ANIMAL INFECTION MODELS
Identifying the Pharmacologic Determinants of Efficacy

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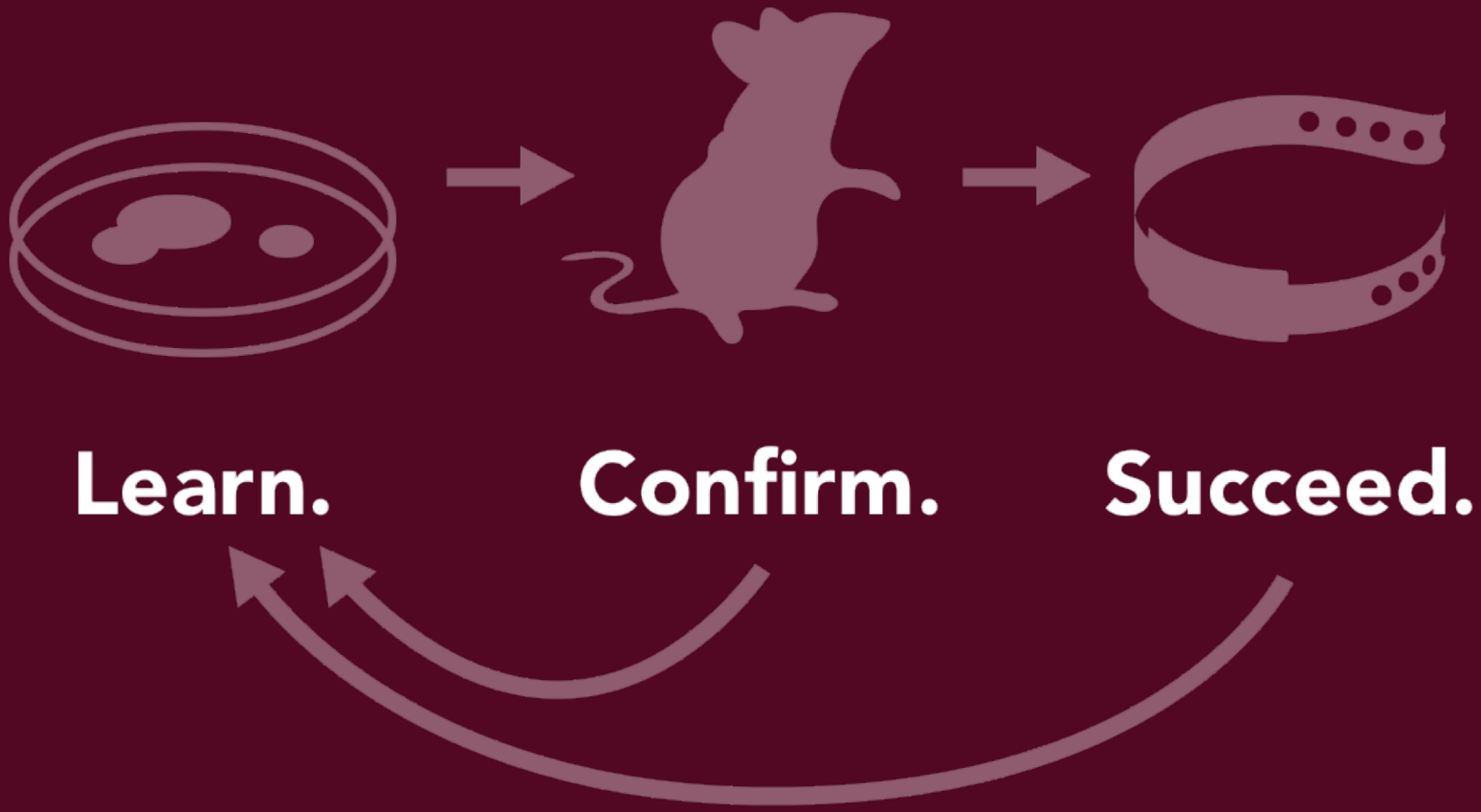
LINKING DRUG EXPOSURE TO EFFECT

Why Do It? — To Make and Confirm Predictions

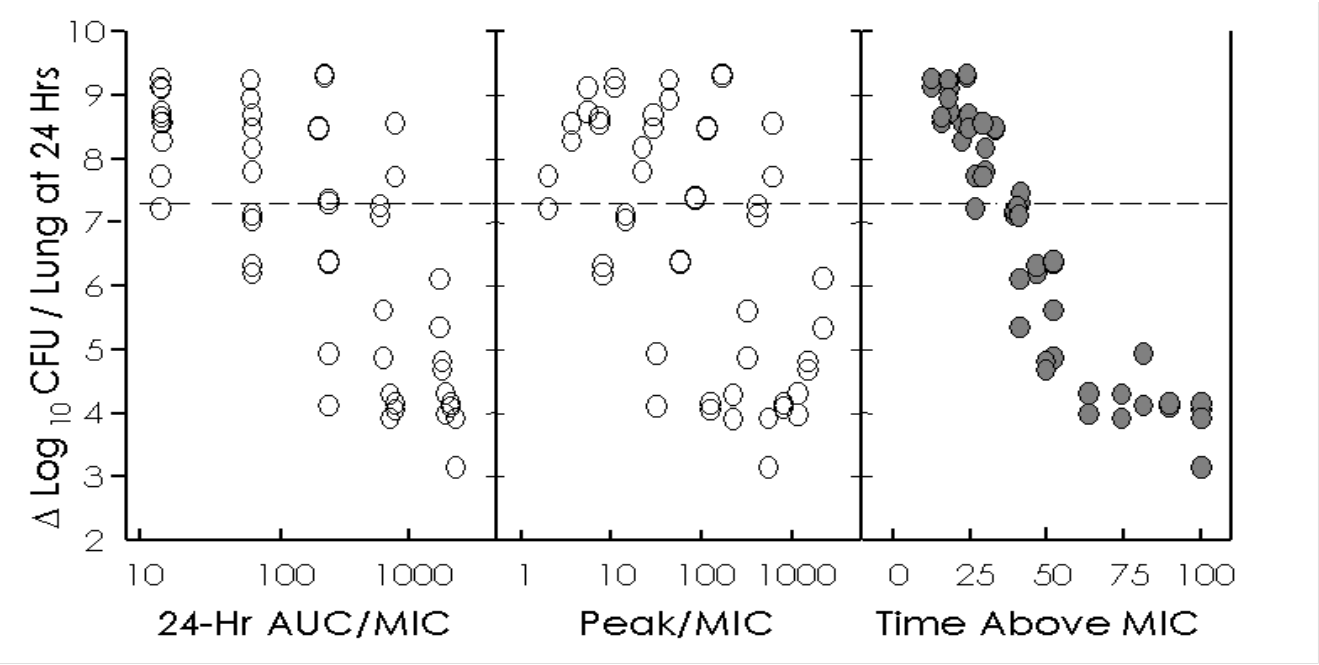


ANIMAL INFECTION MODELS
Principles Dr. Craig Taught Us

- Dose fractionation
- The impact of different variables on exposure requirements for efficacy
  - Protein binding
  - Infecting bacterial pathogen
  - Resistance determinants

DOSE FRACTIONATION
A Tool that Led to Appropriate Dosing Regimens

- Dose-fractionation studies ***literally revolutionized*** our understanding of antibacterial pharmacology



