PD Targets for Various Infection Types: Stasis vs. 1-Log Kill vs. 2 Log Kill

G.L. Drusano, M.D.
Professor and Director
Institute for Therapeutic Innovation
University of Florida

PD Targets – Nosocomial Pneumonia

- To have insight into appropriate cell kill targets in preclinical models, it is necessary to link measures of an appropriate exposure index to bacterial cell kill and then to bridge to man by looking at that same index with regard to outcomes seen in patients
- This was done previously in a paper in CID
- These presentations (Paul and I) are an update; but first, the oldie but goodie

INVITED ARTICLE ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore

Paul G. Ambrose,[1] Sujata M. Bhavnani,[1] Christopher M. Rubino,[1] Arnold Louie,[2] Tawanda Gumbo,[2] Alan Forrest,[1] and George L. Drusano[2]

[1]Institute for Clinical Pharmacodynamics and [2]Emerging Infections and Fungal Pharmacodynamics Laboratory, Ordway Research Institute, Albany, New York

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1058-4838/2007/4401-0015$15.00

Table 2. Pharmacokinetic-pharmacodynamic (PK-PD) targets derived from animal infection models and clinical data.

Disease state, drug	Clinically-derived PK-PD target [reference(s)]	Animal infection model; organism studied	Animal-derived PK-PD target [reference(s)]
Hospital-acquired pneumonia			
Quinolones	*f*AUC_{0-24}:MIC ratio, 62–75 [11, 12]	Neutropenic mouse thigh; gram-negative bacilli	*f*AUC_{0-24}:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]
Community-acquired respiratory tract infections			
Quinolones	*f*AUC_{0-24}:MIC ratio, 34 [22]	Immunocompetent mouse thigh; *Streptococcus pneumoniae*	*f*AUC_{0-24}:MIC ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]
β-Lactams	T>MIC, 40% of the dosing interval [14]	Immunocompetent mouse thigh; *S. pneumoniae*	T>MIC, 30–40% of the dosing interval for 90% animal survival [14]
Telithromycin	AUC_{0-24}:MIC ratio, 3.375 [20]	Neutropenic mouse thigh; *S. pneumoniae*	AUC_{0-24}:MIC ratio, 1000 for stasis [24]
Bacteremia			
Oritavancin	*f*T>MIC, 22% of the dosing interval for *Staphylococcus aureus* [25]	Neutropenic mouse thigh; *S. aureus*	*f*T>MIC, 20% of the dosing interval for a 0.5 log-unit kill [26]
Linezolid	AUC_{0-24}:MIC ratio, 85 for *S. aureus* or *Enterococcus faecium* [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]
Complicated skin and skin structure infections			
Tigecycline	AUC_{0-24}:MIC ratio, 17.9 [28]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 15–20 for stasis [29]
Linezolid	AUC_{0-24}:MIC ratio, 110 [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]

NOTE. AUC_{0-24}:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{max}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.

PD Targets – Nosocomial Pneumonia

- Nosocomial pneumonia is arguably the most difficult to treat common infection in the ICU
- It is a source of major morbidity and is frequently fatal
- It also attended by the densest bacterial burdens
- As will be seen in a few slides, the minimal burden to qualify for the diagnosis is 10^4 CFU/ml in BAL ($10^{5.5}$ CFU/ml corrected for dilution)

PD Targets – Nosocomial Pneumonia

- Let us first look at a murine model of nosocomial pneumonia using *Pseudomonas aeruginosa* as the challenge organism

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3325–3330 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.00006-09

Pharmacodynamics of Levofloxacin in a Murine Pneumonia Model of *Pseudomonas aeruginosa* Infection: Determination of Epithelial Lining Fluid Targets[▽]

