



PK-PD TARGET SELECTION

It's All About the Goal

Paul G. Ambrose, Pharm.D.

Chair, USCAST Executive Committee
President, Institute for Clinical Pharmacodynamics



INSTITUTE *for* CLINICAL
PHARMACODYNAMICS

PK-PD TARGET THRESHOLD SELECTION

It's All About the Goal

- The choice of a rational PK-PD target threshold is dependent upon what it is that you wish to achieve
 - Select a dose that will result in clinical response rates consistent with regulatory approval
 - Support a high and appropriate susceptibility breakpoint
 - Prevent resistance amplification
 - Optimize speed of response
- The disagreements folks have in regard to PK-PD selection often stems from a mismatch in goals

HOW MUCH IS ENOUGH?

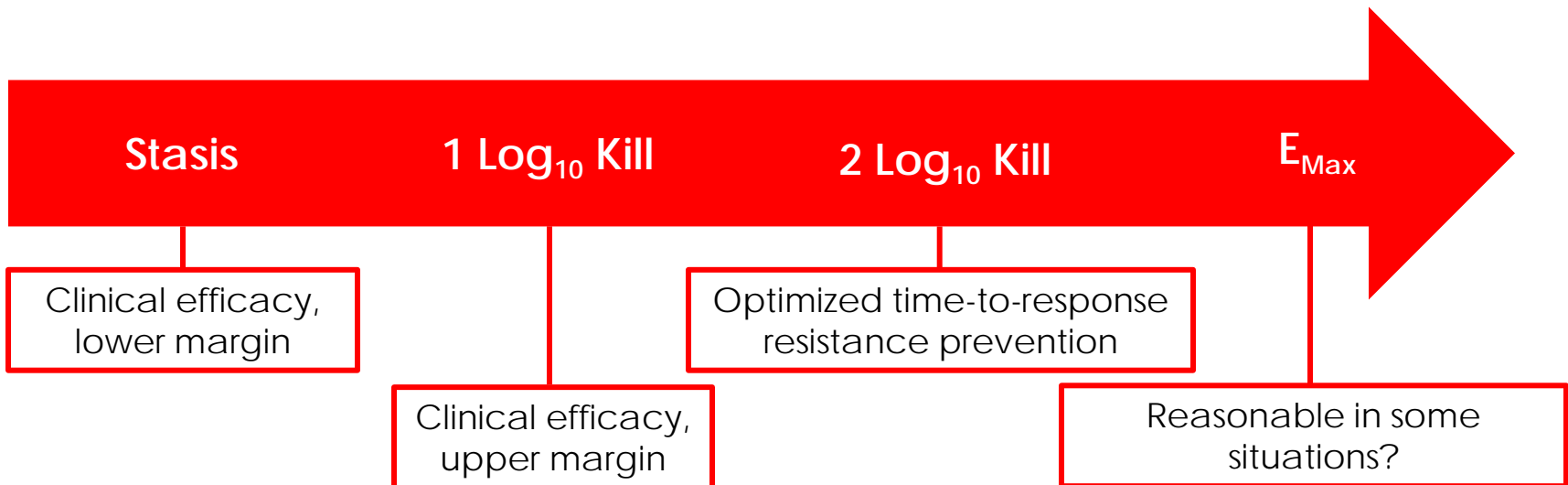
Select the PK-PD Target with the Goal in Mind

Lower Margin

- Intact immune system
- Low inoculum infection
- High no-treatment response rate
- Surgical intervention

