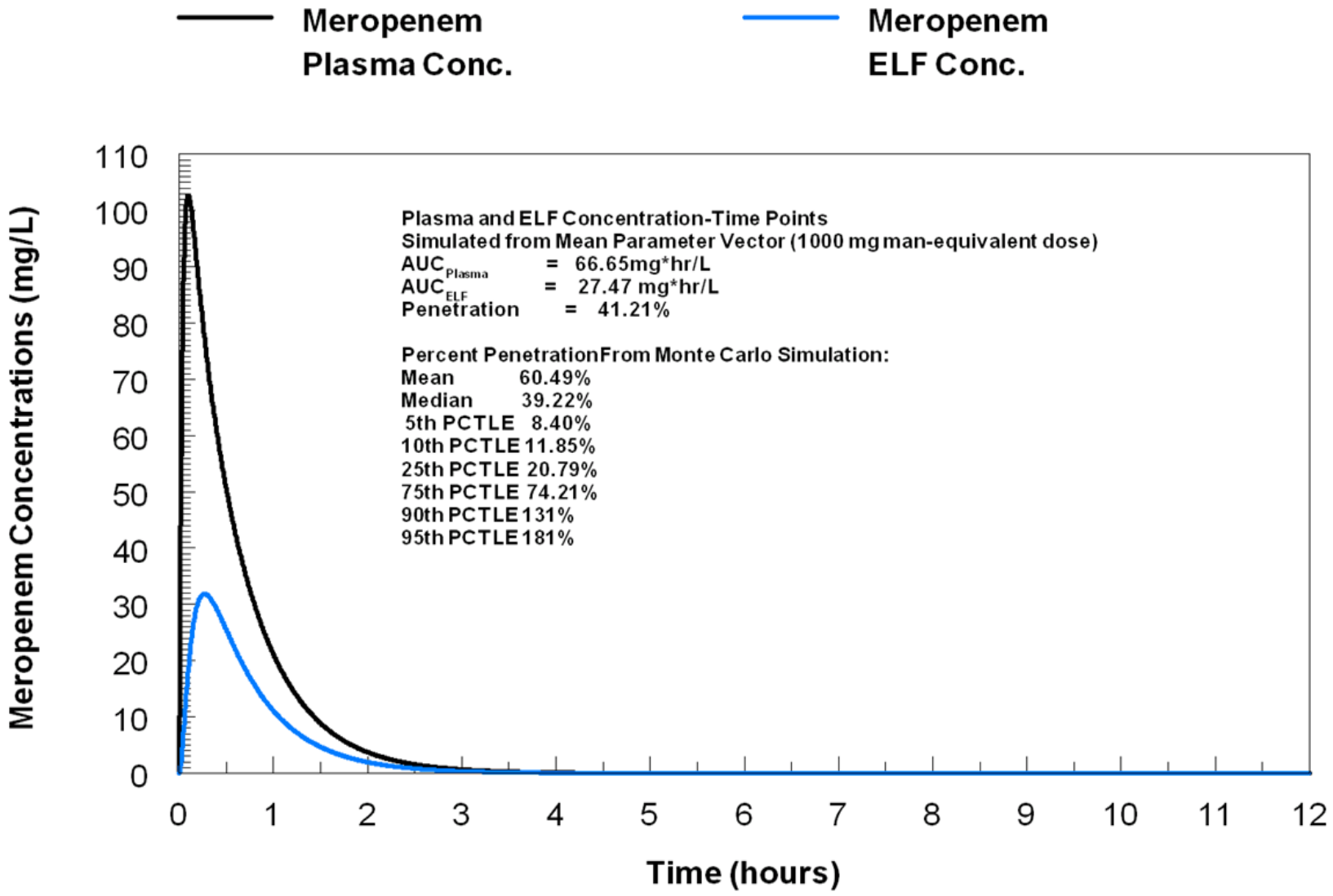
Observed = 0.883 * Predicted + 0.638; $r^2 = 0.914$

