ANTIBIOTIC DEVELOPMENT FOR RESISTANT BACTERIA

A Pharmacometric-Based Solution

Learn. Confirm. Succeed.®

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WARNING! WARNING!!

Potential Conflict of Interest

- My primary scientific interest is PK-PD and furthering this science as a platform for the proper use and development of medicines
- I am President of the Institute for Clinical Pharmacodynamics, which receives monies supporting PK-PD research from government and industry sources

THE CHALLENGE
Antibiotics and Unmet Medical Need

- The challenge is to find a regulatory pathway that balances unmet medical need with data quality and quantity
- PK-PD has long served as a tool for pre-clinical drug evaluation and dose regimen selection for early-stage clinical development[1]
  - However, PK-PD is currently underutilized and could be further leveraged to:
    - Identify the magnitude of antibiotic treatment effect, which is a critical element of non-inferiority study design[2]
    - Provide a paradigm for evaluating limited-sized clinical data in the context of other information to support regulatory decisions

1: Craig WA. Pharmacokinetic-pharmacodynamic parameters: rationale for antibacterial dosing in mice and men. *Clin Infect Dis* 1998; 26:1–12.

2: Ambrose PG, Hammel J, Bhavnani SM, Rubino CM, Ellis-Grosse EJ, Drusano GL. Frequentist and Bayesian pharmacometric-based approaches to facilitate critically needed new antibiotic development: overcoming lies, damn lies, and statistics. *Antimicrob Agents Chemother*. 2012; 56:1466-1470.

ONE PATH FOWARD

Single Randomized Clinical Trial Plus Supporting Clinical and Non-Clinical Data

- Reasonable in the circumstance where:
  - Appropriate preclinical models exist;
  - It is relatively easy to enroll patients with infection associated with wild-type or antibiotic-susceptible pathogens;
  - It is difficult to enroll patients with infection associated with antibiotic–resistant pathogens; and
  - Folks are willing and able to collect blood specimens from the majority of patients for drug assay
- Represents an intermediate regulatory path between one that requires two randomized controlled clinical trials and the animal rule, which requires none

HOW MIGHT THIS WORK?

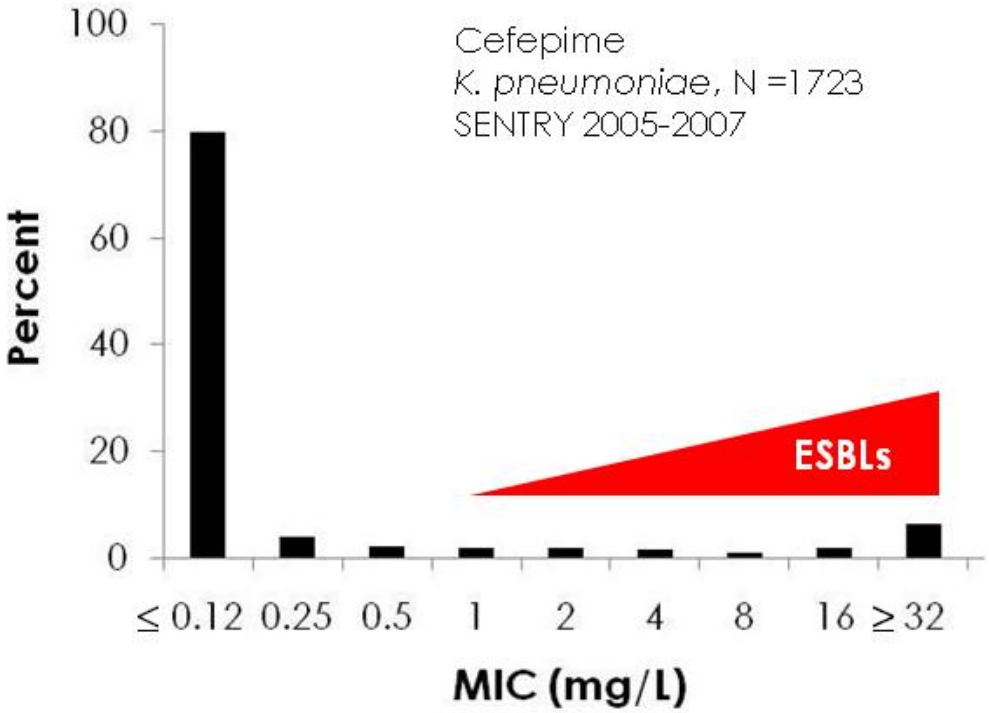
One Randomized Clinical Trial Plus Supporting Clinical and Non-Clinical Data