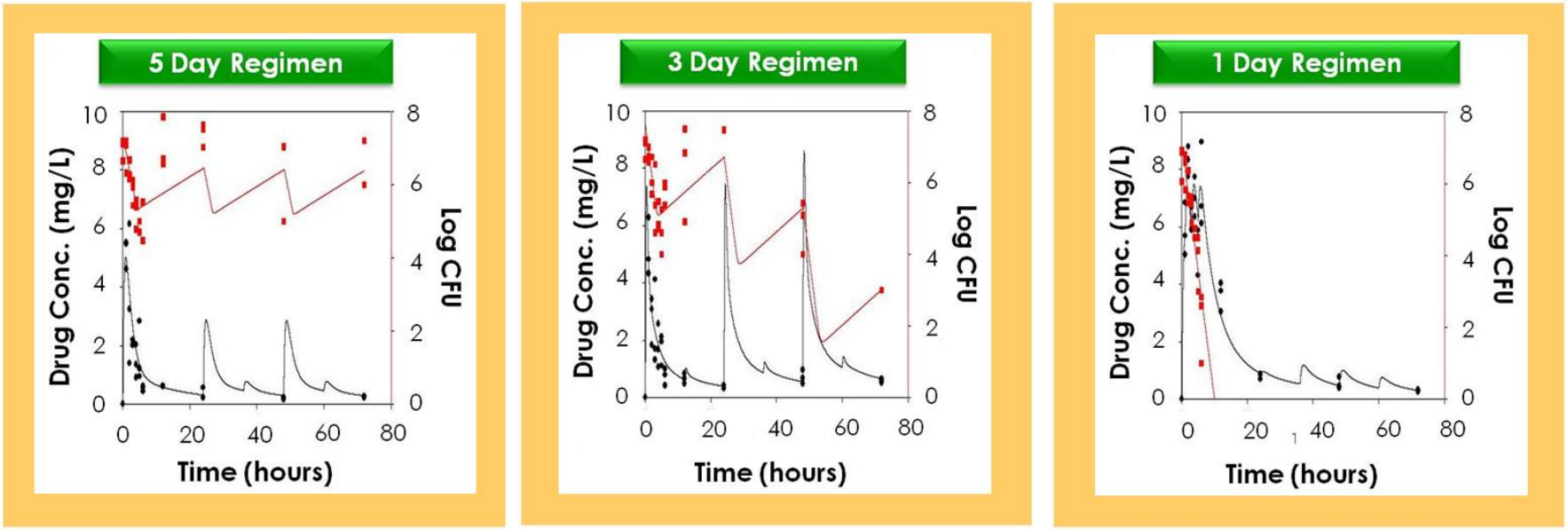
Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosing regimens for broad spectrum cephalosporins. Diagn Micro Infect Dis 1995;22:89-96.

DOSE FRACTIONATION
Does It Work?

- ***Yes!*** Well, the majority of time, anyway
- Dose fractionation is an elegant design which decouples the auto correlation between exposure measures seen in a simple dose-ranging study
- It is critical to understand that the ***dose-fractionation*** study design provides information on ***maintenance regimen performance***
- It ***does not*** provide information on:
  - The impact of ***loading doses,***
  - The ***optimal length of therapy,*** or
  - ***Resistance emergence***

DOSE FRACTIONATION
How Do We Know It Doesn't Always Work?

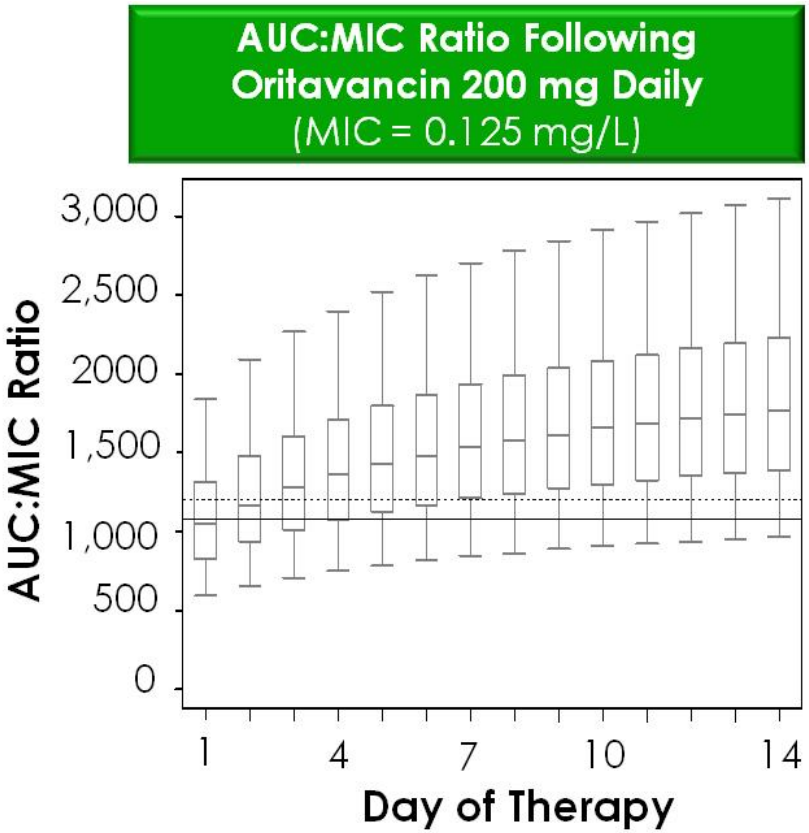
- For azithromycin, **AUC:MIC ratio** is the PK-PD measure most associated with bacterial killing *in vivo*
- Yet the **same AUC** delivered **three different ways** demonstrated **drastically different** bacterial killing

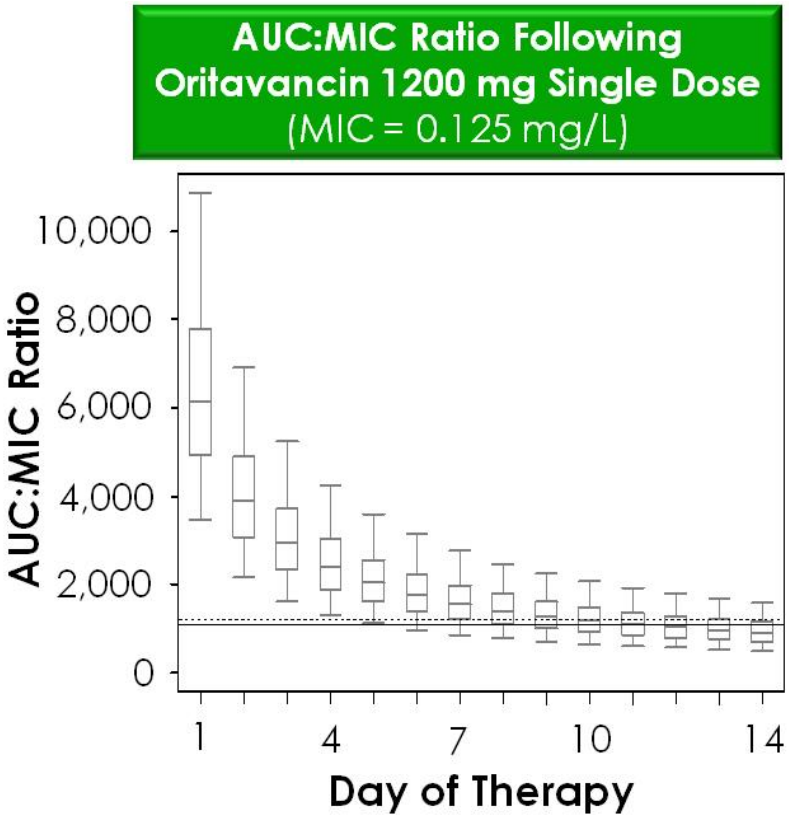


Okusanya OO *et al*. Pharmacokinetics and pharmacodynamics of azithromycin in gerbils with *Haemophilus influenzae* middle ear infection. Presented at 106th American Society for Clinical Pharmacology and Therapeutics, 2005.