Meropenem-Resistant Bacterial Population

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

Meropenem Lung Penetration

P. aeruginosa PAO1 Murine Pneumonia



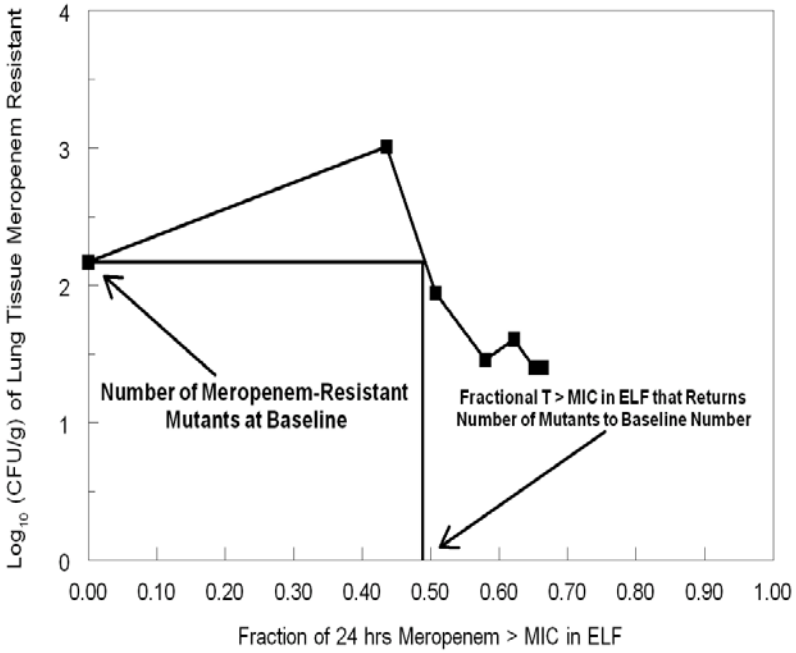
Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

In this instance, because we wished to study resistance suppression, we used a hypermutator Pseudomonas kindly provided by the laboratory of Antonio Oliver

Calculated from the model, for total population organism kill, the ELF exposure required for:

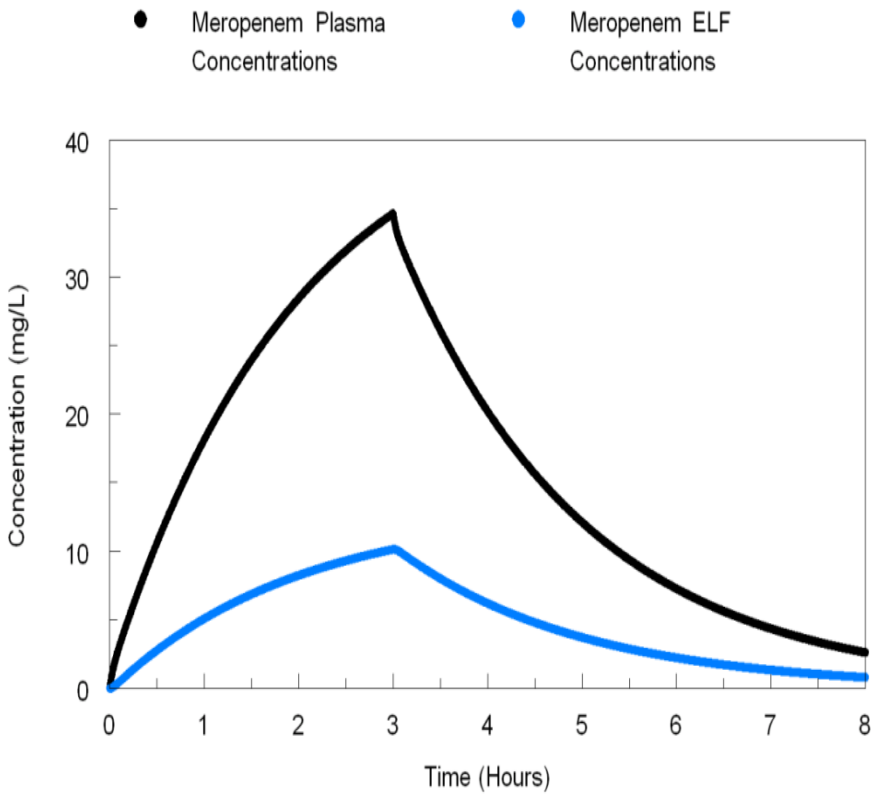
2 Log_{10} (CFU/g) Kill = 0.317 of 24 hrs