Upper Margin

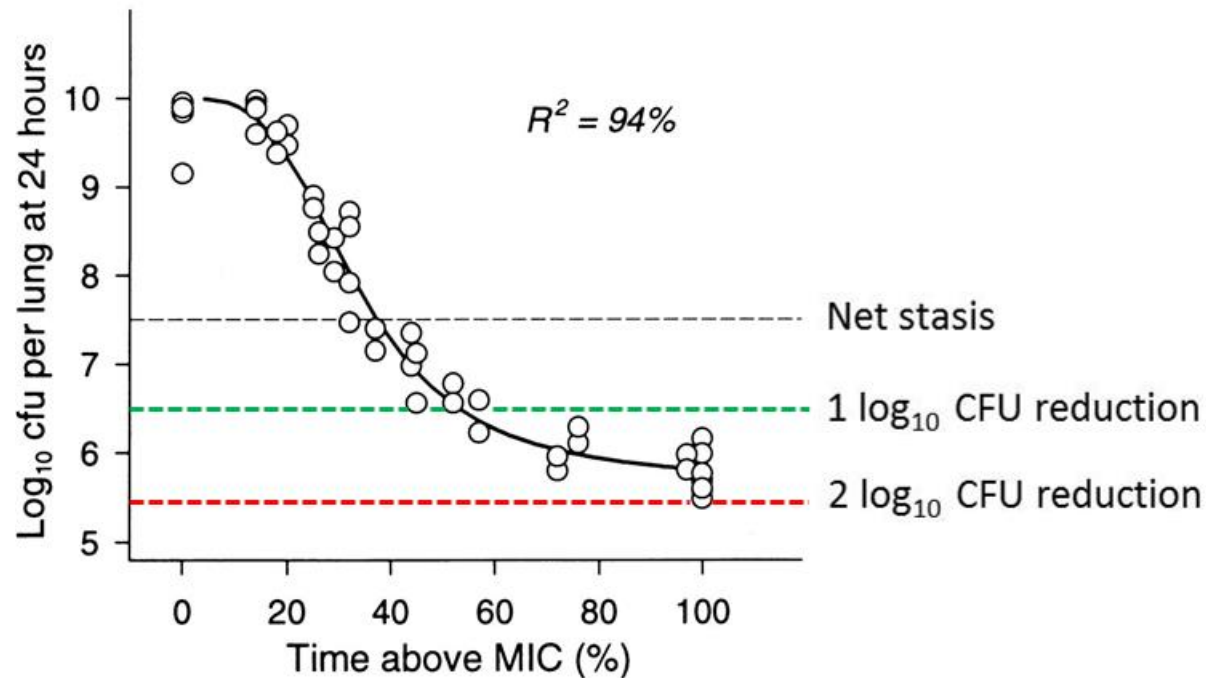
- Neutropenic patient
- High inoculum infection
- Low no-treatment response rate



But before you just say, ***"I want $\geq 2 \log_{10}$ CFU reduction!"***

PK-PD TARGET THRESHOLD SELECTION

Choose Wisely!