ORITAVANCIN
PK-PD Basis of Single-Dose Therapy

- For oritavancin, front loading the exposure allows **effective exposures** to be achieved on Day 1

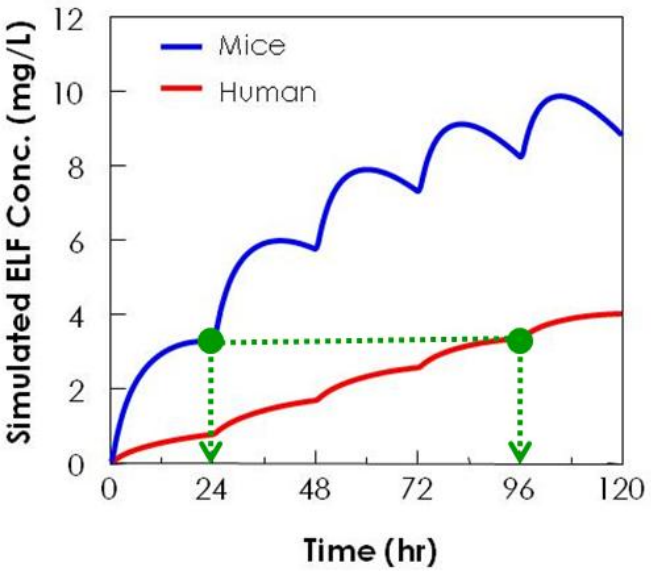




Box plots represent the median and interquartile range for daily average total-drug AUC:MIC ratios based on simulations of 2,000 patients. The associated whiskers represent the 5th and 95th percentile for the daily average total-drug AUC:MIC ratios. The horizontal solid and dashed lines represent the average total-drug AUC:MIC targets of 1078 and 1204 associated with net bacterial stasis and a 1 $\log_{10}$ CFU decline, respectively, based on data from a murine thigh-infection model for *S. aureus* after 48 hrs of study [Okusanya OO, *et al*., ICAAC 2009. Abstract A1-1287]. Data on File, The Medicines Company.

ORITAVANCIN
PK-PD-Based Drug Development Decisions

Assessment of simulated murine and human oritavancin ELF concentration-time profiles over 120 h for *S. aureus* pneumonia



- Efficacious exposures based on a *S. aureus* neutropenic lung infection model were achieved in mice and humans at 24 and 96 hours, respectively
- To overcome differences in rate constants to and from ELF and plasma compartments between humans and mice, a front-loaded dosing regimen in humans would be needed
  - However, a very large loading dose would be needed in patients with pneumonia to match the early and effective exposures achieved in animals
- These data were critical to halting the program for oritavancin treatment of *S. aureus* pneumonia

Bhavnani SM *et al*. Use of PK-PD principles to guide clinical drug development for oritavancin. In: Program and abstracts of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). 2008. Abstract A-51.

Ambrose PG *et al*. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: Look before you leap! Antimicrob Agents Chemother 2010; 51:S103-S110.

DOSE FRACTIONATION
When Do We Need to Know More?

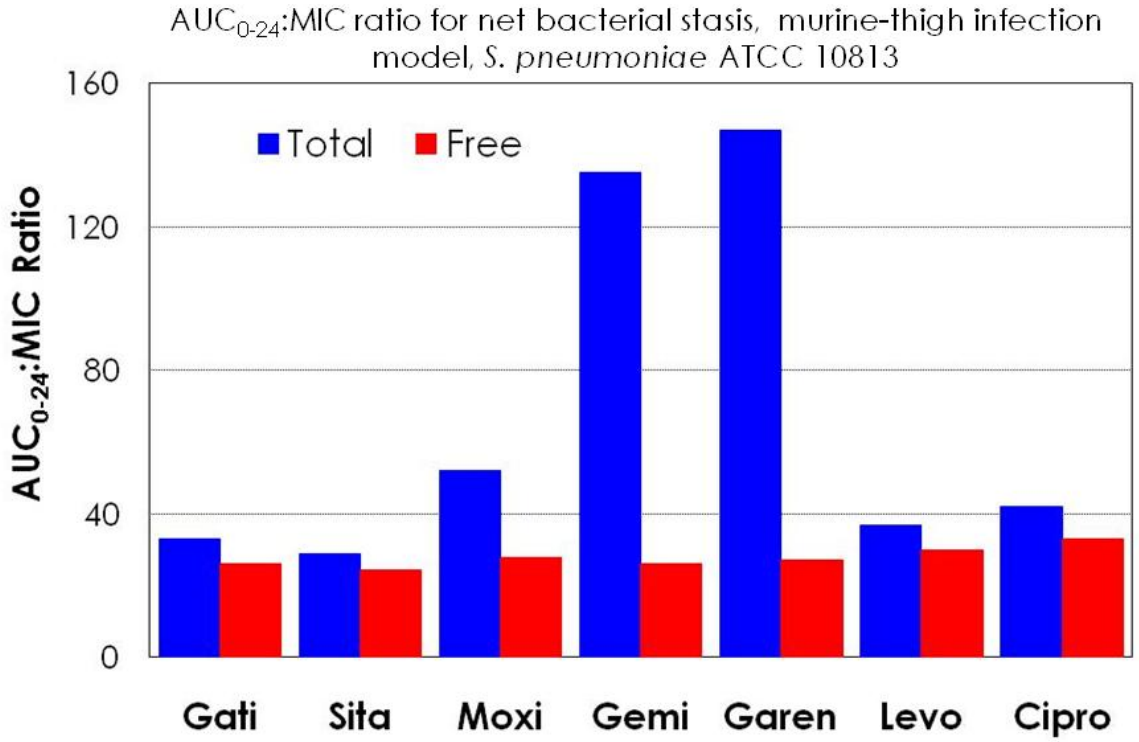
- The question for the drug development scientist is:

  When do we need to know more than a dose-fractionation study design provides?

  - When the drug is from a class for which there are no well-characterized priors
  - When a drug displays marked accumulation in humans
    - May be especially important for a drug with a concentration-dependent pattern of bactericidal activity over a wide-range of concentrations

PROTEIN BINDING
Does It Alter the Exposure Needed for Efficacy?

No, if the PK-PD index is expressed in the free-domain.
A few exceptions do occur.



Andes DR and Craig WA. 40th and 41st ICAAC, 2000 and 2001.

PROTEIN BINDING
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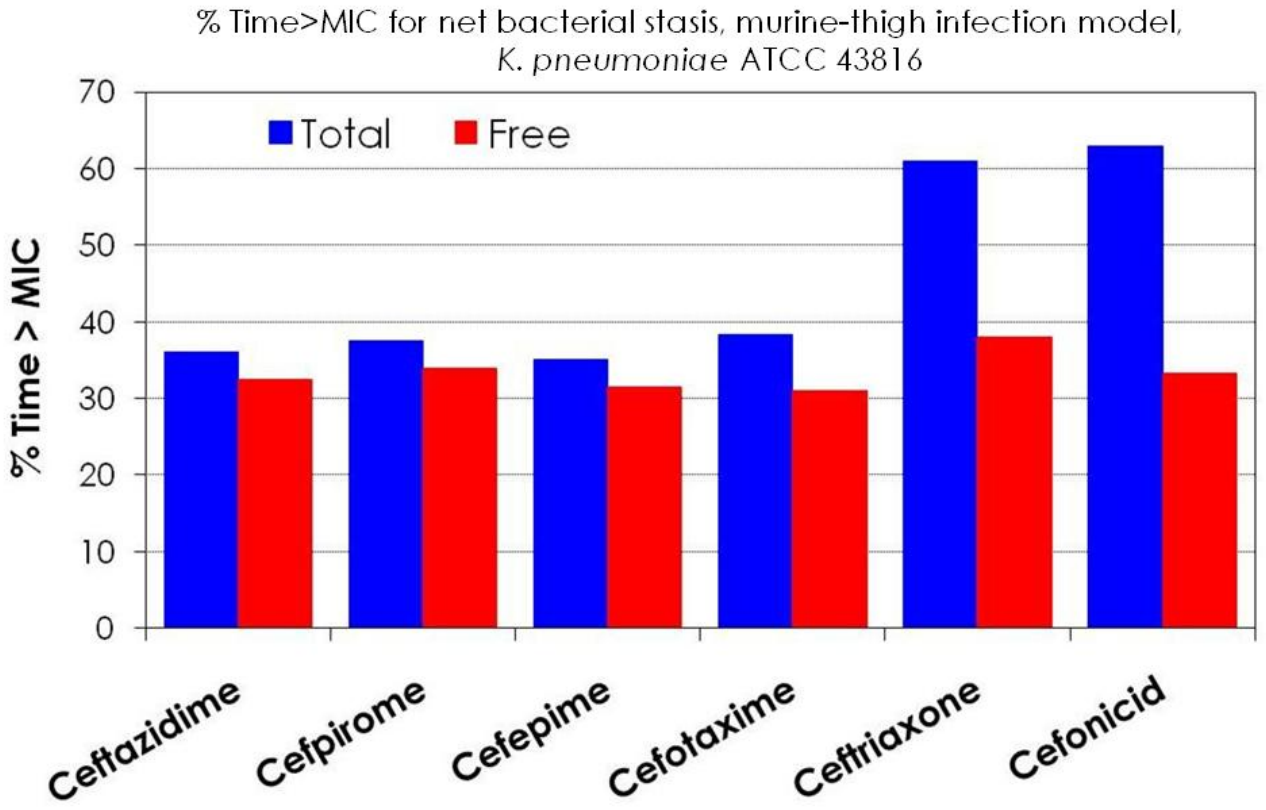


Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides and linezolid. Infect Dis Clin N Am 2003;17:479-502.