3 Log_{10} (CFU/g) Kill = 0.496 of 24 hrs



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

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

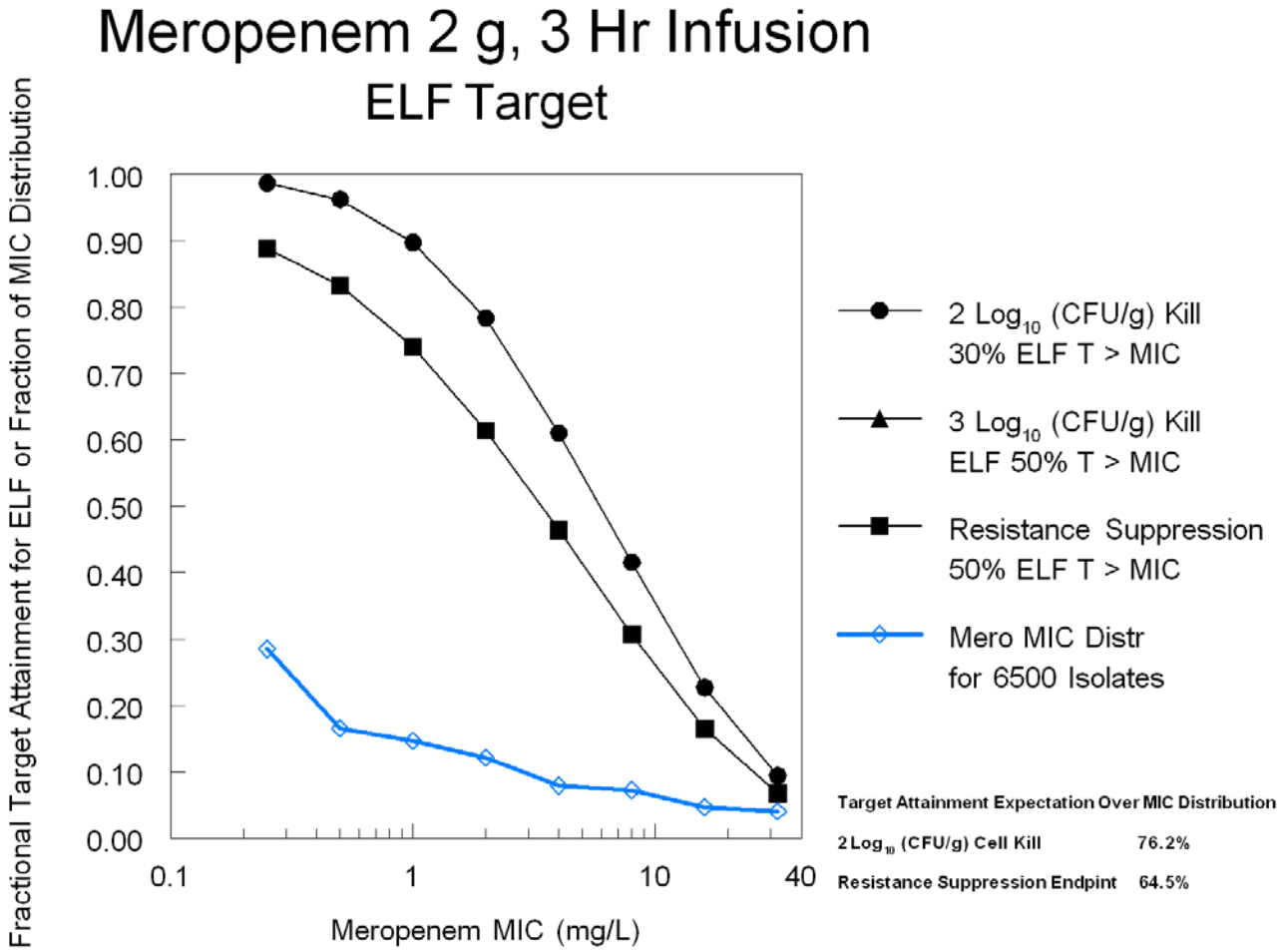
ELF

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



PK/PD Modeling in Drug Development

- Meropenem is an excellent drug as a single agent
- BUT the intense variability in **effect site penetration** does not allow the target attainment for either 2 Log_{10}(CFU/g) cell kill or resistance suppression to rise to an acceptable level, particularly when MIC values are > 1.0 mg/L
- The dirty little secret of antimicrobial therapy is that multiple sources of variability often result in an unacceptable rate of attaining the therapeutic target

Sometimes, single agent therapy just can't get the job done

WHAT ABOUT COMBINATION THERAPY FOR RESISTANCE SUPPRESSION?