...remember that not every antibiotic can attain a 2 log₁₀ reduction in CFU

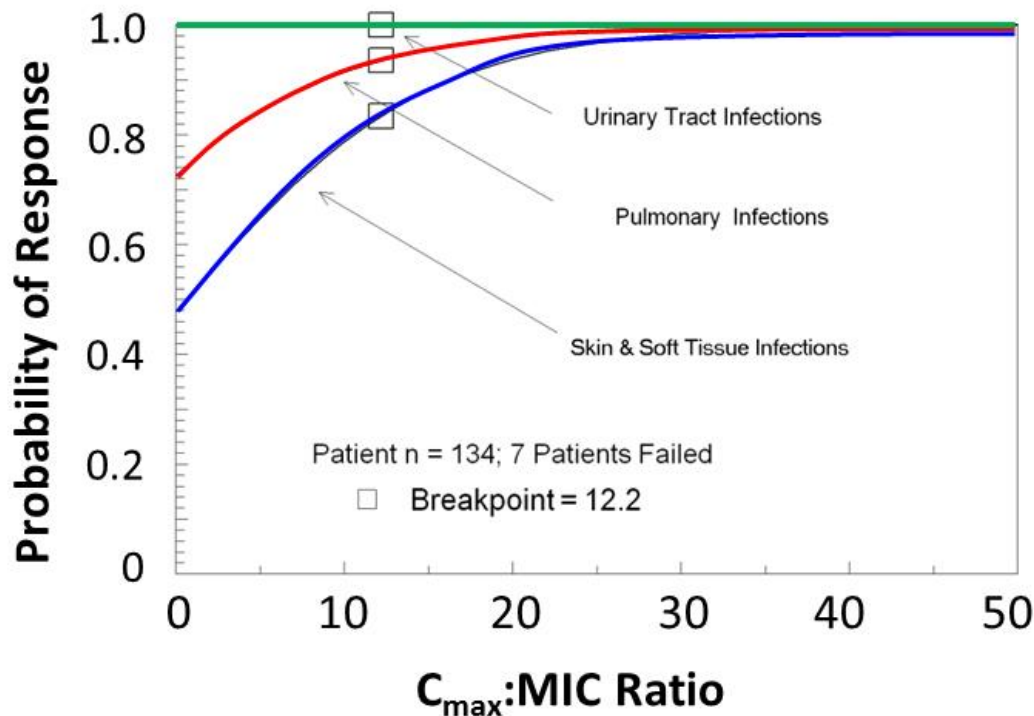
PK-PD TARGET THRESHOLD SELECTION

What We All Agree Upon

- A robust analysis of clinical trial datasets consisting of plenty of successes and failures would be optimal
 - Failures are not in the interest of patients, drug developers, or regulators
 - Should not be a frequent occurrence given the predictive power of our pre-clinical infection models
- Thus, we are often left with robust analyses of clinical datasets with few failures
 - Instead of continuous exposure-response relationships with tight confidence bounds, far more often than not, we only have datasets that can support a CART-derived breakpoint

CASE-IN-POINT

Let's Look at Levofloxacin



- 313 patients
- 272 with PK data
- 134 clinically and microbiologically evaluable
- 7 were clinical failures

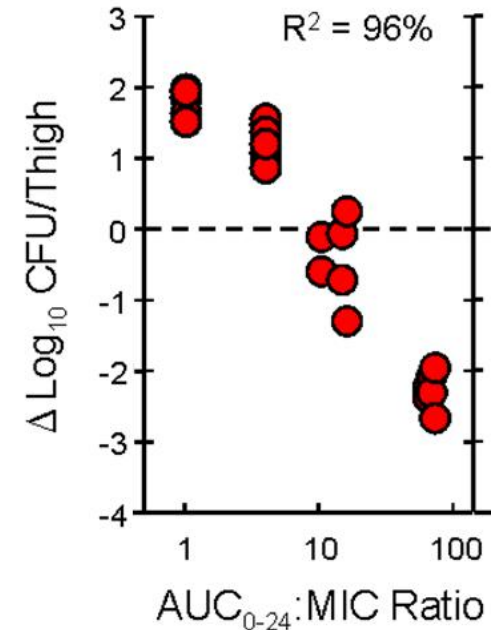
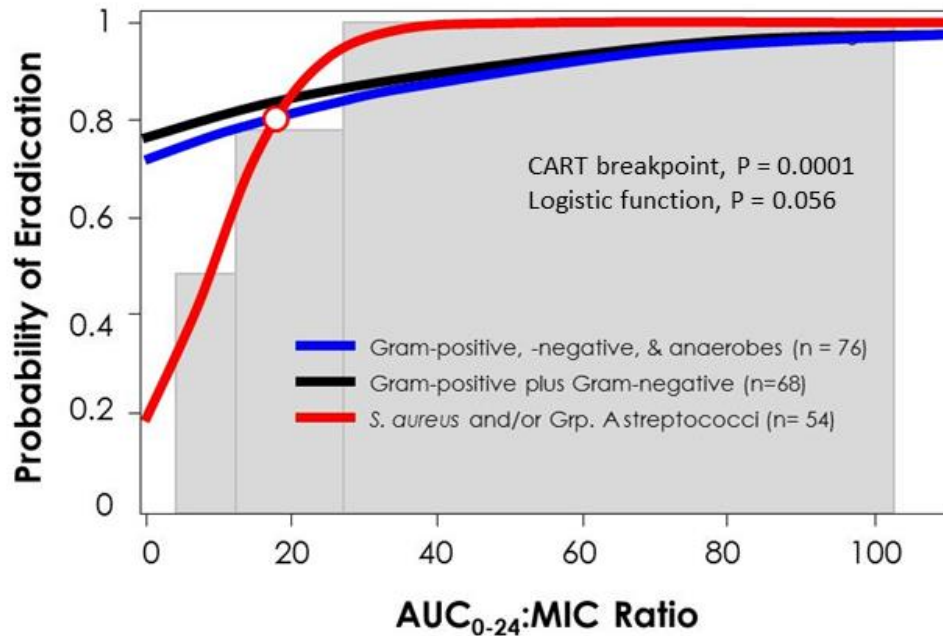
PK-PD TARGET THRESHOLD SELECTION