Arnold Louie, Christine Fregeau, Weiguo Liu, Robert Kulawy, and G. L. Drusano*

PD Targets – Nosocomial Pneumonia

The Model Applied to All the Data Simultaneously

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

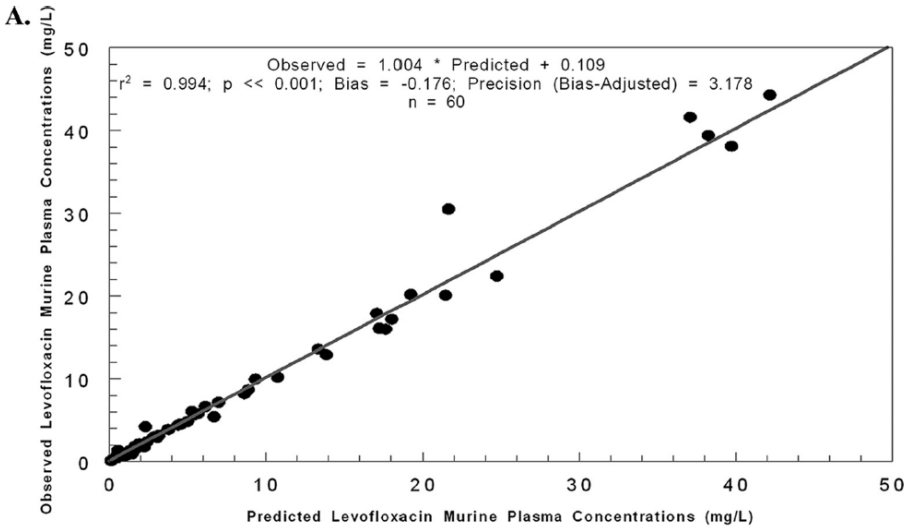
$$dX_2/dt = X_1 \times K_a - [(\mathrm{CL}/F)/(V_c/F) + K_{23} + K_{24}] \times X_2 + K_{32} \times X_3 + K_{42} \times X_4$$

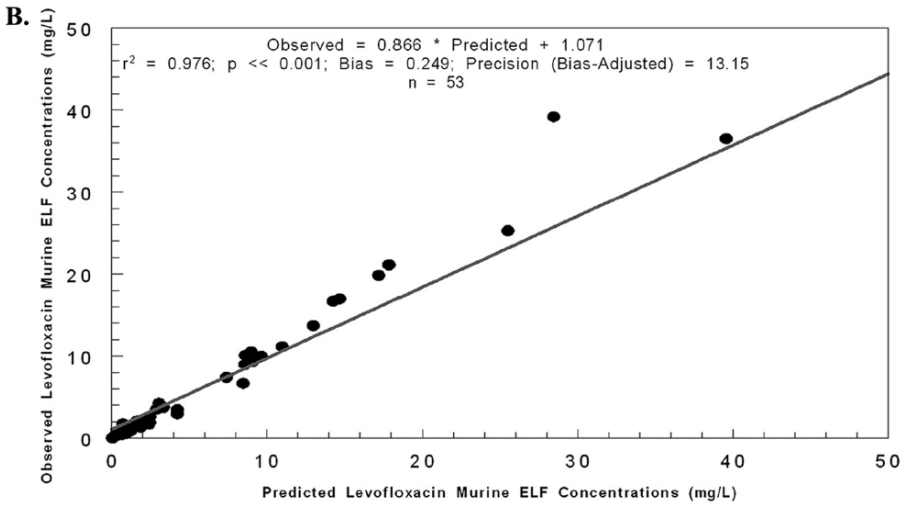
$$dX_3/dt = K_{23} \times X_2 - K_{32} \times X_3$$