LET'S LOOK AT CEFEPIME ALONE AND IN COMBINATION

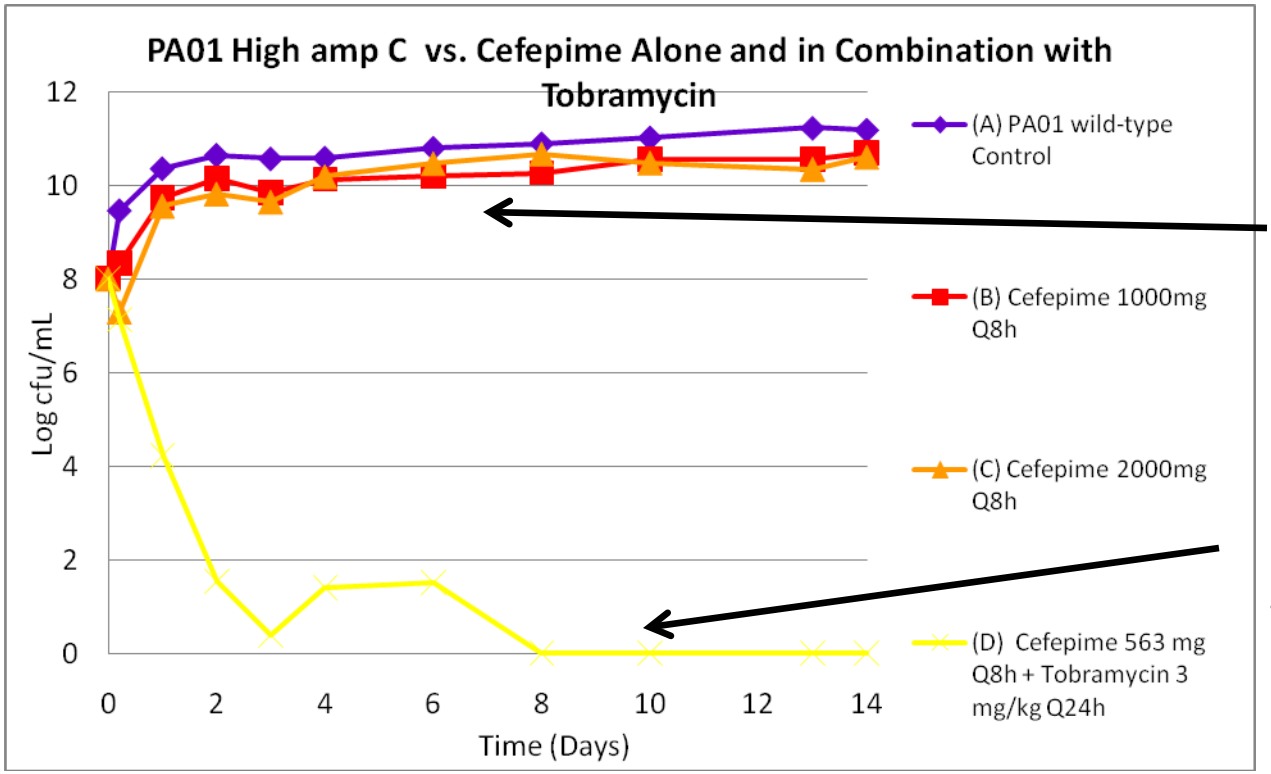
AAC
Journals.ASM.org

Resistance Emergence Mechanism and Mechanism of Resistance Suppression by Tobramycin for Cefepime for *Pseudomonas aeruginosa*

G. L. Drusano,[a*] Robert A. Bonomo,[b,c,e,f] Nadzeya Bahniuk,[a] Juergen B. Bulitta,[a] Brian VanScoy,[a] Holland DeFiglio,[a] Steven Fikes,[a*] David Brown,[a*] Sarah M. Drawz,[d] Robert Kulawy,[a*] and Arnold Louie[a*]

Ordway Research Institute, Albany, New York,[a] and Louis Stokes Cleveland Department of Veterans Affairs Medical Center,[b] and Department of Medicine,[c] Pathology,[d] Pharmacology,[e] and Molecular Biology and Microbiology,[f] Case Western Reserve University School of Medicine, Cleveland, Ohio

Combination Chemotherapy



All these mono-therapy arms emerged resistant

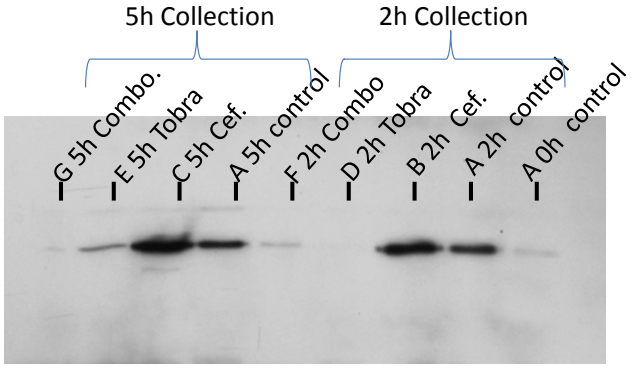
Combination therapy suppressed all resistance amplification

