IDSA

Infectious Diseases Society of America

Why Breakpoints and Whither Breakpoints?

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What is a break point supposed to do?

- Answer: it depends upon whom one asks
- Ask a microbiologist and many would say that a breakpoint should delineate the end of the wild-type distribution
- Ask a clinician and they will likely tell you that the breakpoint provides data that indicates that a patient infected with a specific pathogen will have a good clinical response to “standard” doses of drug

Which one is right?

- Answer: It depends upon which question one wishes to answer
- As there are a lot more clinical uses of the breakpoint, I will concentrate on that question

*Drusano et al. Antimicrob Agents Chemother 2001; 45:13-22

But What Do Breakpoints Mean For Patients?

- When properly developed, breakpoints inform clinicians how best to use drugs in patients.
- Therefore, another question to ask is: "how will using PK/PD speed new drug development and improve our use of existing drugs?"
- The FDA has recently released draft guidance on antibacterial therapies for patients with an unmet need*
- The European Medicines Agency (EMA) workshop last fall featured several presentations on the value of good PK/PD for patients**

*FDA, Draft Guidance for Industry on Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases, Docket No. FDA-2013-D-0744 (2013).
**EMA, Report: Workshop on development of new antibacterial medicines (2012), available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/09/WC500150486.pdf

Are Breakpoints Important? Ask this patient

HAP: complications and mortality in relation to appropriateness of therapy

	Approp ChemoRx (n=284)	Inapprop ChemoRx (n=146)	p-value
Attributable Mortality	16.2%	24.7%	0.03
Complications per patient	1.73±1.82	2.25±1.98	<0.001
Shock	17.1%	28.8%	<0.001
GI Bleeding	10.7%	21.2%	0.001

Alvarez-Lerma *et al* 1996

How is the breakpoint set?

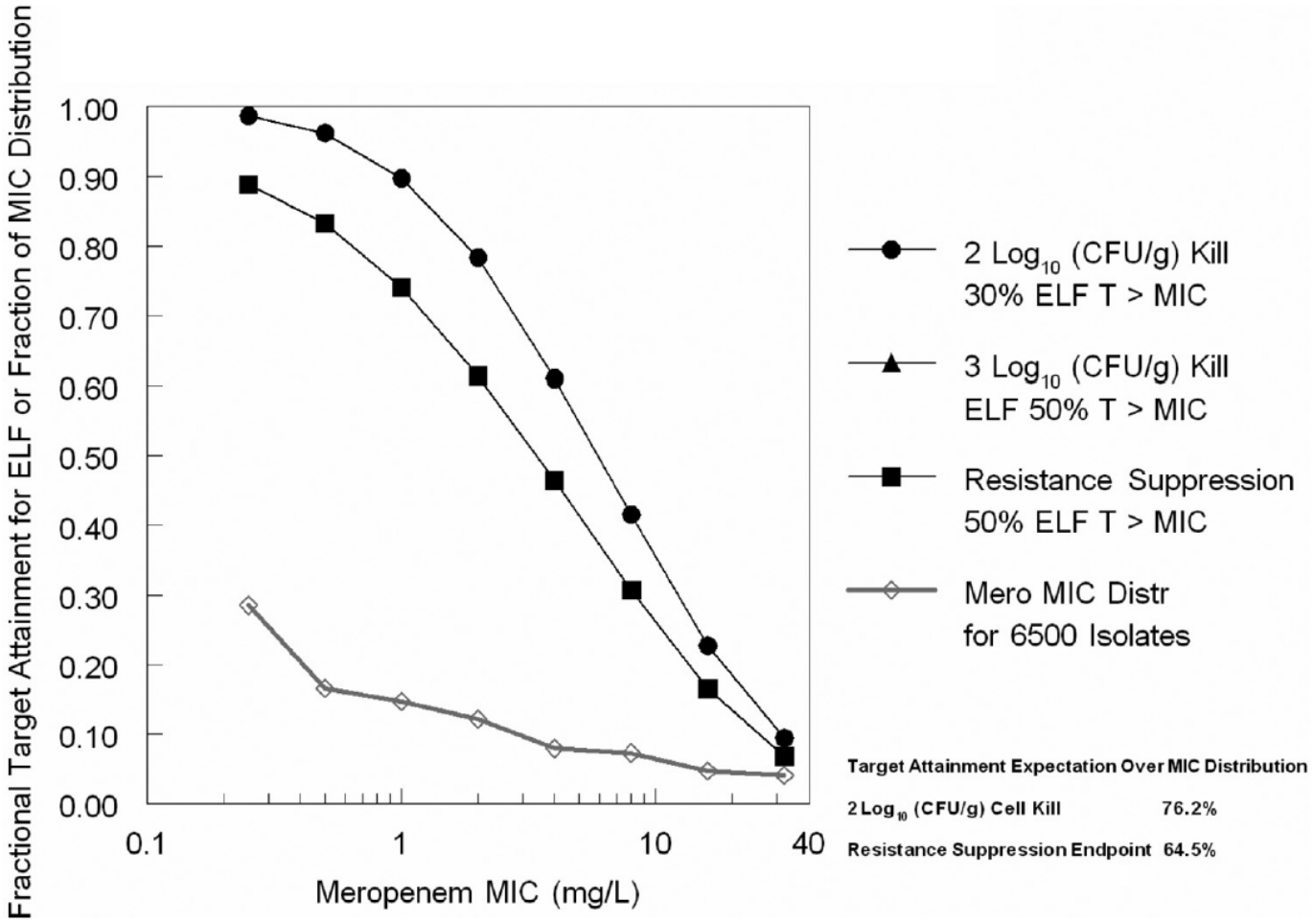
1. Determine a drug exposure that will be likely to drive a specific outcome (this may be derived from microbiological or clinical data)

2. Perform a Monte Carlo simulation using a specific drug dose

3. Using a specific MIC value determine the frequency with which the desired drug exposure (e.g. AUC/MIC ratio, Time>MIC, Trough Concentration/MIC, Peak Concentration/MIC) is attained

4. Repeat the determination for all the MIC values in the distribution (see next slide)

Monte Carlo Simulation Target Attainment Analysis



Drusano GL et al. AAC 2011;55:3406-3412

What questions does this raise?