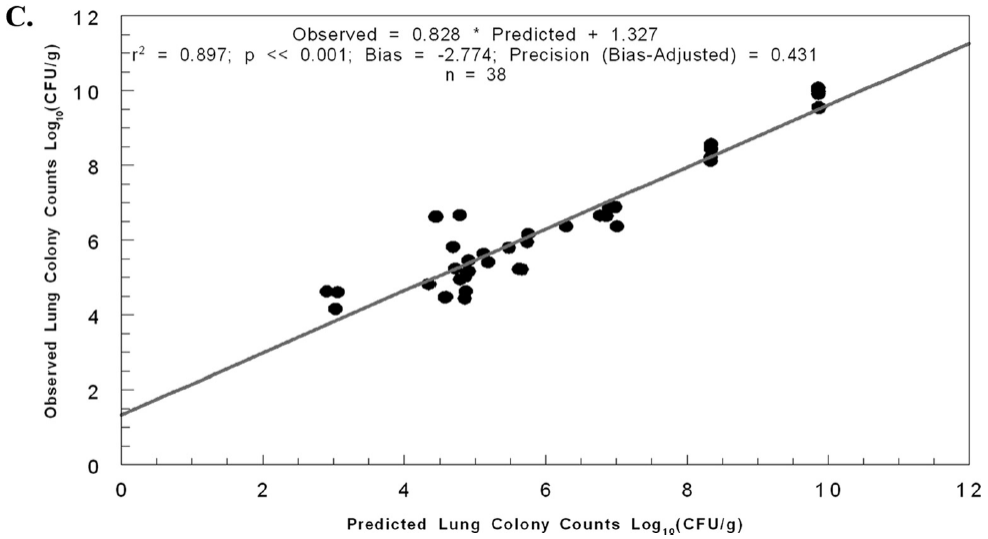
$$dX_4/dt = K_{24} \times X_2 - K_{42} \times X_4$$

$$dX_5/dt = K_{\mathrm{growth}} \times (1 - X_5/\mathrm{POPMAX}) \times X_5 - K_{\mathrm{kill\text{-}max}} \times \{(X_4/V_{\mathrm{ELF}})^H/[\mathrm{EC}_{50}{}^H + (X_4/V_{\mathrm{ELF}})^H]\} \times X_5$$