So, even a very low exposures to both drugs, an 8 Log kill was obtained and all resistance emergence was suppressed

Combination Chemotherapy

- Why did this work?
- As a protein synthesis inhibitor, we hypothesize that the aminoglycoside shuts down the expression of the ampC β-lactamase

Combination Chemotherapy



Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

Conclusions

- It is quite possible to use pre-clinical models to generate target values for various degrees of cell kill as well as resistance suppression for drugs administered alone and in combination
- Fully parametric mathematical modeling allows calculation of the relationship between exposure and cell kill/resistance suppression
- Effect site penetration is often different in animals and man

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

Conclusions

- Bridging to man requires human PK, including effect site penetration estimates
- Without these, there can be a high probability of getting the dose wrong (e.g. murine ELF penetration for ceftobiprole was 69%, whereas human median penetration was 15%)
- Predicting from murine values leads to a dose that is about ¼ of “correct” if one uses the penetration into murine ELF
- Animal data are for target setting only!

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

Conclusions

- The principles demonstrated with meropenem and cefepime can be applied to new agents for MDR pathogens both alone and in combination
- Indeed, we have done this under an RO1 from NIAID for the new aminoglycoside Plazomicin from Achaogen
- By identifying optimal regimens, particularly for resistance suppression, we can protect the utility of new agents for the future

Proving Effectiveness for MDR Pathogens

- For MDR pathogens, small clinical trials can have large probative value regarding drug effectiveness
- We need to demonstrate the relationship between exposure and response
- Animal models and Phase 1 data provide an excellent idea of dose and schedule
- When patients enter, we need to optimize system information
  WHAT DO WE NEED?

What Do We Need?

1) pathogen with an MIC
2) patient-specific data (APACHE II score, SOFA, age, sex, weight, GFR, etc)
3) optimized Fisher Information to get good patient-specific estimates of exposure
4) linkage of exposure measure normalized to MIC to a measure of effect

How Do We Do This? Use off-the shelf technology

1) Stochastic Optimal Design Theory
2) Population PK modeling
3) Bayesian estimation (to bring it back to a single patient)
4) Linkage to outcome with tools such as logistic regression or Cox modeling

THIS HAS BEEN DONE!!!!!!

Pharmacodynamics of Levofloxacin

A New Paradigm for Early Clinical Trials

Sandra L. Preston, PharmD; George L. Drusano, MD; Adam L. Berman; Cynthia L. Fowler, MD; Andrew T. Chow, PhD; Bruce Dornseif, PhD; Veronica Reichl, RN; Jaya Natarajan, PhD; Michael Corrado, MD

JAMA, January 14, 1998—Vol 279, No. 2

MAJOR ARTICLE

Relationship between Fluoroquinolone Area under the Curve:Minimum Inhibitory Concentration Ratio and the Probability of Eradication of the Infecting Pathogen, in Patients with Nosocomial Pneumonia

George L. Drusano,[1] Sandra L. Preston,[1] Cynthia Fowler,[2] Michael Corrado,[3] Barbara Weisinger,[4] and James Kahn[4]

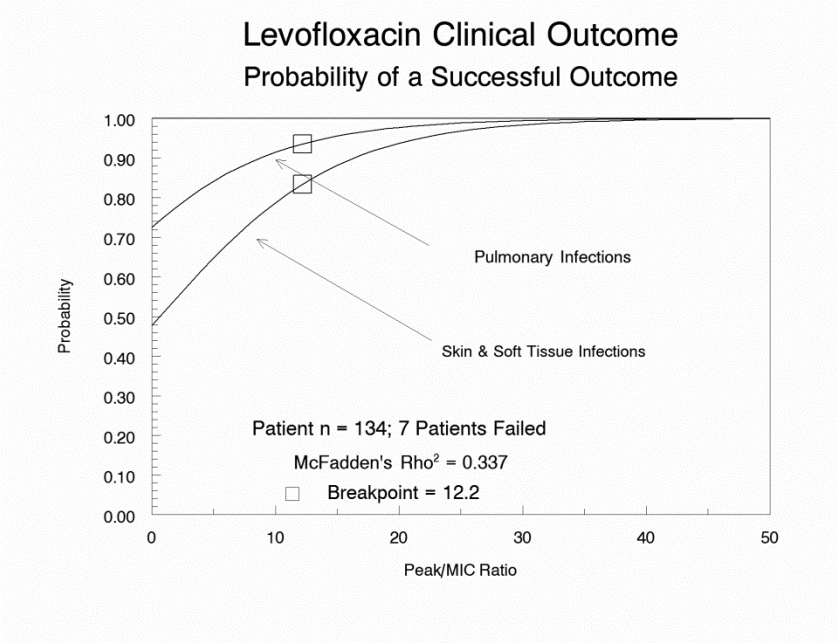
[1]Ordway Research Institute, Albany, New York; [2]Robert Wood Johnson Pharmaceutical Research and Development and [3]Advanced Biologics, Lambertville, and [4]Ortho-McNeil Pharmaceutical, Raritan, New Jersey