1. What is the “correct” exposure to be attained?
2. Did the data come from the clinic (preferred) or from an *in vitro* or animal model system?
3. Where did the pharmacokinetic information come from?
4. Where should the breakpoint be set?

What is the “correct” exposure?

- Answer: It depends on the infection being treated
- For example, skin and skin structure infections can generally be treated more easily; if one is employing preclinical data, exposures driving a static effect or a 1 Log_{10} CFU/g cell kill have a high probability of providing a good clinical outcome
- On the other hand, VABP generally requires approx a 2 Log_{10} CFU/g cell kill (more later)

Targets from Pre-Clinical Models

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	$fAUC_{0-24}$:MIC ratio, 62–75 [11, 12]	Neutropenic mouse thigh; gram-negative bacilli	$fAUC_{0-24}$:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]
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.

INVITED ARTICLE ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

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

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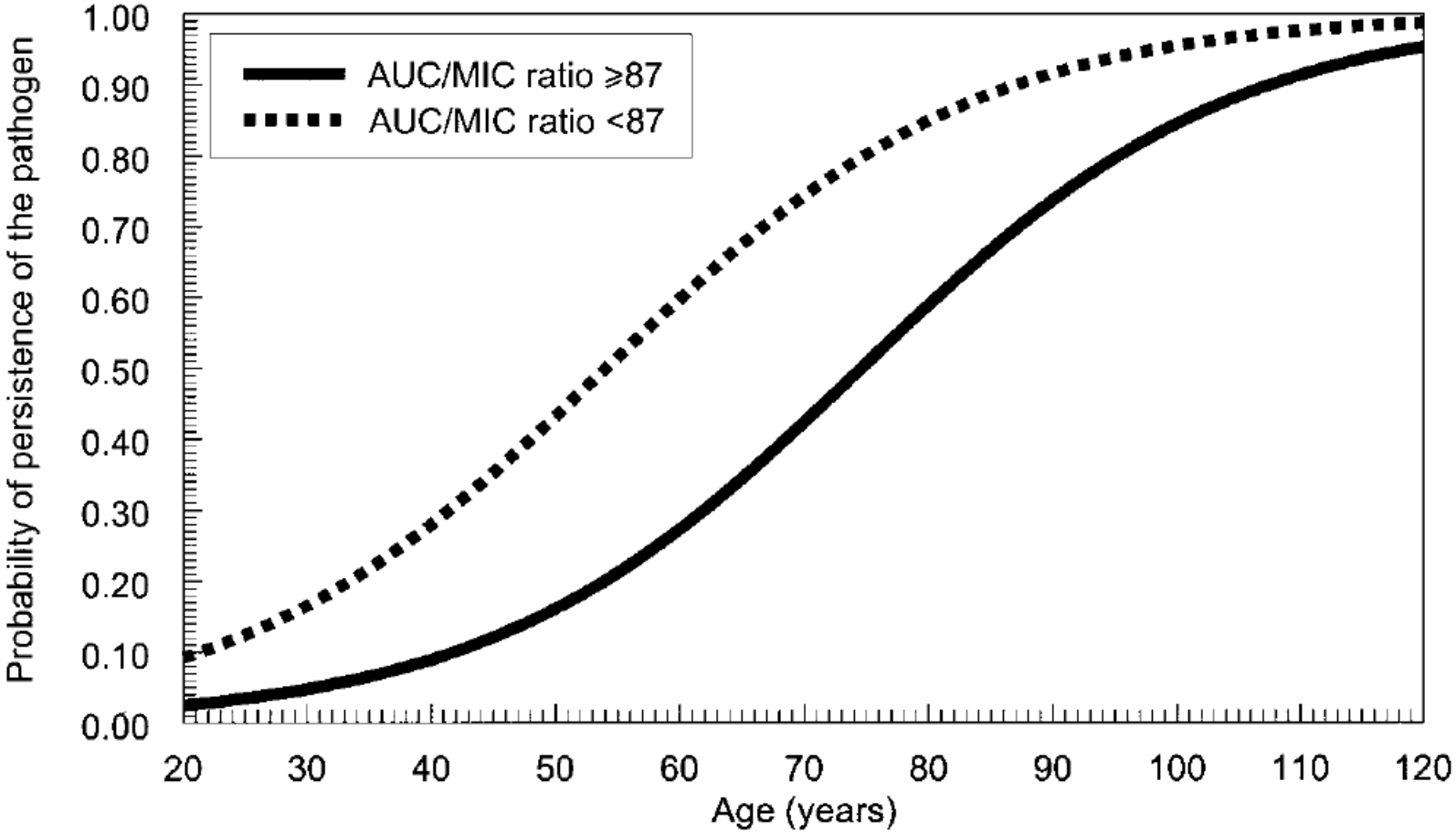
Special Consideration: VABP

- VABP needs a higher effect to be targeted because of the bacterial burden seen in many patients
- If there is time, this can be discussed later

Target From Clinical Study of HABP



Drusano **GL et al J Infect Dis. 2004;189:1590-1597**

Where Did the PK Come From?