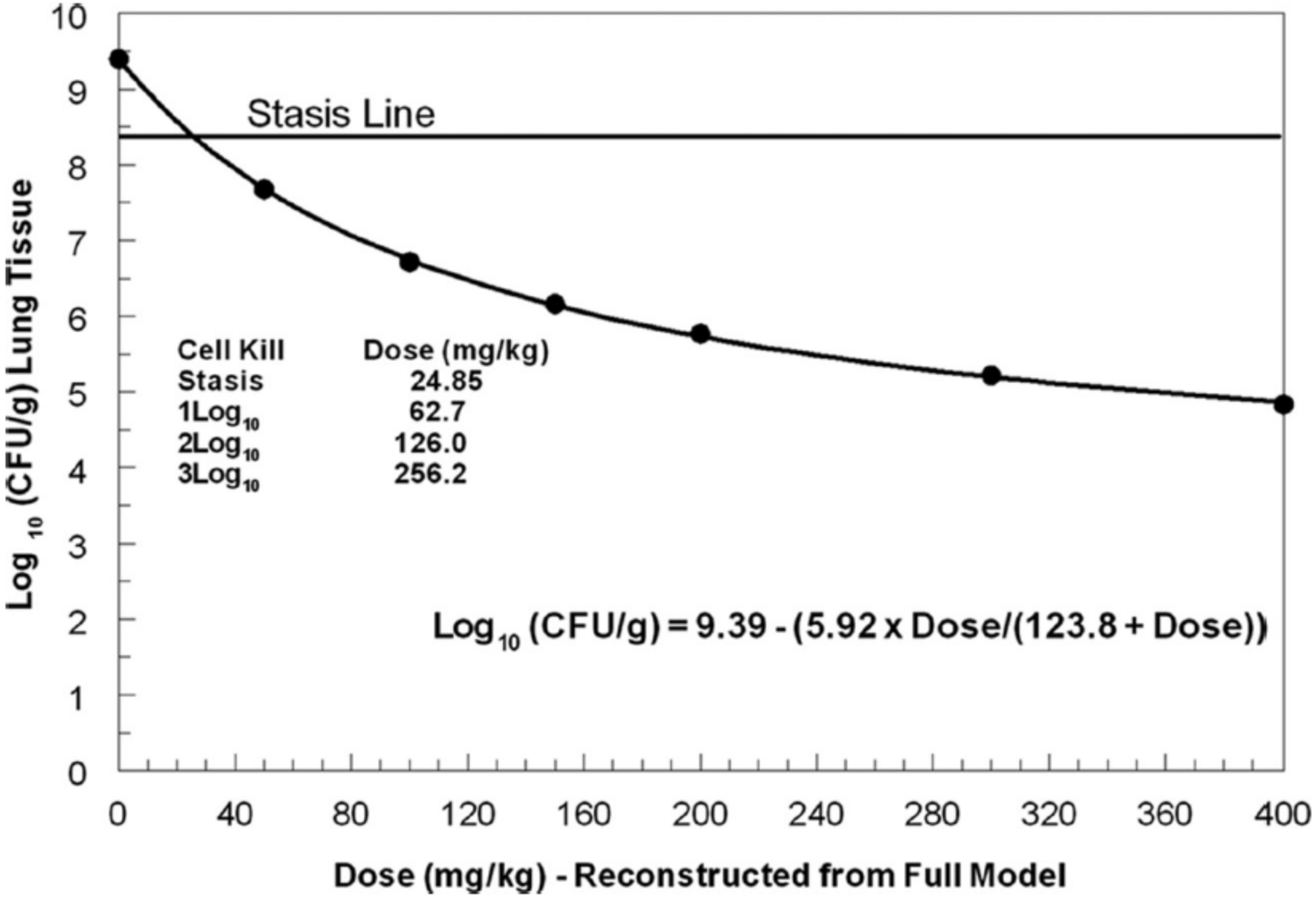
PD Targets – Nosocomial Pneumonia







Levofloxacin Activity in Murine Pseudomonas Pneumonia



Levofloxacin PK in a Murine Pneumonia Model

TABLE 1. Pharmacodynamic parameter values for penetration of levofloxacin into ELF of mice infected with *Pseudomonas aeruginosa* and effect parameters for cell kill

Parameter[a]	Value	
	Median	SD
V_c/F (liters)	0.044	0.18
CL/F (liters/h)	0.078	0.11
K_{23} (h^{-1})	3.33	6.17
K_{32} (h^{-1})	9.22	3.14
K_{24} (h^{-1})	7.92	3.02
K_{42} (h^{-1})	18.6	5.10
V_{ELF} (liters)	0.024	0.20
K_a (h^{-1})	7.81	5.37
K_{growth} (CFU/g/h)	0.12	3.36
$K_{kill\text{-}max}$ (CFU/g/h)	2.95	2.00
EC_{50} (mg/liter)	3.15	3.76
H	14.0	4.96
POPMAX (CFU/g)	7.2×10^9	4.0×10^9
IC_5 (CFU/g)	2.2×10^8	3.1×10^7

[a] IC_5 is the initial condition in the fifth compartment.

Levofloxacin Targets in Mouse and Man in *P. aeruginosa* Murine Pneumonia and HAP

Mouse Pneumonia*

	*f*AUC/MIC Ratio
Stasis	15.9
1 Log10 (CFU/g) Kill	40.2
2 Log10 (CFU/g) Kill	56.5
3 Log10 (CFU/g) Kill	164