The Journal of Infectious Diseases 2004; 189:1590–7

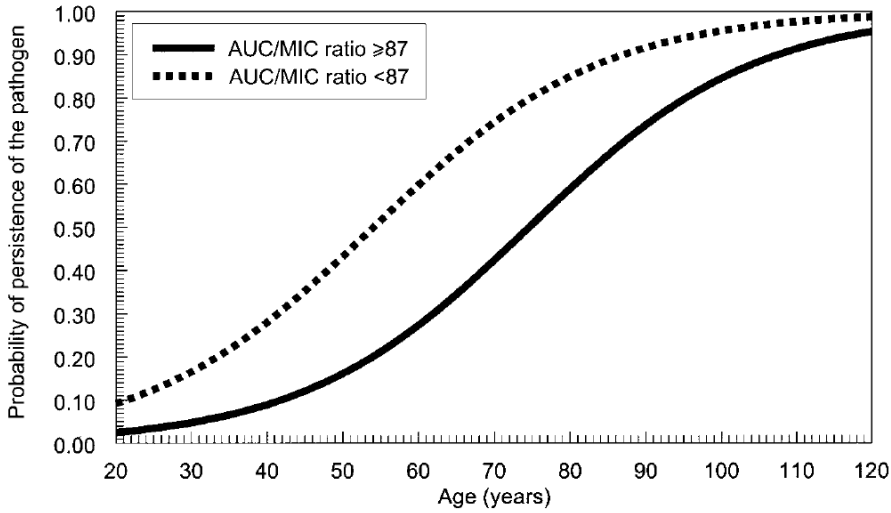
Proving Effectiveness for MDR Pathogens

- These were the first trials where analysis plans were prospectively filed with the FDA
- Below is an example of the output:

Community-Acquired Infections



Nosocomial Pneumonia
N = 47



IT CAN BE DONE!!!!

THANK YOU

FOR YOUR ATTENTION

TABLE 1. Monte Carlo simulations of piperacillin penetration ratios into ELF from the Boselli al et. paper[a]

No. of simulations	Value for piperacillin penetration into ELF			
	Mean	SD	Minimum	Maximum
20	0.460	0.145	0.178	0.714
50	0.452	0.158	0.178	0.853
100	0.455	0.173	0.175	1.171
500	0.467	0.192	0.134	1.171
1,000	0.467	0.195	0.134	1.607
9,999	0.466	0.194	0.077	1.970

[a] Different numbers of iterates were employed, and the impacts of the different iterate numbers on mean value, standard deviation, and minimum and maximal values of ELF penetration were determined.

TABLE 2. Monte Carlo simulations of piperacillin penetration into ELF from the Boselli et al. paper[a]

Seed no.	Value for piperacillin penetration into ELF			
	Mean	SD	Minimum	Maximum
111	0.517	0.204	0.245	0.908
123	0.460	0.145	0.178	0.714
222	0.492	0.173	0.167	0.770
333	0.419	0.147	0.221	0.846
444	0.425	0.217	0.196	1.133
555	0.449	0.217	0.156	1.026
666	0.483	0.128	0.280	0.802
777	0.443	0.184	0.200	0.911
888	0.474	0.169	0.216	0.760
999	0.499	0.138	0.294	0.831

[a] In each instance, 20 iterates were employed, and a different seed number was employed for the simulation. The impact of having a small sample size on the determination of the mean and standard deviation of ELF penetration, as well as the minimum and maximal values, was determined.

Combination Chemotherapy

- So, we have a clear idea that combination therapy helps suppress resistance within bounds
- How much cefepime and tobra need to be given to achieve the twin goals of good cell kill and resistance suppression?
- We used the following literature:

1. Boselli et al. Crit. Care Med. 2003;31:2102–2106.
2. Inciardi JF, Batra KK. AAC. 1993; 37:1025–1027.
3. Tam VH et al. AAC. 2003;47:1853–1861.
4. Carcas et al. Clin Pharmacol Ther. 1999; 65:245–250.