What We All Agree Upon

- We end up with...
 - A good understanding of target patient population PK
 - Less informative PK-PD efficacy relationships
- The clinical PK-PD relationships end up being confirmatory rather than discriminatory
- Thus, we rely upon viewing the clinical data in the context of results from animal infection models
 - The translational linkages between pre-clinical and clinical data become critical

CASE-IN-POINT

Let's Look at Tigecycline



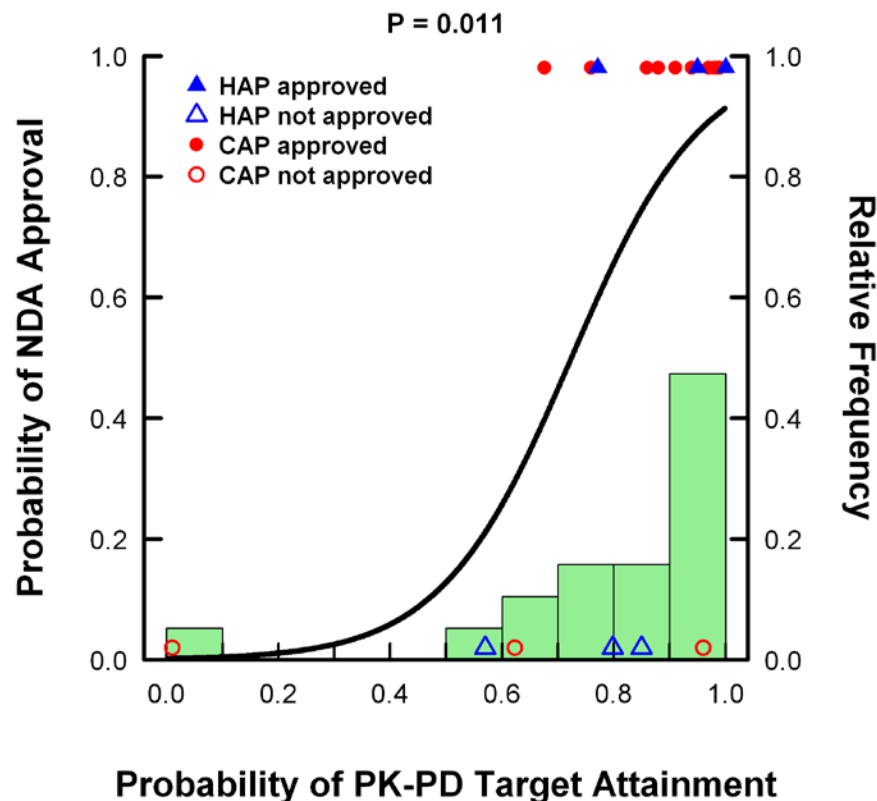
The $AUC:MIC$ ratio necessary for a high clinical response rate (>17.9) is similar to that needed for net bacterial stasis in animals (15-20)

Meagher A, Passarell J, Cirincione B, Van Wart S, Liolios K, Babinchak T, Ellis-Grosse EJ, Ambrose PG. Exposure-response analysis of the efficacy of tigecycline in patients with complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2007;51:1939-1945.

van Ogtrop ML, Andes D, Stamstad TJ, Conklin B, Weiss WJ, Craig WA, and Vesga O. 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.