PK-PD TARGET
Does It Vary by Pathogen?

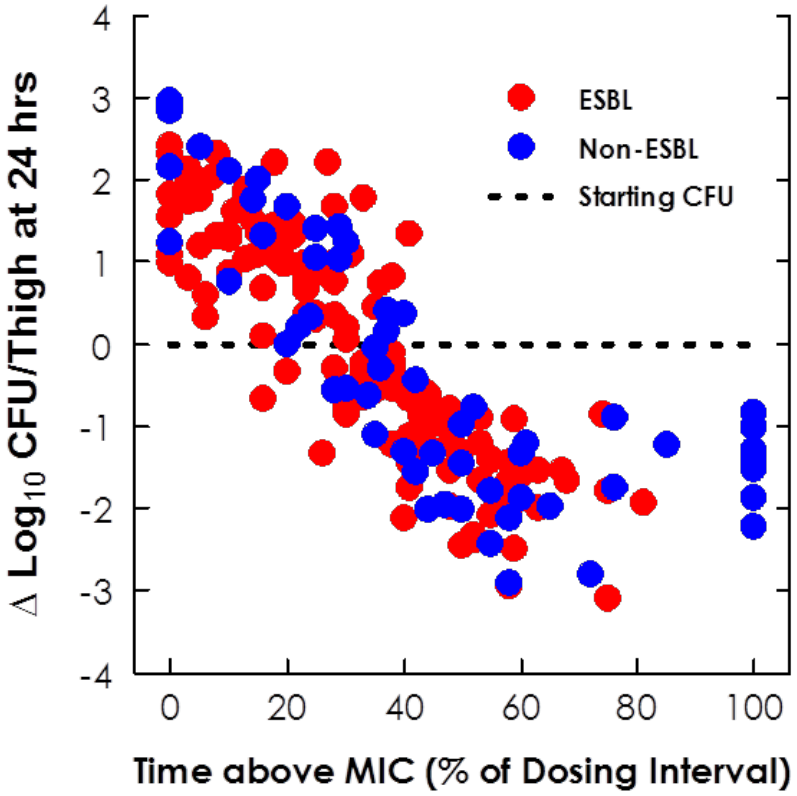
Yes, generally Gram-negative bacilli require greater exposure compared with Gram-positive organisms

Class	Organism	%Time>MIC	
		Stasis	Maximum Kill
Penicillins	Gram-negative	30-40	60-70
	Pneumococci	25-35	35-50
	Staphylococci	20-30	40-50
Cephalosporins	Gram-negative	40-50	70-80
	Pneumococci	35-40	40-50
	Staphylococci	20-30	40-50
Carbapenems	Gram-negative	20-30	40-50
	Pneumococci	15-25	30-45
	Staphylococci	10-20	25-40

Data courtesy of Dr. William A. Craig.

RESISTANCE
Does It Alter the Exposure Needed for Efficacy?

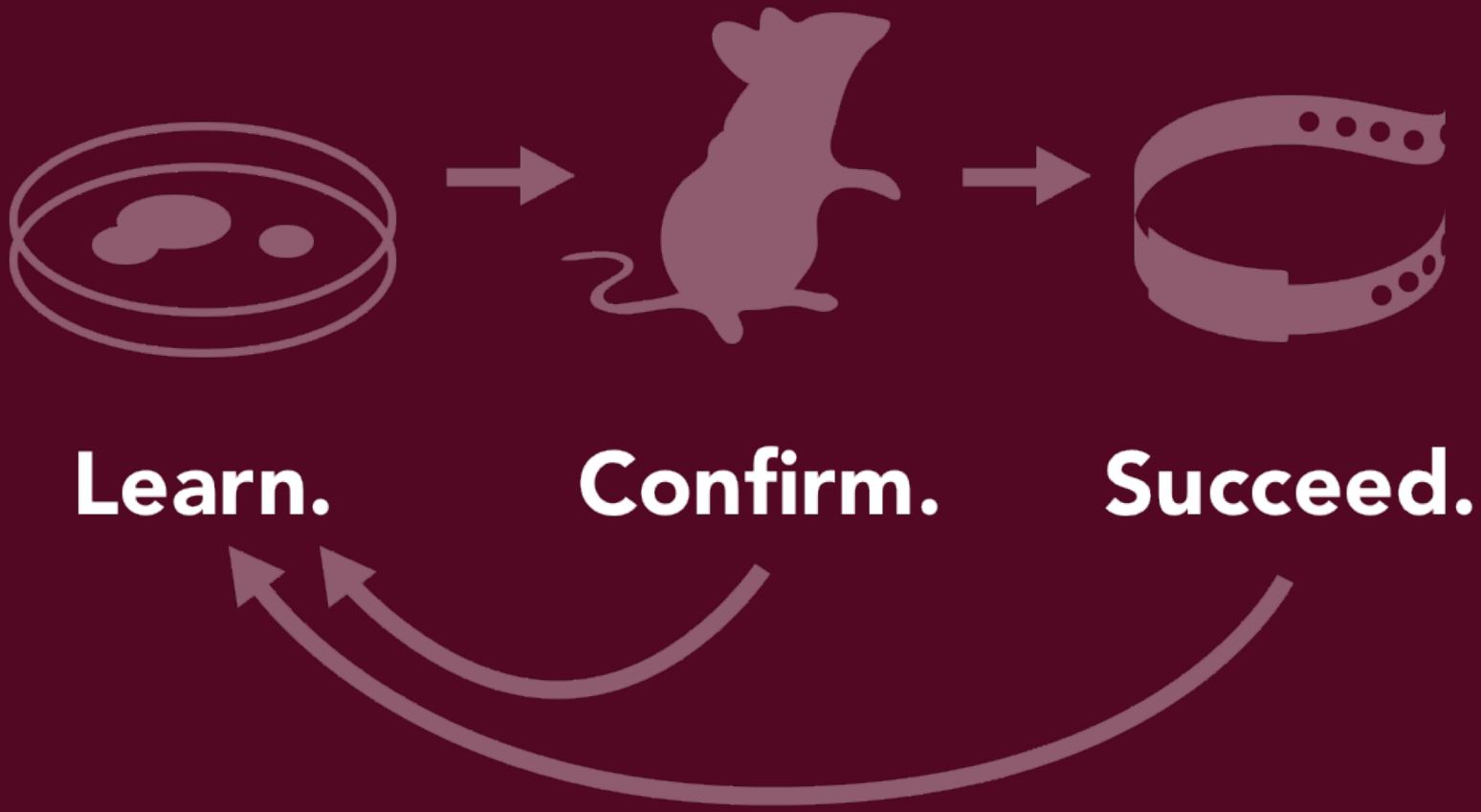
No. It is not the presence or absence of particular resistance determinants that predict outcome but rather, the drug exposure indexed to MIC



Craig WA and Andes DR. Treatment of infections with ESBL-producing organisms: pharmacokinetic-pharmacodynamic considerations. Clin Microbiol Infect 2005;11:10-17.

MAKING AND CONFRIMING PREDICTIONS

Show Me the Money!