Combination Chemotherapy

- Targets: from the last regimen:
  1. The T>MIC for cefepime was 24.7%
  2. AUC/MIC for tobra was 58.06
  3. Penetration for cefepime 100% (ref #1)
  4. Penetration for tobra was 50% (ref #4)
- For 2 g Q8h for cefepime, target attainment (MCS) was >99% for an MIC of 8 mg/L (Ref #3)
- We then examined a tobra MCS-7 mg/kg/d (Ref #2)
- Probability of target attainment for both were calculated as the product of the individual target attainments (see next slide)

Combination Chemotherapy

TABLE 2 Target attainment for suppression of emergence of resistance for cefepime plus tobramycin[a]

Tobramycin MIC (mg/liter)	Target attainment (% of 9,999 simulated subjects)
0.25	100
0.5	100
1.0	70
2.0	<1
4.0	0

[a] Cefepime and tobramycin were administered at doses of 2 g every 8 h and 7 mg/kg/day, respectively. The rates of cefepime's target attainment for the 2-g-every-8-h dose are 100% at an MIC of 4 mg/liter and 99.5% at an MIC of 8 mg/liter.

Combination Chemotherapy

- Tobra is the key to the regimen for resistance suppression
- BUT we run out of gas at an MIC of 0.5 – 1.0 mg/L
- How good will the regimen be at your institution?
  - obviously the tobra and cefepime MIC distributions will have a direct impact

Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

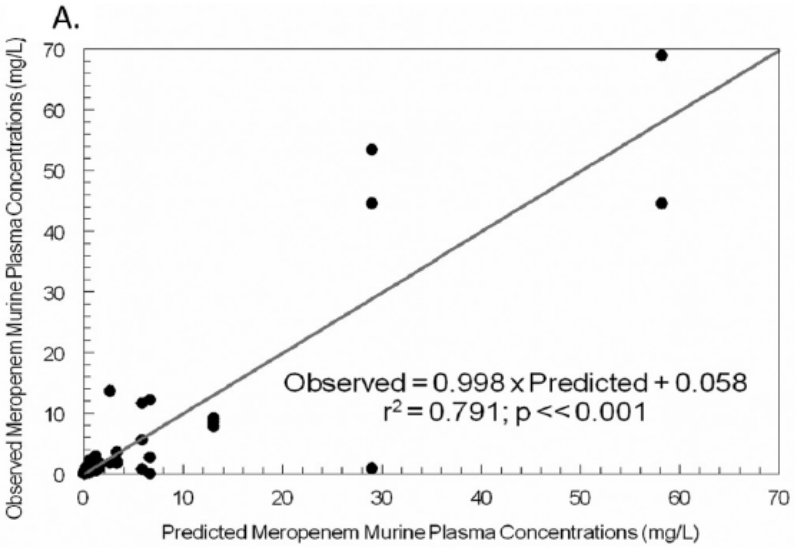
Penetration of Meropenem into Epithelial Lining Fluid (ELF) in 39 Patients with Ventilator-Associated Pneumonia

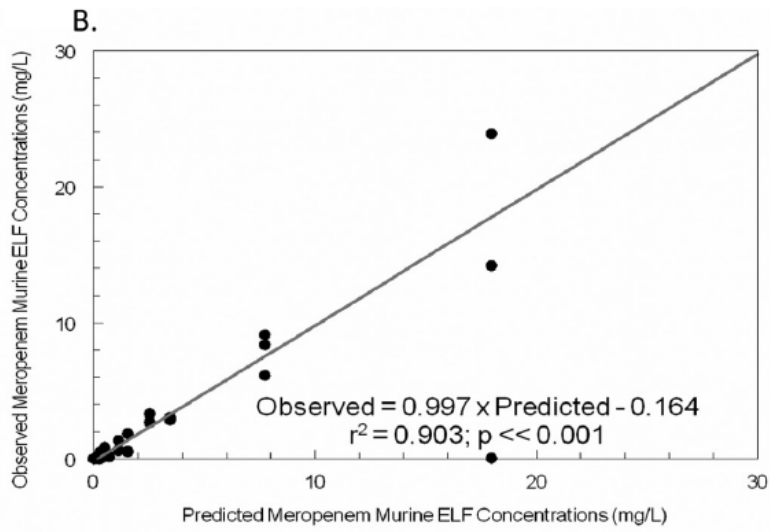
TABLE 3. Parameter estimates from the population pharmacokinetic analysis from 39 patients with ventilator-associated pneumonia