PK-PD TARGET THRESHOLD SELECTION

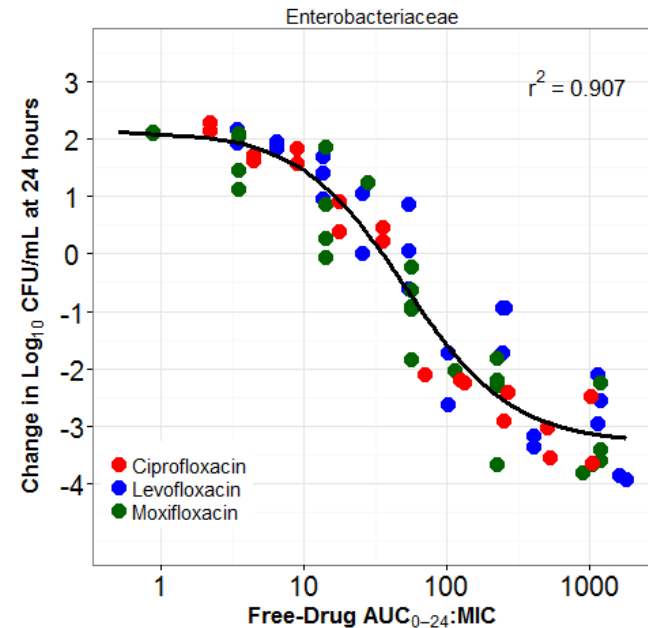
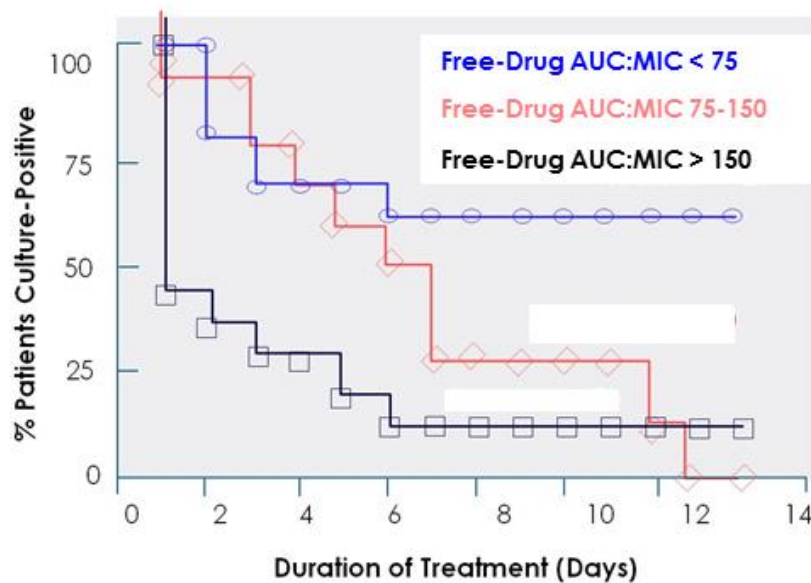
We Can Also Look Across NDAs



- Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment (1996-2011)¹
 - PK-PD target: 1-2 \log_{10} CFU decrease from net stasis
- Indications included community- and hospital-acquired pneumonia
 - 17 antibiotics in total with 14 regulatory approvals and 6 failures