PK-PD IN MAN
Analyses of Clinical Data

The number of drug classes and indications studied to date continues to grow, providing the opportunity to improve our knowledge about translating from animal infection models

Aminoglycoside

β-Lactams

Fluoroquinolones

Glycopeptides

Ketolides

Lipoglycopeptides

Lipopeptides

Macrolides

Oxazolidinones

Pleuromutilins

Tetracyclines

Bacteremia

Community-Acquired Respiratory Tract Infections

Endocarditis

Intra-Abdominal Infections

Nosocomial Pneumonia

Skin and Skin Structure Infection

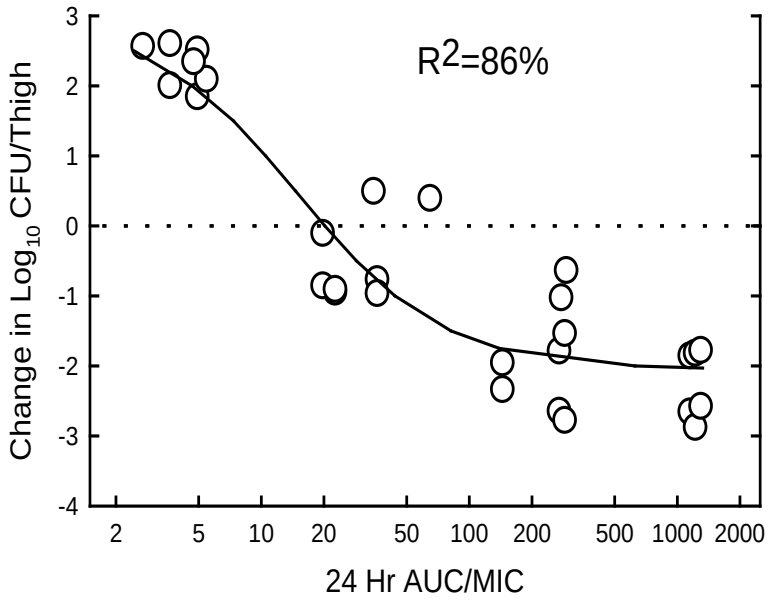
TB Meningitis

Typhoid Fever

Urinary Tract Infections

EXPOSURE-RESPONSE IN VIVO
Tigecycline Against Enterobacteriaceae

Data for 3 Enterobacteriaceae isolates studied in a neutropenic murine-thigh infection model[a]



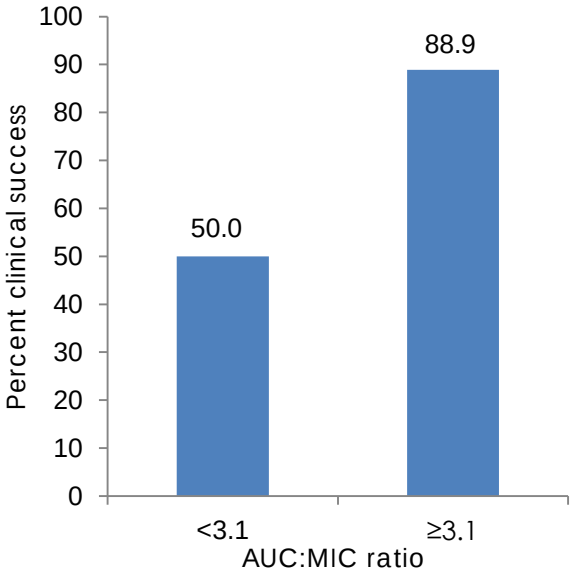
Bacterial reduction endpoint	AUC:MIC ratio targets for efficacy	
	Total-drug	Free-drug[b]
Net bacterial stasis	20.2	2.63
1-$\log_{10}$ CFU reduction	43.9	5.71
2-$\log_{10}$ CFU reduction	626	81.4

a. van Ogtrop ML *et al*. *In vivo* pharmacodynamic activities of two glycylcyclines (GAR-936 and WAY 152,288) against various Gram-positive and Gram-negative bacteria. Antimicrob Agents Chemother 2000; 44:943-949.

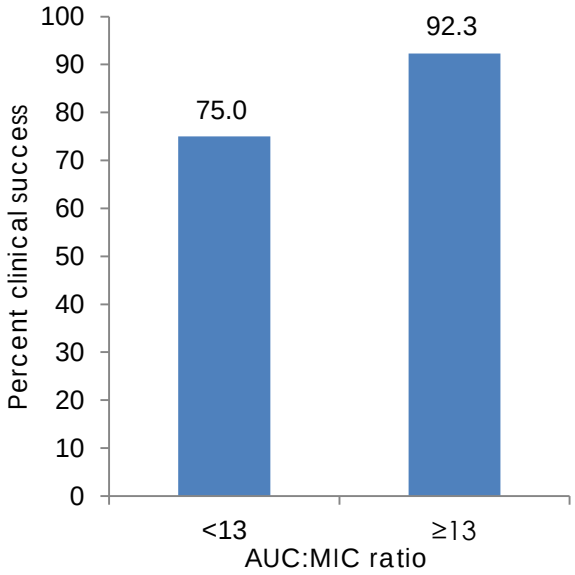
b. Crandon JL *et al*. Pharmacodynamics of tigecycline against phenotypically diverse *Staphylococcus aureus* isolates in a murine thigh model. Antimicrob Agents Chemother 2009; 53:1165-1169.

CLINICAL EXPOSURE-RESPONSE
Tigecycline-Treated Patients with cIAI

Percentages of Successful Clinical Response in Tigecycline-Treated Patients with cIAI by Total-Drug AUC:MIC Ratio Threshold



All evaluable patients (n=123)



Patients with Enterobacteriaceae at baseline (n=97)

Bhavnani SM *et al*. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010; 54:1207-1212.

CLINICAL AND NON-CLINICAL DATA
Translating from Mice to Men

Comparison of Tigecycline AUC:MIC ratio Targets for Enterobacteriaceae Efficacy

Bacterial reduction endpoint	Non-clinical data from a murine-thigh infection model[a]		Clinical data from patients with cIAI and Enterobacteriaceae at baseline[b]	
	Total-drug	Free-drug[c]	Total-drug	Free-drug[d]
Net bacterial stasis	20.2	2.63		
1-$\log_{10}$ CFU reduction	43.9	5.71	13	2.6
2-$\log_{10}$ CFU reduction	626	81.4		

a. van Ogtrop ML *et al*. *In vivo* pharmacodynamic activities of two glycylcyclines (GAR-936 and WAY 152,288) against various Gram-positive and Gram-negative bacteria. Antimicrob Agents Chemother 2000; 44: 943-949.

b. Bhavnani SM *et al*. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010; 54:1207-1212.

c. Crandon JL *et a*l. Pharmacodynamics of tigecycline against phenotypically diverse *Staphylococcus aureus* isolates in a murine thigh model. Antimicrob Agents Chemother 2009;53:1165-1169.

d. Tygacil package insert. Wyeth Pharmaceuticals, Inc. Philadelphia, PA. December 2014.

CLINICAL EXPOSURE-RESPONSE
Tigecycline-Treated Patients with cIAI

Final Multivariable Logistic Regression Model for Factors Predictive of Clinical Success

Independent variable	Estimate	Odds ratio (95% CI)	P-value
Intercept	-9.831		< 0.001
Weight <94 kg[a]	1.849	6.35 (1.25, 32.4)	0.026
Absence of *P. aeruginosa* in baseline cultures[b]	2.317	10.1 (1.43, 72.0)	0.021
APACHE II score <13[c]	2.390	10.9 (1.28, 93.3)	0.029
Race = non-Hispanic[d]	2.503	12.2 (2.12, 70.6)	0.005
Diagnosis = complicated appendicitis or cholecystitis[e]	2.545	12.7 (2.27, 71.5)	0.004
AUC:MIC ratio ≥3.1[f]	3.497	33.0 (3.27, 333)	0.003

a. Reference group included patients weighing ≥94 kg (n=19).
b. Reference group included patients with *P. aeruginosa* in baseline cultures (n=10).
c. Reference group included patients with APACHE II scores ≥13 (n=6).
d. Reference group included patients who are of Hispanic race (n=25).
e. Reference group included diagnoses of peritonitis due to perforation of small/large intestine, intra-abdominal hepatic, or splenic abscess, or other (n=37).
f. Reference group included patients with AUC:MIC ratio <3.1 (n=6).