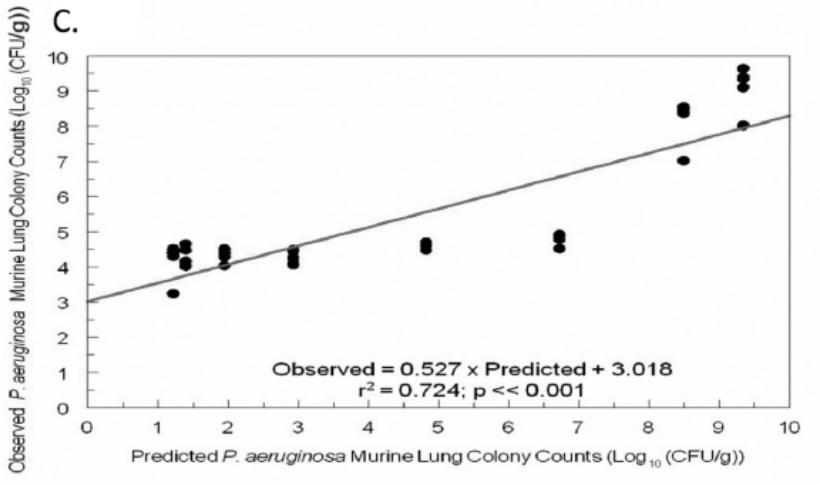
Parameter[a]	V_c (liters)	CL (liters/h)	K_{12} (h^{-1})	K_{21} (h^{-1})	K_{13} (h^{-1})	K_{31} (h^{-1})	V_{ELF} (liters)
Mean	12.6	15.2	8.32	14.1	10.1	14.2	30.4
Median	6.68	13.5	3.15	11.2	8.02	15.4	24.2
SD	13.3	9.71	9.82	11.8	8.63	11.4	25.2

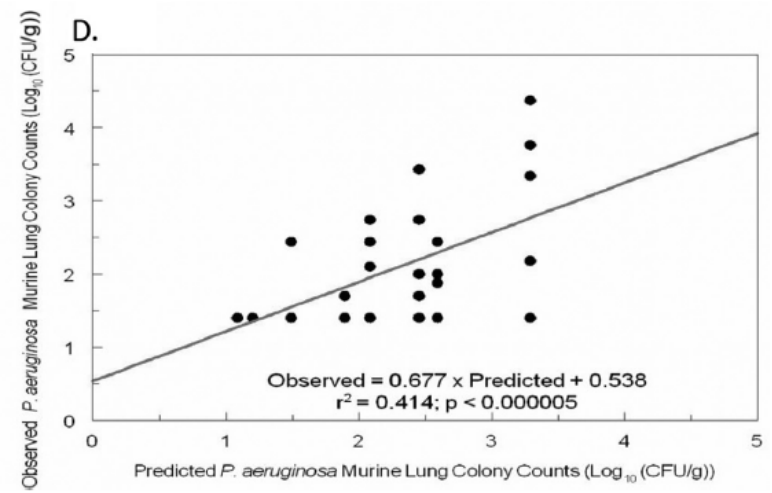
[a] V_c, volume of the central compartment; CL, plasma clearance; K_{12}, K_{21}, K_{13}, K_{31}, first order intercompartmental transfer rate constants; V_{ELF}, volume of the ELF compartment.

Fit of the Model to the Data (Pre-Bayesian Step) for all Four System Outputs: A) Plasma Data B) ELF Data C) Total Bacterial Population D) Meropenem-Resistant Population









Optimal Dosing Regimens of Novel Antimicrobials Against MDR Pathogens

$$dX_1/dt = -X_1 \cdot K_a$$

$$dX_2/dt = X_1 \cdot K_a - [(CL/F/V_c/F) + K_{23}] \cdot X_2 + K_{32} \cdot X_3$$

$$dX_3/dt = K_{23} \cdot X_2 - K_{32} \cdot X_3$$

$$dX_4/dt = K_{\text{growth-s}} \cdot \{[1 - (X_4 + X_5)] / \text{POPMAX}\} \cdot X_4$$

$$- K_{\text{kill-max-S}} \cdot \{(X_3/V_{\text{ELF}})^{\text{H-s}}/[EC_{50\text{-S}}{}^{\text{H-s}} + (X_3/V_{\text{ELF}}{}^{\text{H-s}})]\} \cdot X_4$$

$$dX_5/dt = K_{\text{growth-r}} \cdot \{[1 - (X_4 + X_5)] / \text{POPMAX}\} \cdot X_5$$

$$- K_{\text{kill-max-r}} \cdot \{(X_3/V_{\text{ELF}})^{\text{H-r}}/[EC_{50\text{-r}}{}^{\text{H-r}} + (X_3/V_{\text{ELF}}{}^{\text{H-r}})]\} \cdot X_5$$