HABP

***f*AUC/MIC Ratio and Response**

Ciprofloxacin (retrospective)75.0 (≥75 – 80.4% response; <75 – 44% response)**

Levofloxacin (prospective)* 62.0 (≥62 – 90% response; <62 – 43% response)**

***Louie A, C Fregeau, W Liu, R Kulawy, GL Drusano. AAC. 2009;53:3325-3330**

****Forrest A, DE Nix, CH Ballow et al. AAC. 1993;37:1073-1081**

*****Drusano GL, SL Preston, C Fowler, M Corrado, B Weisinger, J Kahn. JID. 2004;189:1590-1597**

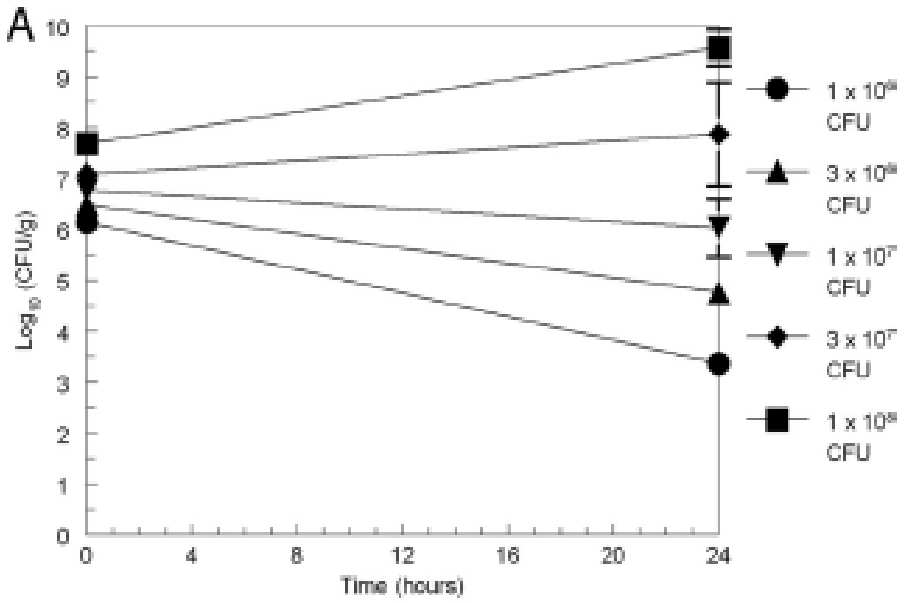
PD Targets – Nosocomial Pneumonia

So, why is nosocomial pneumonia hard to treat?

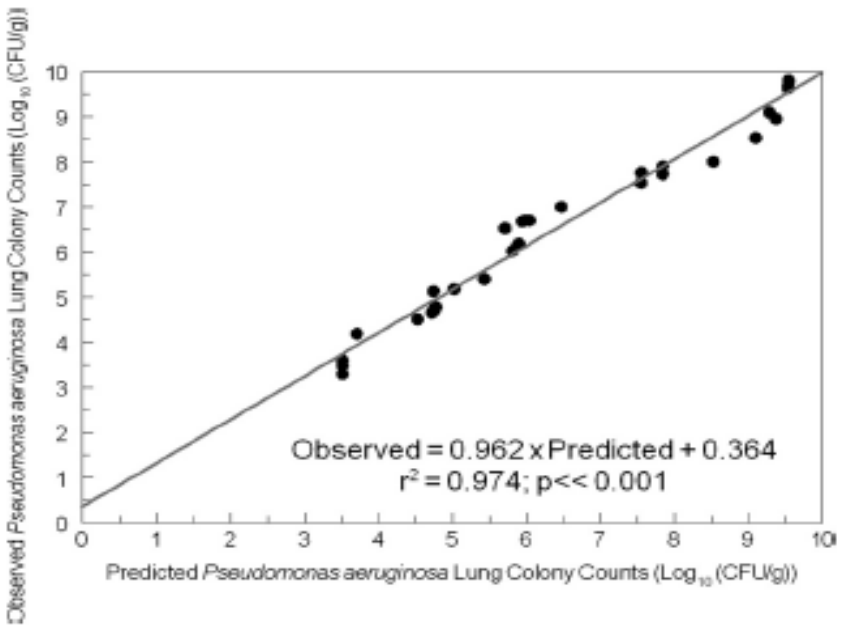
Granulocyte Kill of *P. aeruginosa*

PD Targets – Nosocomial Pneumonia

Saturation of Granulocytes



Fit of a Michaelis-Menten Model to the Data



This means that the minimum bacterial cell kill to unsaturate the granulocytes is a 2 Log_{10}(CFU/g) kill (and 3 Logs is better)
Antimicrob Agents Chemother 2011;55:2693-2695

PD Targets – Nosocomial Pneumonia

- In the next experiment, mice were neutrophil replete and had *P. aeruginosa* pneumonia
- There were 18 active cohorts and 2 cohorts of no-treatment controls
- Plazomicin was administered in a dose ranging fashion with “humanized” dosing
- 2 hour treatment delay; after 24 h of Rx (h 26) plazomicin administration stopped
- At this point the drug concentration in ELF was 0.25 x MIC
- The final cohorts were sacrificed at h 50