Meropenem Pharmacokinetic Parameters Drawn from Different Sources:

110 Volunteers; 46 Non-Ill Patients

TABLE 3. Population PK modeling for imipenem and meropenem: mean parameter vector and covariance matrix

Drug and value	Vc (liter)	K_{cp} (h^{-1})	K_{pc} (h^{-1})	CI (liter/h)
Imipenem				
Mean	14.48	0.26	0.79	13.38
Covariance matrix	6.26			
	−0.29	0.17		
	−1.13	0.70	0.30	
	−1.13	−0.58	0.76	1.42
Meropenem				
Mean	13.38	2.42	9.73	13.57
Covariance matrix	12.52			
	−0.61	14.21		
	24.29	31.77	134.28	
	2.67	0.89	5.29	1.13

~10% CV

VABP Patients

Parameter[a]	V_c (liters)	CL (liters/h)
Mean	12.6	15.2
Median	6.68	13.5
SD	13.3	9.71

CV% =64-72%

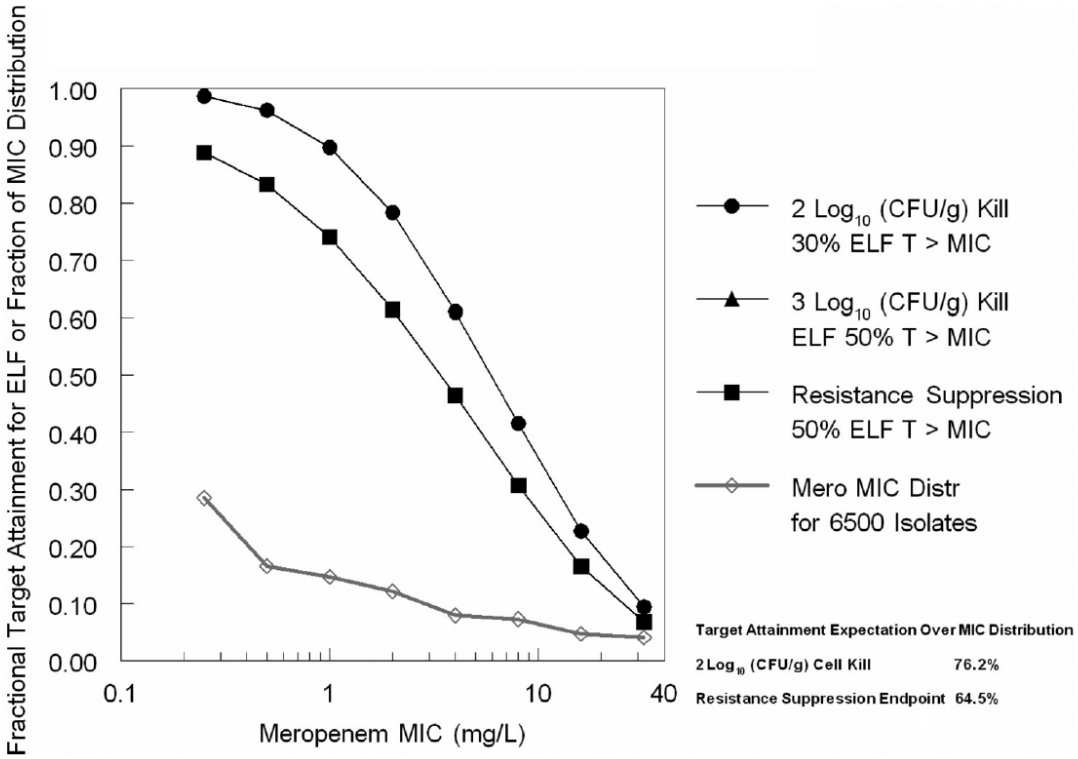
Lomaestro BM and GL Drusano. AAC 2005;49: 461-463

Drusano GL et al. AAC 2011;55:3406-3412

The same could be shown for levofloxacin or other drugs

Where should the breakpoint(s) be set? 90%? attainment? 70% attainment? (mother-in-law breakpoint)

- The answer is that there is no "correct" answer. If 90% target attainment is correct, why not 95% or 85%?
- What role does the sickness of the patient play in the decision?
- The actual choice of breakpoint is a consensus event