Bhavnani SM *et al*. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010; 54:1207-1212.

CLINICAL EXPOSURE-RESPONSE
Tigecycline-Treated Patients with cIAI

Probability of Clinical Success in the Presence of One Unfavorable Factor

Factor[a]	Probability
Weight ≥94 kg	0.968
Presence of *P. aeruginosa* in baseline cultures	0.950
APACHE II score ≥13	0.947
Race = Hispanic	0.941
Diagnosis = abscess, peritonitis due to perforation or other	0.938
AUC:MIC ratio <3.1	0.855

a. Remaining factors were set to the condition favoring clinical response. The following conditions represented the most favorable for optimizing clinical response: weight <94 kg, absence of *P. aeruginosa* in baseline cultures, APACHE II score <13, race = non-Hispanic, diagnosis = complicated appendicitis or cholecystitis, and AUC:MIC ratio ≥3.1.

Bhavnani SM *et al*. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010; 54:1207-1212.

CLINICAL EXPOSURE-RESPONSE
Tigecycline-Treated Patients with cIAI

Probability of Clinical Success in the Presence of Two Unfavorable Factors[a]

Factor one	Factor two[b]	Probability
Weight ≥94 kg	Presence of *P. aeruginosa* in baseline cultures	0.751
	APACHE II score ≥13	0.737
	Race = Hispanic	0.714
	Diagnosis = perforation	0.706
	AUC:MIC ratio <3.1	0.481
Presence of *P. aeruginosa* in baseline cultures	APACHE II score ≥13	0.637
	Race = Hispanic	0.610
	Diagnosis = perforation	0.600
	AUC:MIC ratio <3.1	0.367
APACHE II score ≥13	Race = Hispanic	0.593
	Diagnosis = perforation	0.583
	AUC:MIC ratio <3.1	0.350
Race = Hispanic	Diagnosis = perforation	0.555
	AUC:MIC ratio <3.1	0.324
Diagnosis = abscess or peritonitis due to perforation	AUC:MIC ratio <3.1	0.316

a. Each pair of unfavorable factors is shown only once.
b. Remaining factors were set to the condition favoring clinical response. The following conditions represented the most favorable for optimizing clinical response: weight <94 kg, absence of *P. aeruginosa* in baseline cultures, APACHE II score <13, race = non-Hispanic, diagnosis = complicated appendicitis or cholecystitis, and AUC:MIC ratio ≥3.1.

Bhavnani SM *et al*. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010; 54:1207-1212.

NEW DEVELOPMENT PATHWAYS
Increasing Weight of PK-PD Data

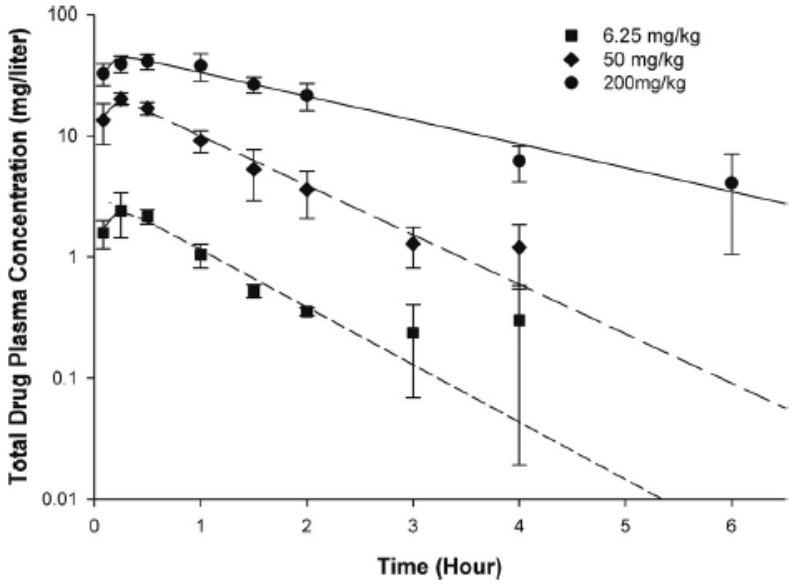
- PK-PD based non-clinical data helps de-risk drug development and strengthens NDA submissions
- Greater weight is put on such data for drugs for unmet medical need and for which recruitment of large numbers of patients is challenging
- Given the importance of such data, it is critical to optimize study design and analysis of data from animal infection models

DESIGN AND ANALYSIS CONSIDERATIONS
Some Common Problems

- Mismatch between animal infection model used and indication of interest
- Poorly characterized animal PK and limited range of studied doses
- Lack of effect site PK
- Inadequate growth control
- Size of baseline inoculum
- Misspecification of outliers

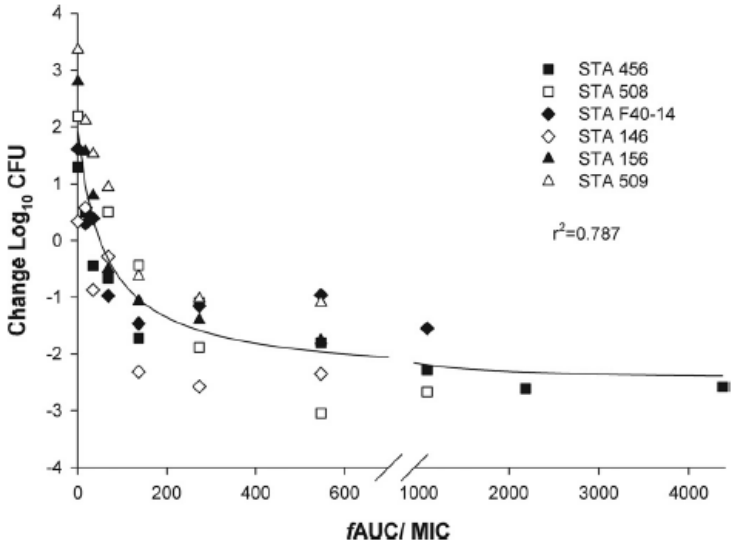
DESIGN AND ANALYSIS CONSIDERATIONS
Poorly Characterized Pharmacokinetics

Pharmacokinetic Studies



- Single GSK2140944 dose of 6.25 to 200 mg/kg were studied
- 8 blood samples were collected over 4-6 hours; 3 BAL samples were collected over 3-4 hours

In vivo efficacy in a neutropenic lung infection model

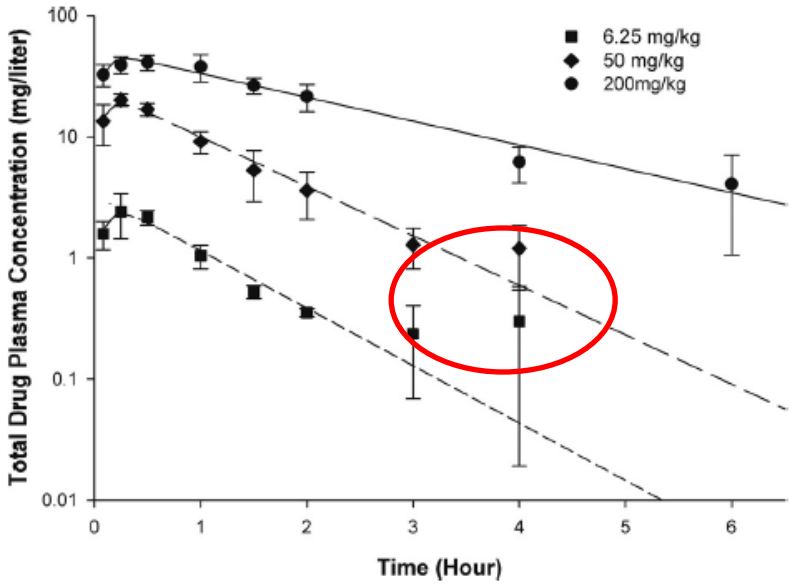


- GSK2140944 doses of 1.56 to 400 mg/kg q6h were evaluated

Wonhee S *et al*. Antimicrob Agents Chemother 2015; 59:4956-4961.