PK-PD TARGET THRESHOLD SELECTION

Time to Response



AUC:MIC ratios of 75-150 and >150 had the same response rate by Day 11 but larger exposures shortened the time to event

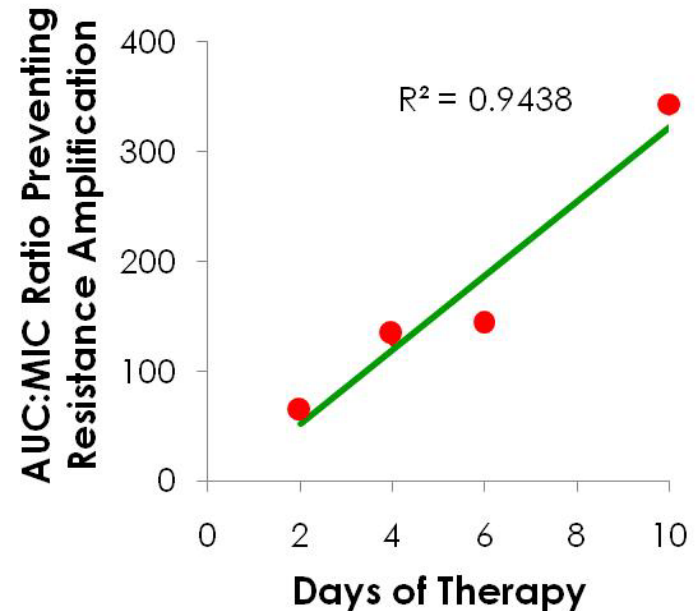
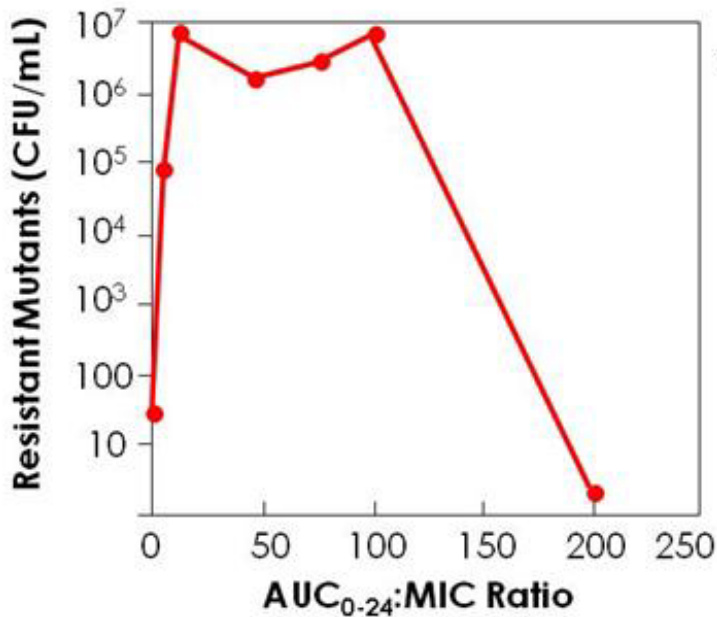
The AUC:MIC ratio necessary for a 2- \log_{10} CFU reduction in animals is similar to that resulting in the most rapid response

Forrest A, Nix SE, Ballow CH, Schentag, JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073-1081.

USCAST Fluoroquinolone Breakpoint Report (2015), <http://www.uscast.org/news/quinolone-in-vitro-susceptibility-test-interpretive-criteria-evaluations-report>.