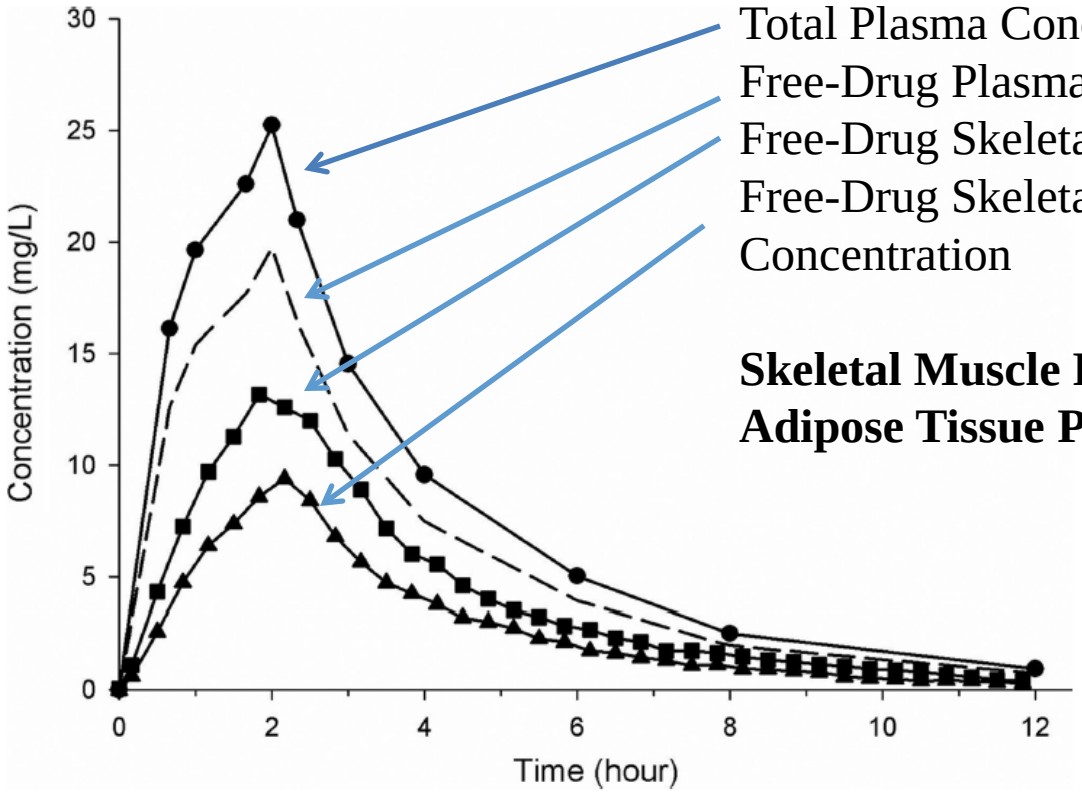
Drusano GL et al. AAC 2011;55:3406-3412

Breakpoints

- What about different doses?
- For different doses, the result is straightforward: for drugs with linear pharmacokinetics (most, but NOT all), doubling the dose increases the breakpoint by one dilution (1000 mg Q8h to 2000 mg Q8h changes a breakpoint from (for example) 2 mg/L to 4 mg/L

What About Different Indications?

Breakpoints – What about Different Indications? - SSTI

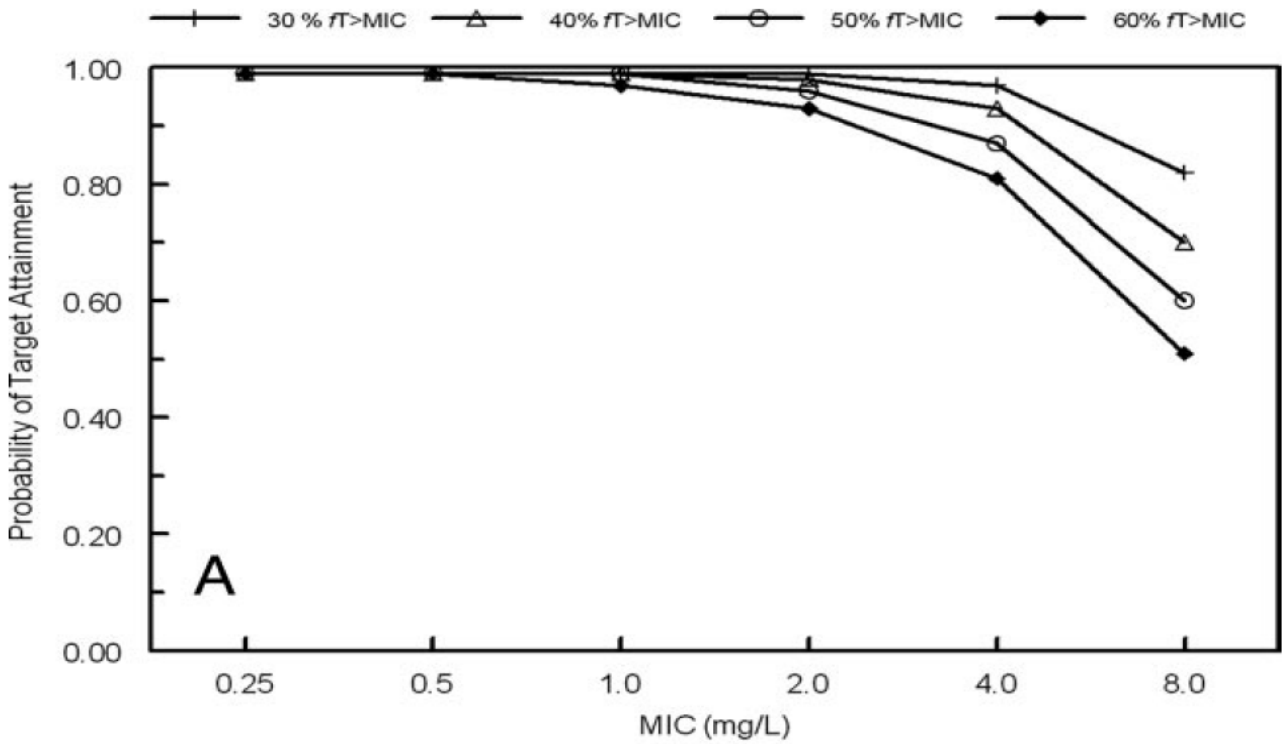


Total Plasma Concentration
Free-Drug Plasma Concentration
Free-Drug Skeletal Muscle Concentration
Free-Drug Skeletal Adipose Tissue Concentration