DESIGN AND ANALYSIS CONSIDERATIONS
Poorly Characterized Pharmacokinetics

Pharmacokinetic Studies



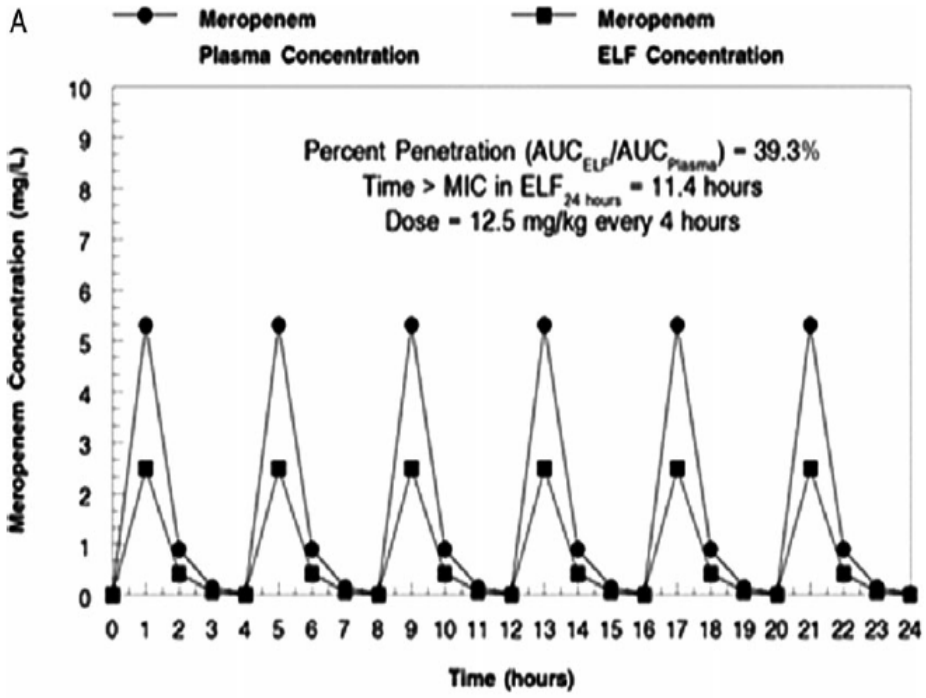
Study Design Implications

- PK profiles after 3 hours suggest the presence of a 2nd compartment
  - Needed longer PK sampling period for the higher doses to confirm
- Highest dose studied for efficacy was 400 mg/kg q6h; PK was only studied up to 200 mg/kg
  - By assuming linearity beyond the dose range studied, there is a risk of calculating both %Time>MIC and AUC with error
- If plasma PK are poorly estimated, this affects ELF PK and plasma and ELF PK-PD
- Can this be fixed with modeling?

Wonhee S *et al*. Antimicrob Agents Chemother 2015; 59:4956-4961.

DESIGN AND ANALYSIS CONSIDERATIONS

Optimizing Design and Analysis



Pharmacokinetic Studies

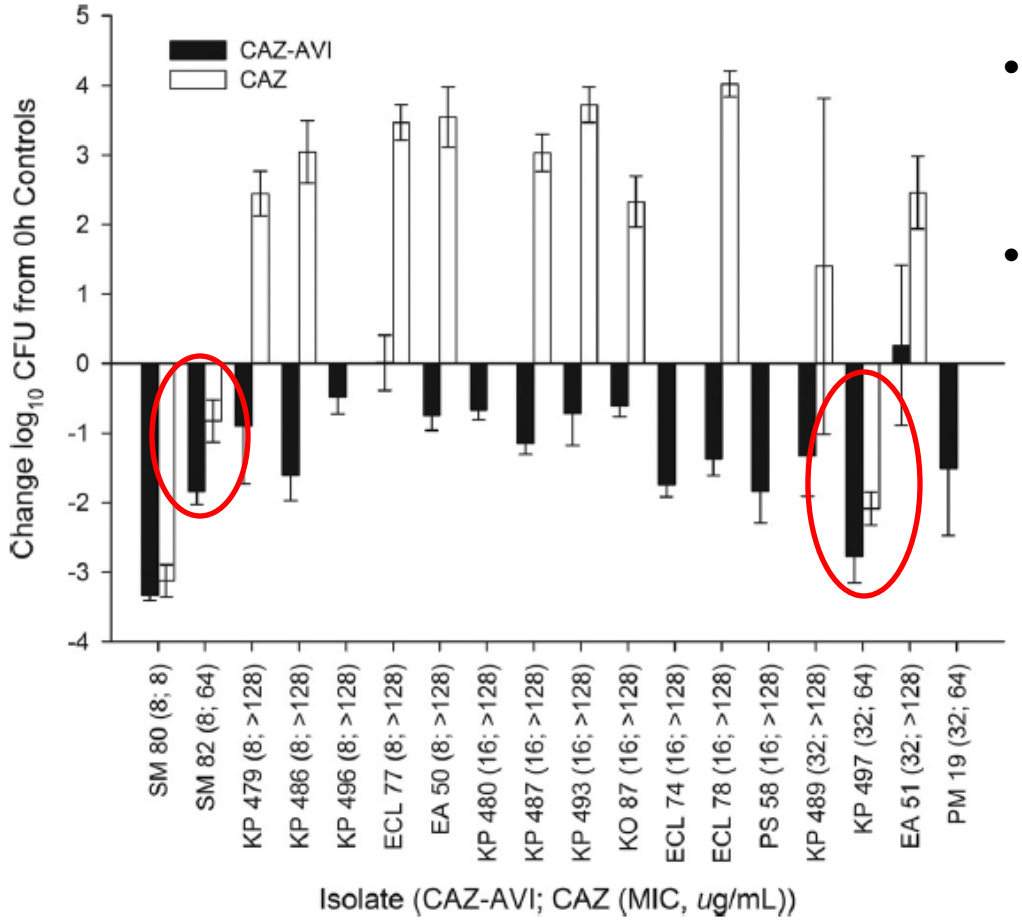
- Meropenem dose range: 50 to 400 mg/kg
- Plasma and ELF data were obtained at the same time points over 6 hours
- PK data were co-modeled
  - A linear three-compartmental model best described the murine PK data

In Vivo Efficacy Studies

- Highest meropenem dose studied for efficacy in a neutropenic murine Pseudomonas pneumonia model was 50 mg/kg q4h

Louie A *et al*. Combination treatment with meropenem plus levofloxacin is synergistic against *Pseudomonoas aeruginosa* infection in a murine model of pneumonia. J Infect Dis 2015; 211: 1326-33.