PD Targets – Nosocomial Pneumonia

These three differential equations account for the drug in the mouse both in the plasma as well as in the Epithelial Lining Fluid (ELF)

$$\frac{dX_1}{dt} = -X_1 \cdot K_a, \tag{1}$$

$$\frac{dX_2}{dt} = X_1 \cdot K_a - [(\mathrm{CL}/F/V_c/F) + K_{23})] \cdot X_2 + K_{32} \cdot X_3, \tag{2}$$

$$\frac{dX_3}{dt} = K_{23} \cdot X_2 - K_{32} \cdot X_3, \tag{3}$$

and

$$\frac{dX_4}{dt} = K_{24} \cdot X_2 - K_{42} \cdot X_4, \tag{4}$$

This equation accounts for bacterial kill by the antibiotic

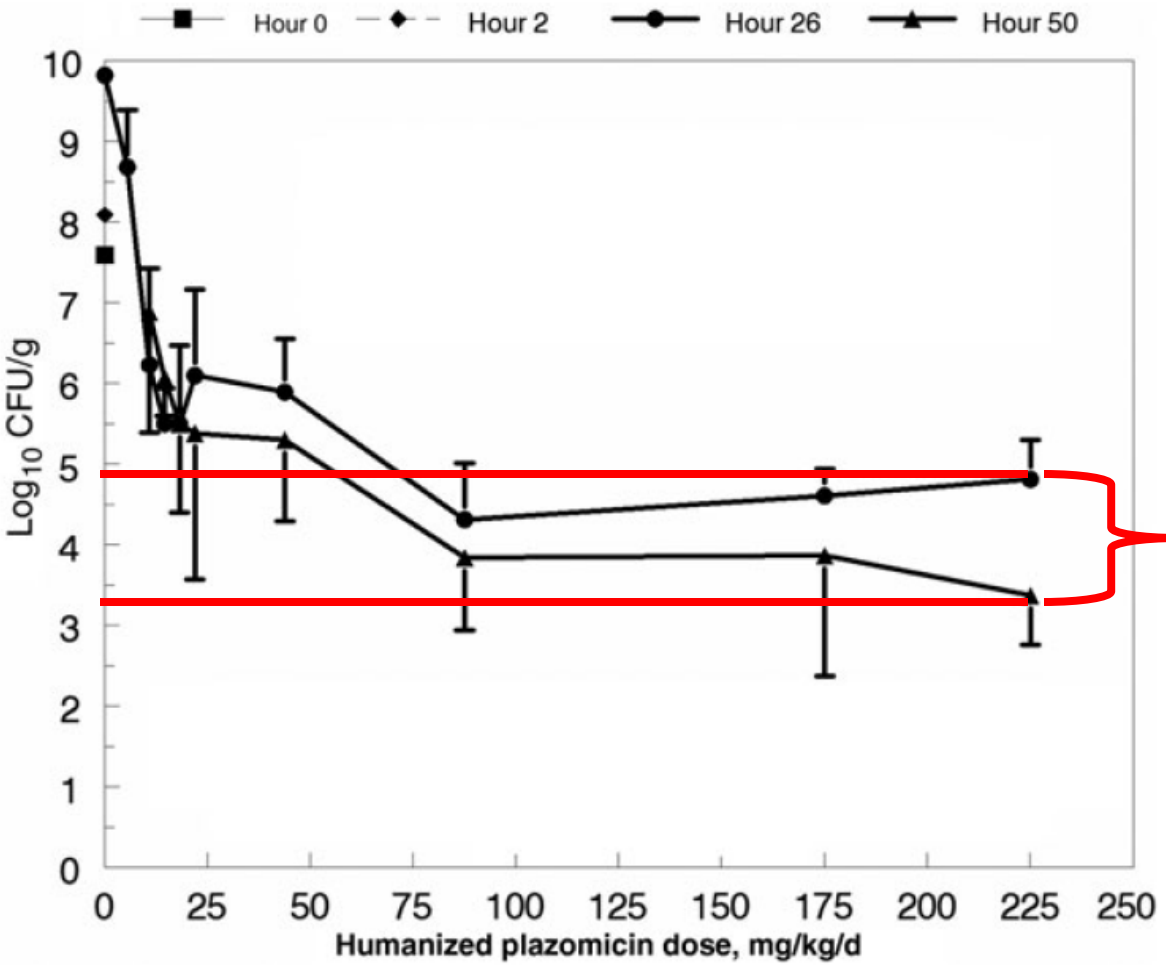
$$\mathrm{Plazo}_{\mathrm{Kill}} = \frac{(X(4)/V_{\mathrm{ELF}})^{\mathrm{H}}}{(C^{\mathrm{H}}_{50\text{-}Plazo\text{-}Kill} + (X(4)/V_{\mathrm{ELF}}))^{\mathrm{H}}} \tag{5}$$