Skeletal Muscle Penetration – 69%
Adipose Tissue Penetration – 49%

Barbour A, et al AAC 2009;53:2773-2776

Breakpoints – What about Different Indications? - SSTI



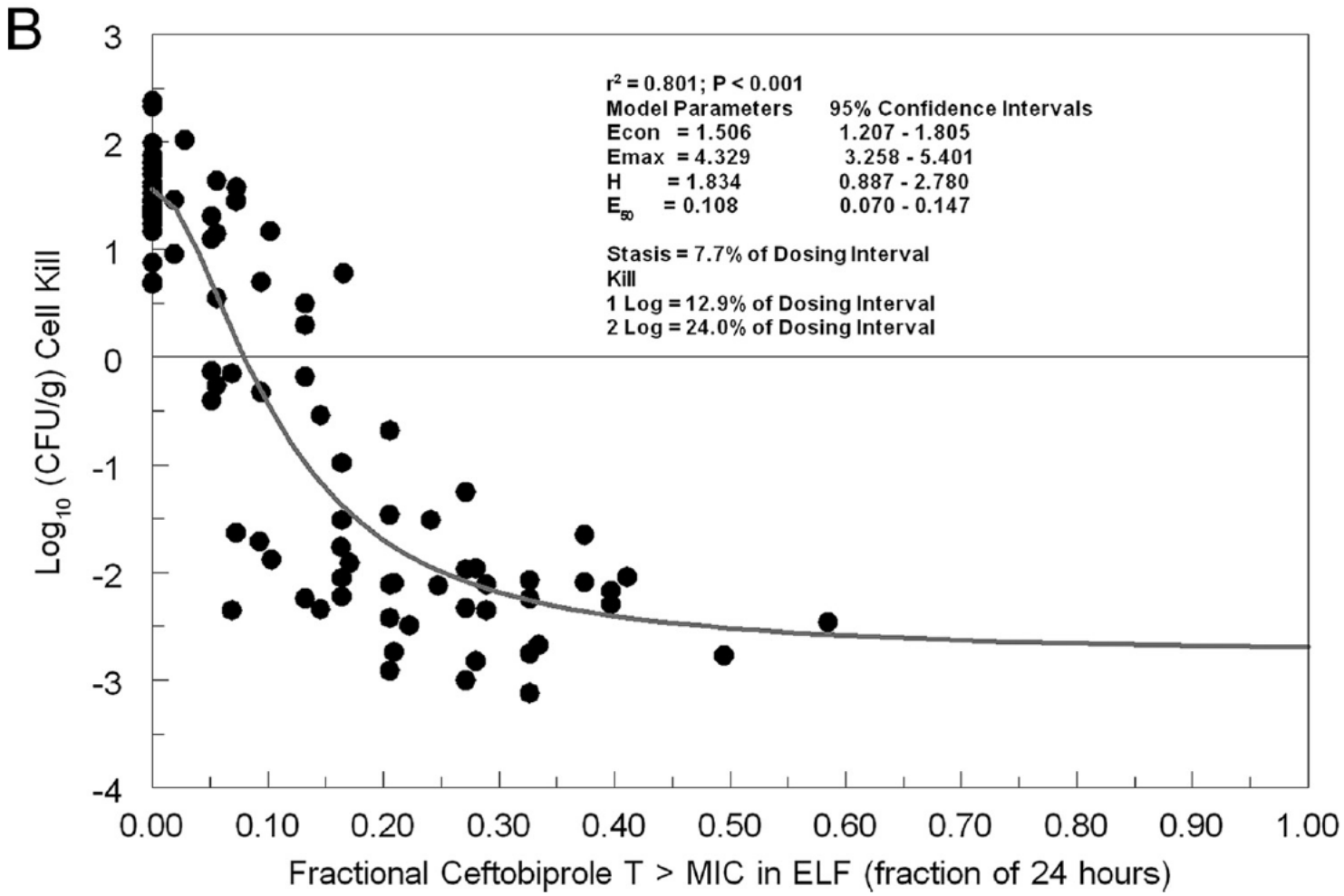
Ceftobiprole 500 mg Q8h IV as a 2 hour infusion
Target attainment was for free drug in plasma

Lodise et al. AAC 2007;51:2378-2387

Noel et al. AAC 2008;52:37-44. In a randomized double-blind trial, ceftobiprole cured 91.8% of patients with MRSA and 93.3% of all *Staphylococcus aureus*-infected patients

What about Different Indications?

HABP/VABP – Target ID in a Murine Pneumonia Model



Rodvold et al. AAC 2009;53:3294-3301

What about Different Indications?

HABP/VABP – ELF Penetration in Volunteers

TABLE 1. Population parameter values for ceftobiprole from healthy volunteers

Parameter[a] (unit)	Mean	Median	SD
V_c (liters)	2.849	2.374	1.409
K_{23} (h^{-1})	6.171	4.744	4.504
K_{32} (h^{-1})	5.207	2.652	5.691
K_{24} (h^{-1})	5.512	6.021	2.276
K_{42} (h^{-1})	2.962	1.957	2.422
CL (liters/h)	5.162	5.380	0.685
V_{ELF} (liters)	39.10	44.79	13.43
$K_{hydrolysis}$ (h^{-1})	44.74	39.46	33.22