DESIGN AND ANALYSIS CONSIDERATIONS
Diagnosing Unexpected Findings

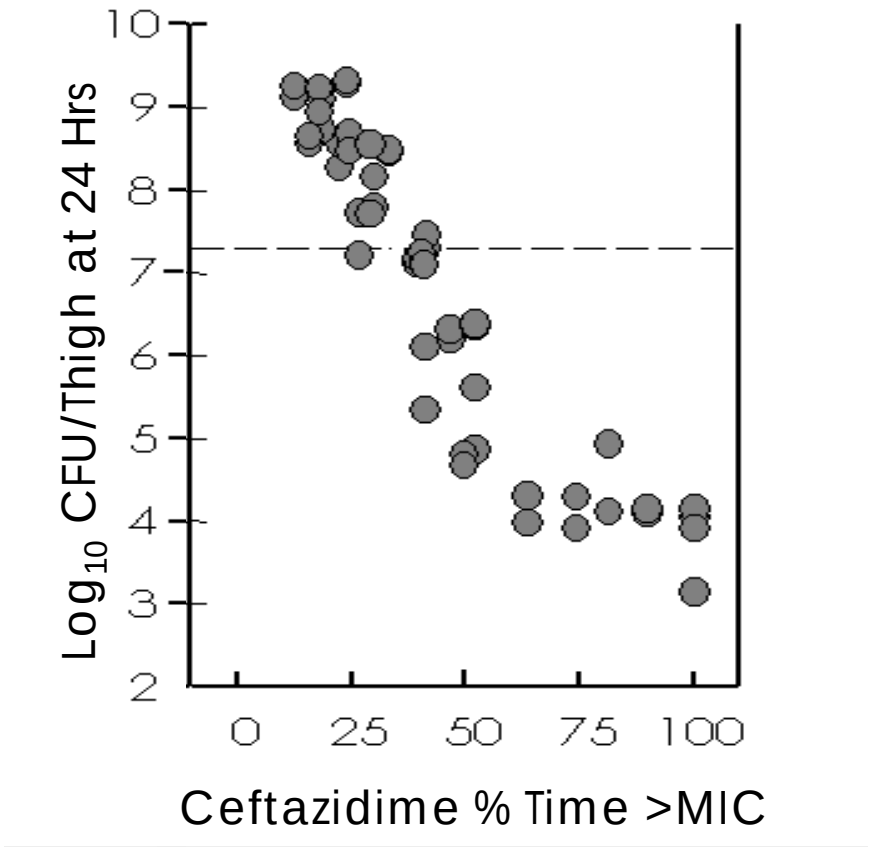


Study Findings

- Inverted U shape function between MIC and change in $\log_{10}$ CFU
- Question: What does the by-isolate growth control data show?
  - A lack of growth in the 2- and 24-hour growth controls can lead to overestimation of the efficacy of the drug
  - Does this explain why ceftazidime showed efficacy at MIC = 64 µg/mL (%Time>MIC = 0)?
  - Are very high doses of avibactam PK contributing unexpected kill?
    - PK not available but unlikely

MacVane SH *et al. Antimicrob Agents Chemother* 2014;58:6913-6919.

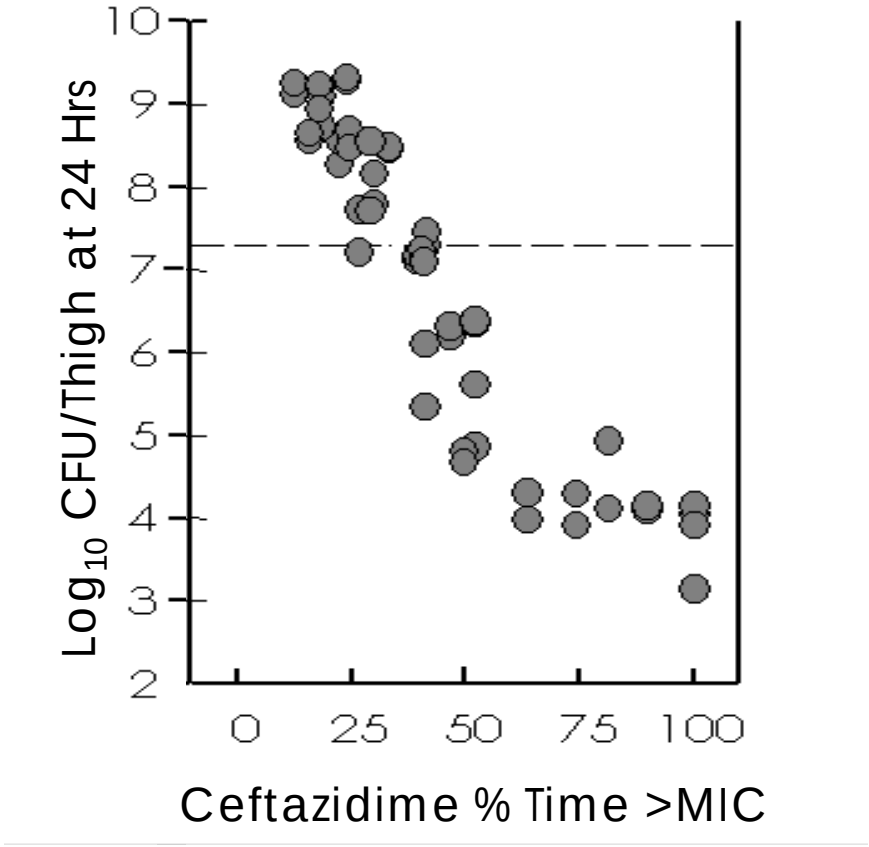
DESIGN AND ANALYSIS CONSIDERATIONS
Diagnosing Unexpected Findings

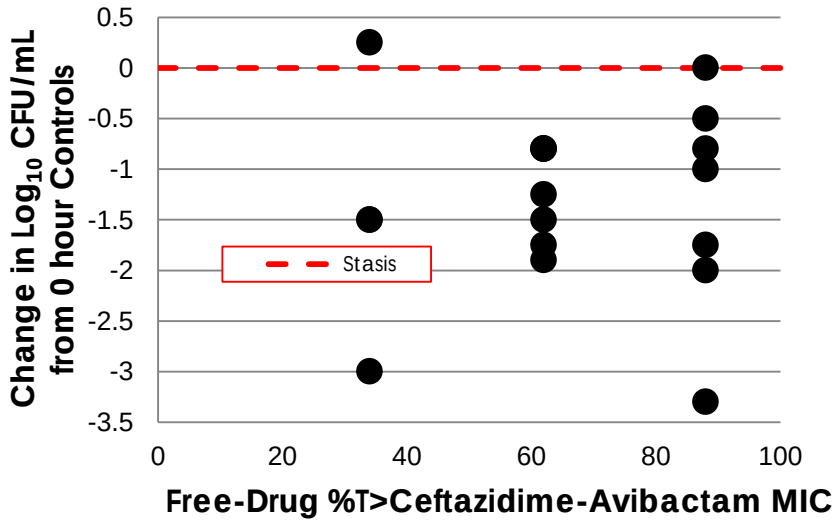


- This is the relationship between ceftazidime %T>MIC and change in log_{10}CFU that Dr. Craig showed us many years ago
- If we have studied a given β-lactamase inhibitor properly, this relationship should be replicated using a β-lactamase-producing isolate

Craig WA. Pharmacodynamics of antimicrobials: General concepts and applications. In: Antimicrobial Pharmacodynamics in Theory and Clinical Practice. C.H. Nightingale, T. Murakawa, P.G. Ambrose Eds. Marcel Dekker, Inc. NY, NY.

DESIGN AND ANALYSIS CONSIDERATIONS
Diagnosing Unexpected Findings





- A relationship between ceftazidime/avibactam %T>MIC and change in $\log_{10}$CFU is difficult to see; trend looks counterintuitive

Craig WA. Pharmacodynamics of antimicrobials: General concepts and applications. In: Antimicrobial Pharmacodynamics in Theory and Clinical Practice. C.H. Nightingale, T. Murakawa, P.G. Ambrose Eds. Marcel Dekker, Inc. NY, NY.

MacVane SH *et al*., Antimicrob Agents Chemother 2014;58:6913-6919.

DESIGN AND ANALYSIS CONSIDERATIONS
Misspecification of Outliers

- Beware of analyses in which large amounts of data were excluded without a valid definition for outliers
  - Outliers must be identified statistically and excluded to allow a valid analysis of the data
  - It is not acceptable to empirically exclude large amounts of data
- A method for assessing potential outliers should be part of the analysis plan
  - One example: If the difference between the fitted and observed values is ≥3 standard errors and if exclusion of the data point significantly improves the fit to the other observations, the data point can be considered an outlier and excluded from the analysis

NON-CLINICAL INFECTION MODELS
Prospectus

- Optimal use of existing non-clinical models
  - Use of *in vitro* and *in vivo* systems to study dose fractionation and identify PK-PD index associated with efficacy
  - Use of *in vivo* systems to study dose range and identify the magnitude of PK-PD index required for different levels of efficacy
  - Use of *in vitro* systems to study interesting dosing regimens and the impact of duration of therapy on resistance
- Continue development of animal infection models
  - *In vivo* models that better reflect specific disease states
  - Increasing duration of treatment

Lasting Contributions to the Field of Antimicrobial Pharmacokinetics and Pharmacodynamics

Scientist, Ambassador, Mentor
William A Craig

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