PK-PD TARGET THRESHOLD SELECTION

Preventing Resistance Amplification

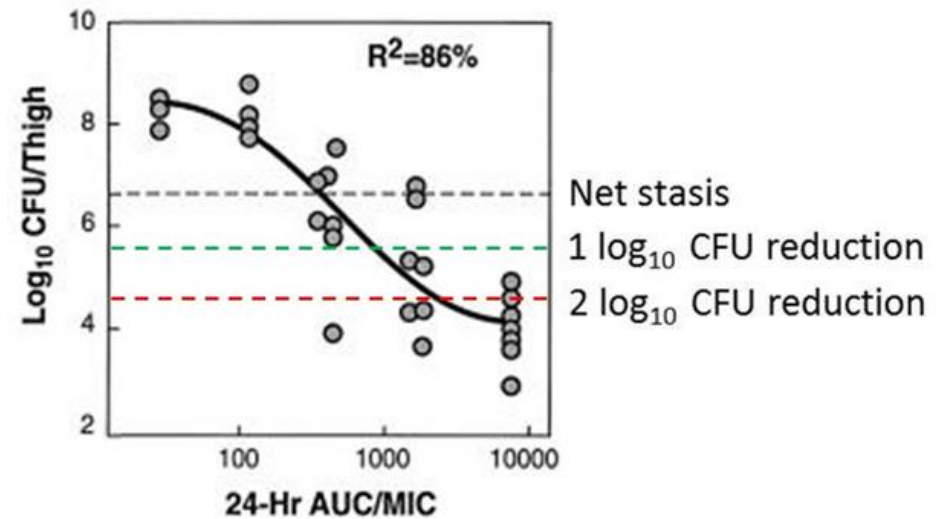
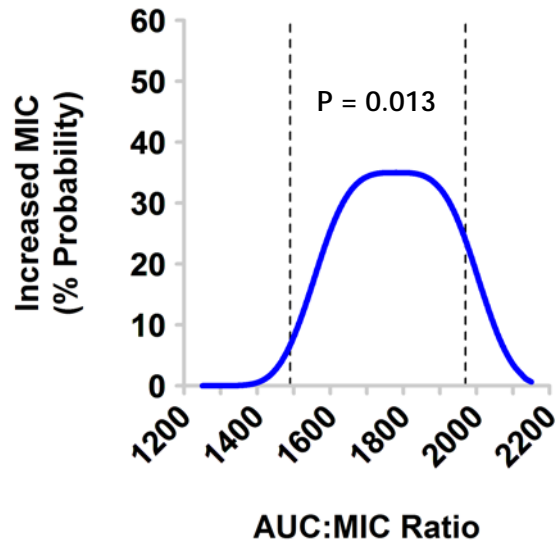


The relationship between drug exposure and resistance amplification takes the form of an inverted-U

The longer one treats, the greater the drug exposure needs to be to suppress resistance amplification

PK-PD TARGET THRESHOLD SELECTION

Preventing Resistance Amplification



The AUC:MIC ratio necessary
2 log₁₀ CFU reduction in animals is
similar to that suppressing
resistance amplification in patients

AUC:MIC ratio	% probability of increased MIC at 30 days ^{a,b}	Number of increased MIC events	Total
<1480	0	0	21
≥1480 - <1970	27.8	5	18
≥1970	8.1	6	62
Total		11	101

Log rank p = 0.013

a. Kaplan-Meier estimated.