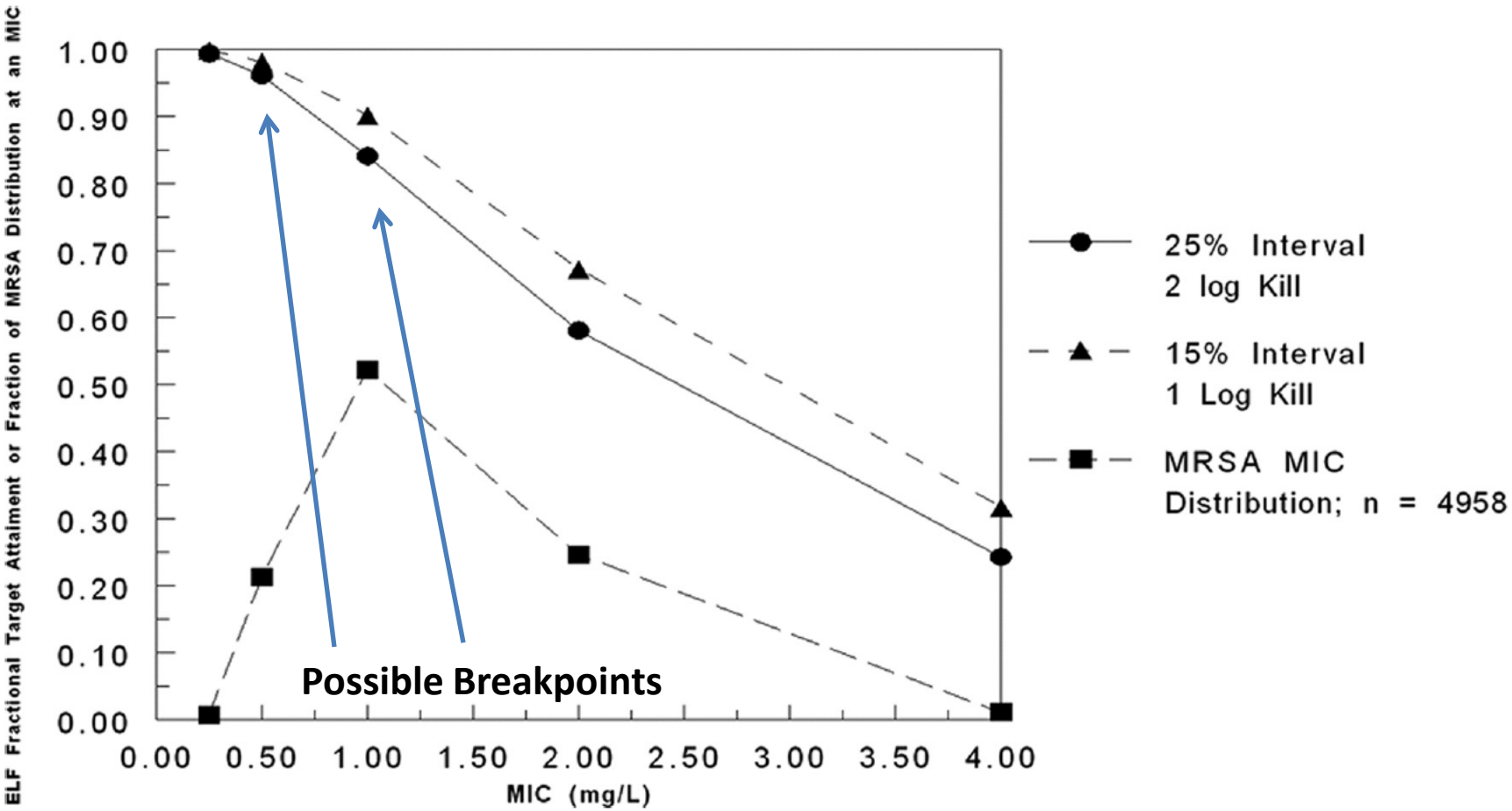
[a] V_c, volume of the central compartment; K_{23}, K_{32}, K_{24}, and K_{42}, first-order intercompartmental transfer rate constants; CL, clearance; V_{ELF}, volume of the ELF compartment; $K_{hydrolysis}$, first-order rate constant of hydrolysis of prodrug to active ceftobiprole.

TABLE 2. Penetration of ELF by ceftobiprole in healthy volunteers from a 9,999-subject simulation

Parameter (unit)	Mean	Median	SD	Percentile			
				10th	25th	75th	90th
AUC_{plasma} (mg · h/liter)	98.7	98.1	13.1	82.4	89.3	107.1	115.6
AUC_{ELF} (mg · h/liter)	25.2	15.0	35.9	4.20	7.67	30.1	55.5
Penetration (%)	25.5	15.3	36.6	4.32	7.89	30.4	55.7

Rodvold et al. AAC 2009;53:3294-3301

Breakpoints – What about Different Indications? – HABP/VABP – Target Attainment



Rodvold et al. AAC 2009;53:3294-3301

What about Different Indications?

HABP/VABP – OUTCOME

- The HABP/VABP trial with ceftobiprole failed, specifically in the VABP patients
  - **HABP** 154/199 (77.4%) for ceftobiprole vs. 145/190 (76.3%) for ceftazidime/linezolid
  - **VABP** 20/52 (38.5%) for ceftobiprole vs. 34/60 (56.7%) for ceftazidime/linezolid
- Penetration in the murine model into ELF was 69%; in volunteers it was a median of 15.3%
- Target attainment, if calculated from murine plasma targets, exceeded 95%

What about Different Indications?

HABP/VABP – OUTCOME

- **Please Note!** You CAN use plasma target attainment IF the targets are derived from clinical trial data
- In this instance, there is no issue about differing site penetration in pre-clinical models vs. man

What about Different Indications?

- ELF target, bridged to man, showed circa 80% attainment overall for a 2 Log kill and a breakpoint at 1 mg/L
- This was for *S. aureus* – Gm-negative organisms had higher MIC values and would be expected to have much lower target attainment rates
- VABP failed*

*Noel GJ, Strauss R, Shah A, Bagchi P. *Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: ASM 2008.

What about Different Indications?

ABSSSI – OUTCOME

- The measured skin penetration was 69%
- Skin had good success (>90%)

Conclusions

Conclusions

- Breakpoints can be set in a rational manner
- Early on, when no clinical data are available, preclinical models may guide breakpoint determination
- Data from clinical trials are preferable
- PK information should be requisite in clinical trials
- How about breakpoints by dose?