and

This differential equation accounts for bacterial growth and bacterial death by: 1) drug kill and 2) Granulocyte kill

$$\frac{d(\mathrm{CFU/g})}{dt} = (K_{\mathrm{gmax}} \cdot (1 - (\mathrm{CFU/g}/\mathrm{Popmax})) \cdot \mathrm{CFU/g} - K_{\mathrm{killmax}} \cdot \mathrm{Plazo}_{\mathrm{Kill}} \cdot \mathrm{CFU/g} - (K_{\mathrm{killWBC}} \cdot \mathrm{CFU/g})/(\mathrm{WBC}_{\mathrm{Kill50}} + \mathrm{CFU/g})) \cdot \mathrm{CFU/g}, \tag{6}$$

Therapy of Nosocomial Pneumonia



1.5 Log_{10}(CFU/g) bacterial kill by granulocytes over 24 hours without drug attained by unsaturating the granulocytes with plazomicin Rx

J Infect Dis 2014;210:1319-1324

PD Targets – Nosocomial Pneumonia

- Plazomicin clearly has a major effect of the bacterial burden
- At the end of 24 hours after therapy initiation, virtually no Plazomicin remains.
- When bacterial burdens are approximately 10^6 CFU/g or above, counts are either steady or rise slightly over the next 24 hours.
- At higher drug exposures colony counts decline below saturation point and granulocytes kill more organisms over hrs 26-50

Granulocytes and Chemotherapy: Optimizing Outcome

Why is this important?

To meet the definition of ventilator-requiring hospital-acquired bacterial pneumonia (VRHABP), 10^4 CFU/ml in broncoalveolar lavage (BAL) fluid are required.

Previous data from patients* demonstrates that BAL results in a 30-100 fold dilution. This is approximately a 1.5-2.0 Log_{10} (CFU/ml) dilution, meaning that the ***lowest*** burden qualifying as documented pneumonia is really $3x10^5$ to 10^6 CFU/ml.

Zaccard *et al*+ looked at bilateral BAL in patients with suspected VRHABP. There were 134 samples from patients with *P. aeruginosa*, *Enterobacter* spp, *K. pneumonia*, *Acinetobacter* spp and *Serratia marcescens*

Correcting for dilution (not in the original paper), the burdens distributed as below:

$\geq 3x10^5$-$<3x10^6$	$\geq 3x10^6$-$<3x10^7$	$\geq 3x10^7$-$1x10^8$	Total
49 (36.6%)	50 (37.3%)	35 (26.1%)	134 (100%)

Circa 63% of patients have burdens that exceed the half-saturation point (K_m) of granulocytes at baseline!

* Antimicrob Agents Chemother. 2011;55:1606-1610

+ J Clin Microbiol. 2009;47:2918-2924

PD Targets – Nosocomial Pneumonia

- So, what Log kill do we need to achieve ?
  1 Log kill achieves near maximal granulocyte unsaturation circa 36.6% of the time
  2 Log kill achieves near maximal granulocyte unsaturation circa 62.7% of the time
  3 Log kill achieves near maximal granulocyte unsaturation circa 100% of the time
- But 3 Log kill is very hard to achieve

PD Targets – Nosocomial Pneumonia

- So, Paul is always telling me “DON’T THROW OUT THE BABY WITH THE BATH WATER!!!”
- And I agree with the sentiment
- There is a reasonable amount of evidence that a 2 Log10 (CFU/g) bacterial kill is helpful for achieving good outcomes in this pathologic process
- If a drug was being developed for MDR pathogens that could not achieve this target, would I reject it? – NO
- But, we should recognize what is a worthy target
- **Can we get patients better faster?**
- **Do we need to think about combination therapy?**
- Now, on to Paul

Thank You for
Your Attention!