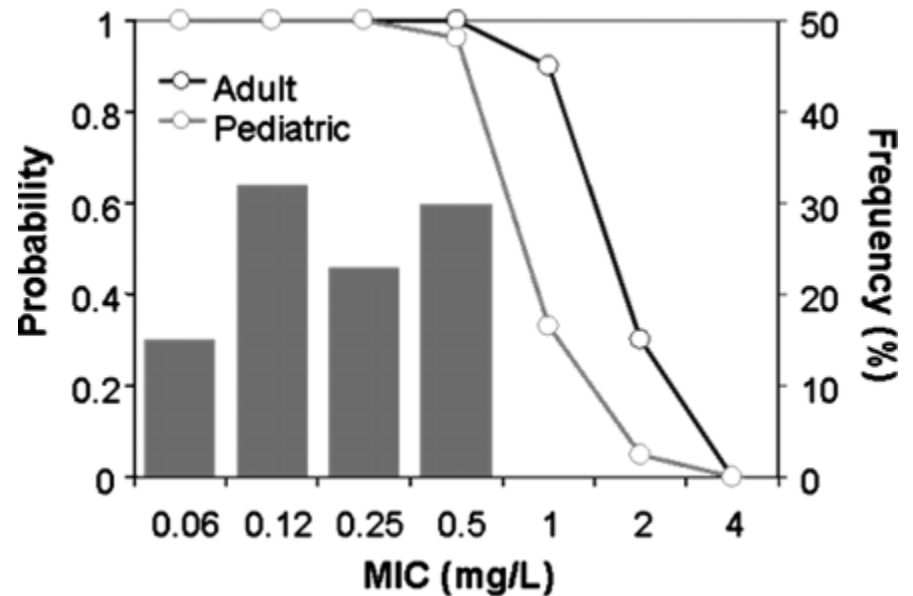
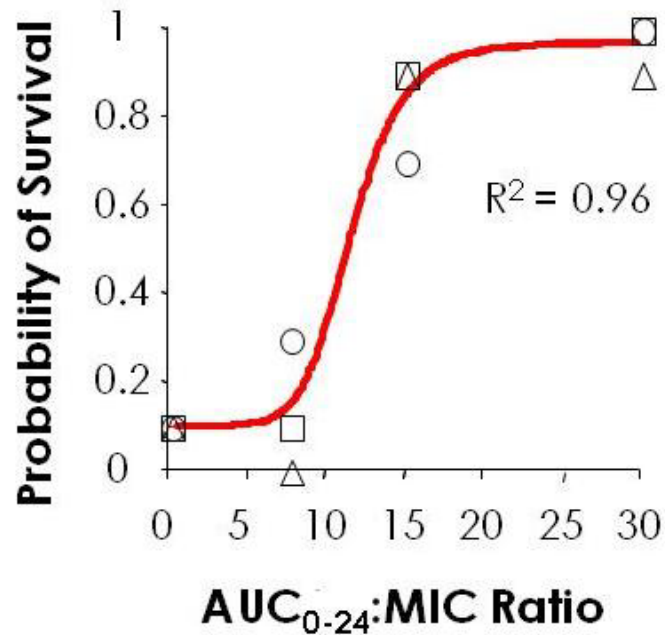
b. Increased MIC was defined as a ≥4 fold increase in MIC relative to baseline. The observation period ended at Day 42.

Bhavnani SM. Daptomycin exposure and the probability of creatine phosphokinase elevations. [Abstract 1862]. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. Sept. 9-12, 2012.

Safdar N, Andes D, Craig WA. *In vivo* pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 2004;48:63-68.

PK-PD TARGET THRESHOLD SELECTION

When Benefit Outweighs Any Risk



SUSCEPTIBILITY BREAKPOINTS

Our View of the Future

- A world without susceptibility breakpoints!
 - A MIC breakpoint makes about as much sense as an AUC breakpoint
- It's really about the probability of attaining effective exposures in a given patient and infection site
 - A single susceptibility breakpoint does not cover the majority of clinical circumstances

FINAL THOUGHTS

A Prescriptive Opinion

- We are in an era of unmet medical need so great that we have reached a point of making trade offs
- What is the explicit trade off?
 - The certainty associated with 2 large clinical trials for...
 - The certainty of small clinical datasets underpinned by robust PK-PD data
- I, for one, think this approach is sensible
- However, I believe EMA and US FDA should be prescriptive (albeit, minimally)
 - Companies risk time and money; patients risk their lives

A collection of petri dishes containing bacterial cultures on agar. Some dishes show a uniform red color, while others show white, fuzzy colonies of varying sizes and shapes. The dishes are arranged in a cluster, with some in the foreground and others in the background.

THANK YOU FOR YOUR ATTENTION



INSTITUTE *for* CLINICAL
PHARMACODYNAMICS