Conclusions

- In the circumstance where drug PK is linear, the issue is clear: doubling the dose also increases the breakpoint by 2-fold
- Great caution is required for non-linear PK
- WHAT ABOUT DIFFERENT INDICATIONS?
- Here, the data are reasonably clear: SSTI is not VABP, is not complicated UTI, where renally cleared drugs are concentrated
- Clinicians are smart: they can deal with different breakpoints by indication

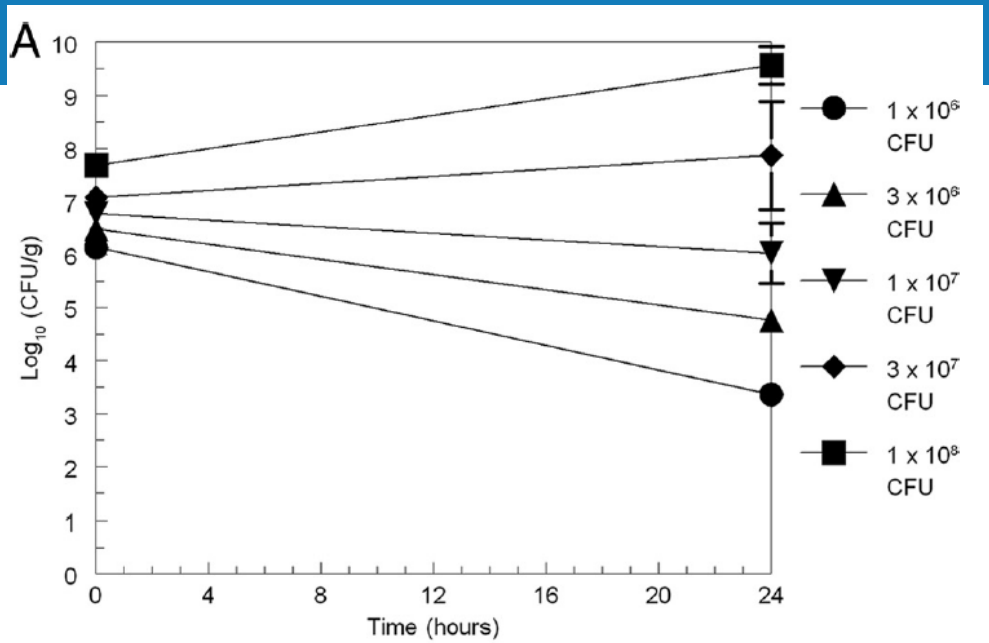
Conclusions

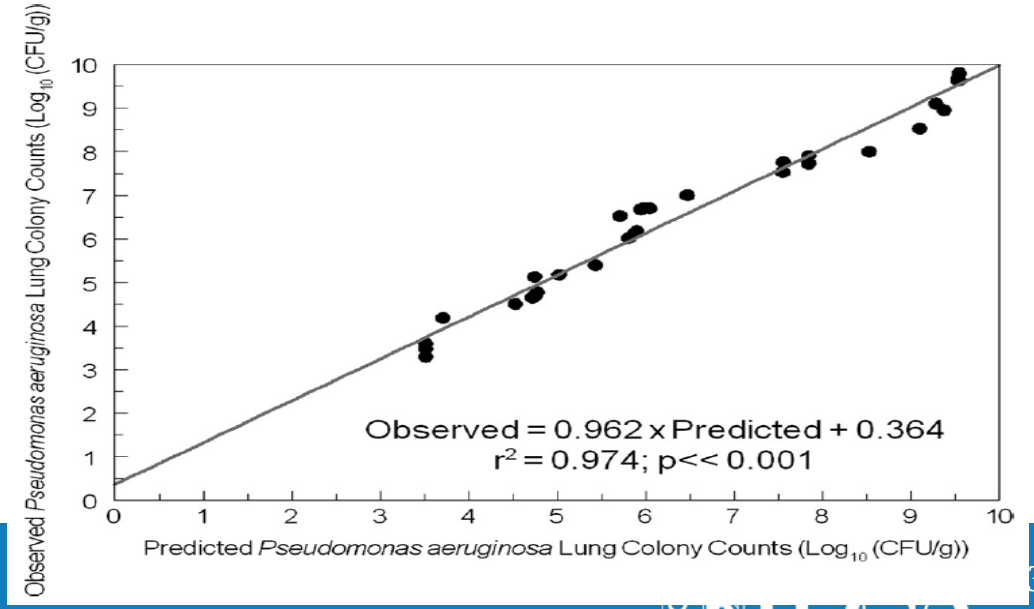
- They know the difference between meningitis, SSTI, VABP and complicated UTI
- This is the age of information technology
- We can do this
- Outcomes depend on validity of choice of regimens based on MIC
- For different indications, different breakpoints make sense for many antimicrobial agents
- Ultimately, we must ask how using PK/PD will speed new drug development and improve our use of existing drugs <u>for improved patient care</u>.

Thank You for
Your Attention

Appendix Slide 1: Granulocyte Kill of *P. aeruginosa*

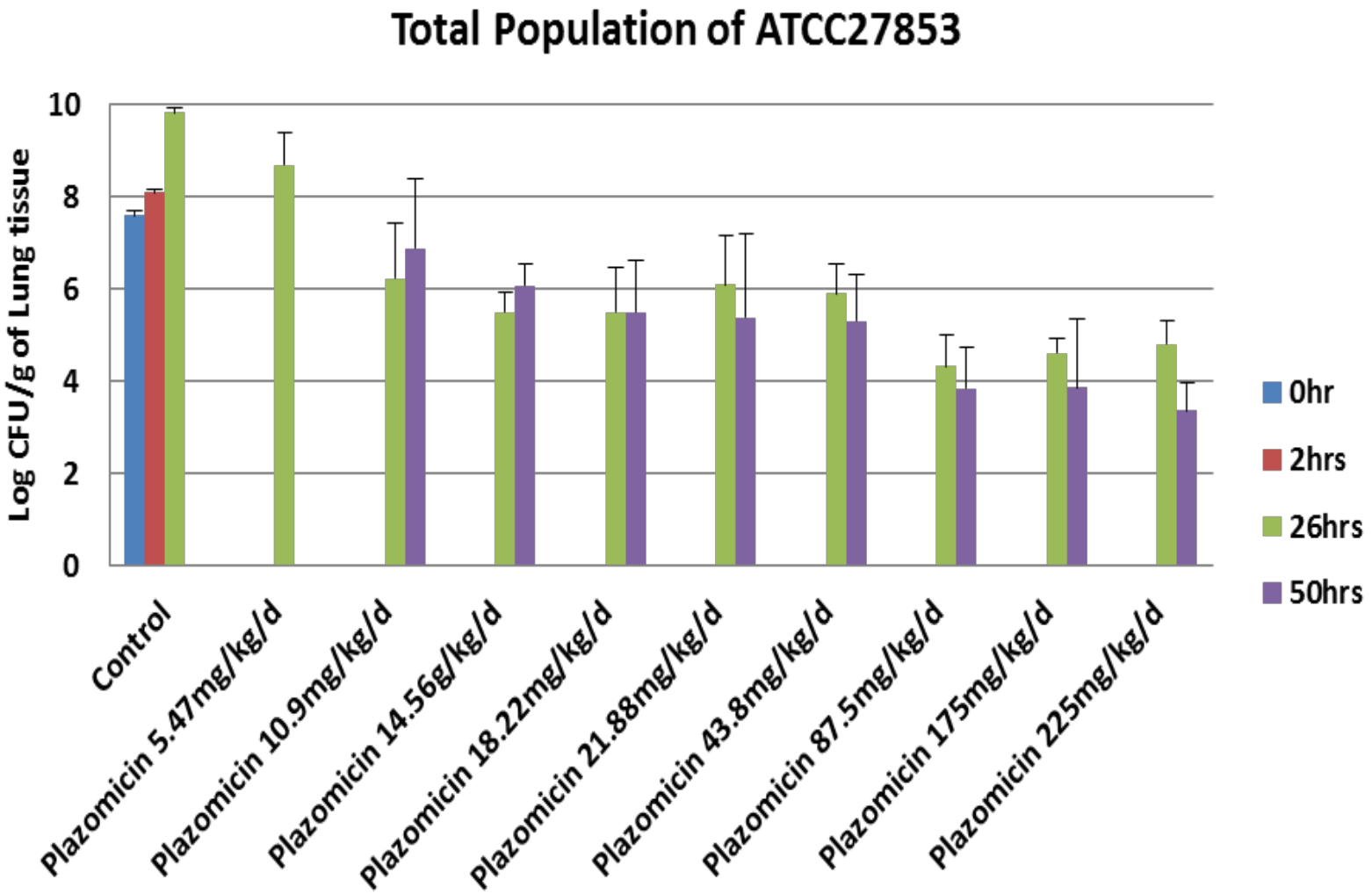
- These data were generated in a murine pneumonia model
- A Michaelis-Menten model was fit to the data
- As can be seen the model fit the data well
- The K_m was 2.15×10^6 CFU/g





Antimicrob Agents Chemother 2011;55:2693-2695

Appendix Slide 2:
WBC and Plazomicin vs *P. aeruginosa*



Appendix Slide 3:
WBC and Plazomicin vs *P. aeruginosa*

	K_g	K_{kill}	C_{50}	H	POPMAX	IC5	WBC_{MaxK}	WBC_{K50}
Units	H^{-1}	H^{-1}	mg/L	--	Col Cts	Col Cts	H^{-1}	Col Cts
Mean	0.252	1.937	3.811	1.899	9.99×10^9	7.95×10^7	0.365	2.66×10^6
Median	0.073	0.888	4.393	1.468	9.95×10^9	6.00×10^7	0.348	3.13×10^6
SD	0.398	1.817	1.672	0.835	1.81×10^5	2.15×10^8	0.035	1.06×10^6

Previous WBC_{K50} was $2.15 \times 10^6 \pm 2.66 \times 10^6$ (murine pneumonia model)
Previous WBC_{K50} was $4.30 \times 10^6 \pm 2.56 \times 10^6$ (murine thigh model)

Appendix Slide 4:
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:

$\geq 5x10^5$-$<5x10^6$	$\geq 5x10^6$-$<5.0x10^7$	$\geq 5x10^7$-$1.0x10^8$	Total
49 (36.6%)	50 (37.3%)	35 (26.1%)	134 (100%)

- **One quarter to one half** of patients are in the granulocyte saturation range at baseline!

* Antimicrob Agents Chemother. 2011;55:1606-1610
\+ J Clin Microbiol. 2009;47:2918-2924

Appendix Slide 5:
Granulocytes and Chemotherapy: Optimizing Outcome

- Hitting as hard as possible early has the best likelihood of getting the bacterial burden below the Km as quickly as possible
- This gets granulocytes back in the game and adds 1-2 Log_{10}(CFU/g) bacterial clearance over the first 24 hours.
- This may lower the relapse rate for Non-Fermentors, particularly for shorter courses of therapy
- To have the best probability of a good clinical outcome, we must hit hard and early