- Pre-clinical infection model(s)
  - Demonstrate the impact of resistance determinant presence on the magnitude of the PK-PD index required for efficacy
- Single randomized comparative trial
  - Will enroll patients infected with wild-type pathogens
  - Sparse PK collection from all patients will allow for the construct of efficacy exposure-response relationship
  - Will contribute significantly to a drug's safety database
- Smaller non-comparative trial
  - Will enroll mostly patients infected with resistant pathogens
  - Sparse PK collection from all patients allows for the integration of results across the program

A REAL-LIFE EXAMPLE
β-Lactam for ESBL-Producing Bacteria

- Let's pretend we are developing an intravenous cephalosporin for the treatment of wild-type and ESBL-producing Enterobacteriaceae
- In this example, we are going to synthesize data from 3 sources
  - Pre-clinical infection model
  - Phase 3 randomized controlled clinical trial
  - A non-comparative study

THE QUESTION
Does the Mechanism of Resistance Matter?

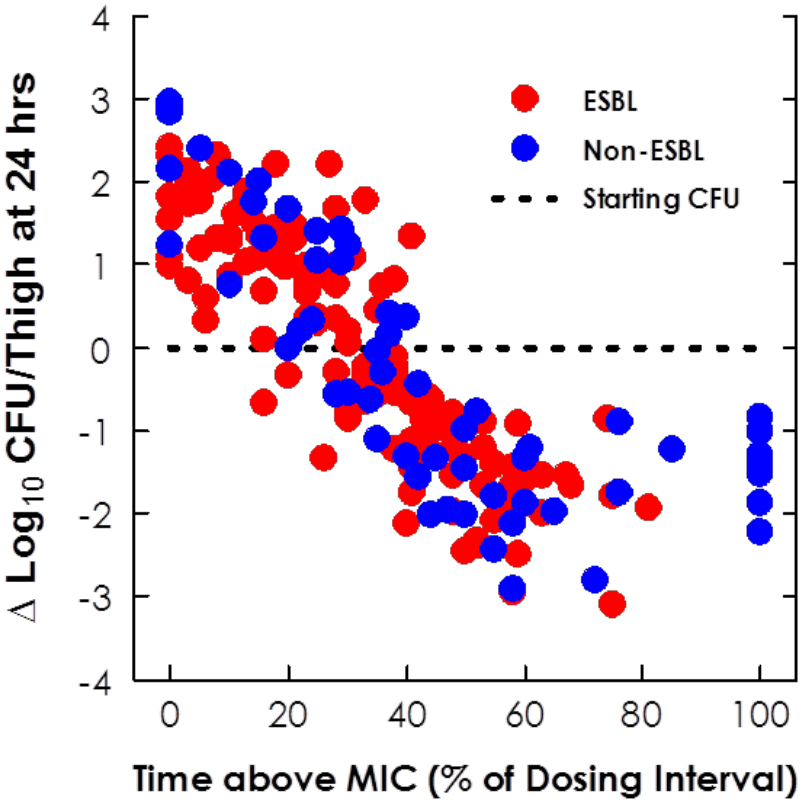


Key Question: What drives response? Is it the reason an MIC is elevated or drug exposure?

Minimum inhibitory concentration distribution for cefepime against 1723 *K. pneumoniae* N. American clinical isolates collected during 2005-2007 by the SENTRY Surveillance Program. Data provided as a courtesy by Ronald N. Jones.

INFORMATION SOURCE ONE

Exposure-Response in Mice



The Answer: 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.

PK-PD INFECTION MODELS
What Do We Do with the Data?

- Pharmaceutical companies use animal-derived exposure-response relationships to select dose and dosing interval for study in Phase 2 and Phase 3 clinical trials
- Regulatory agencies (FDA, EMA) and consensus bodies (CLSI) use such animal-derived exposure-response relationships as decision support for *in vitro* susceptibility interpretive criteria

Key Question: Do pre-clinical PK-PD infection models forecast regulatory approval?

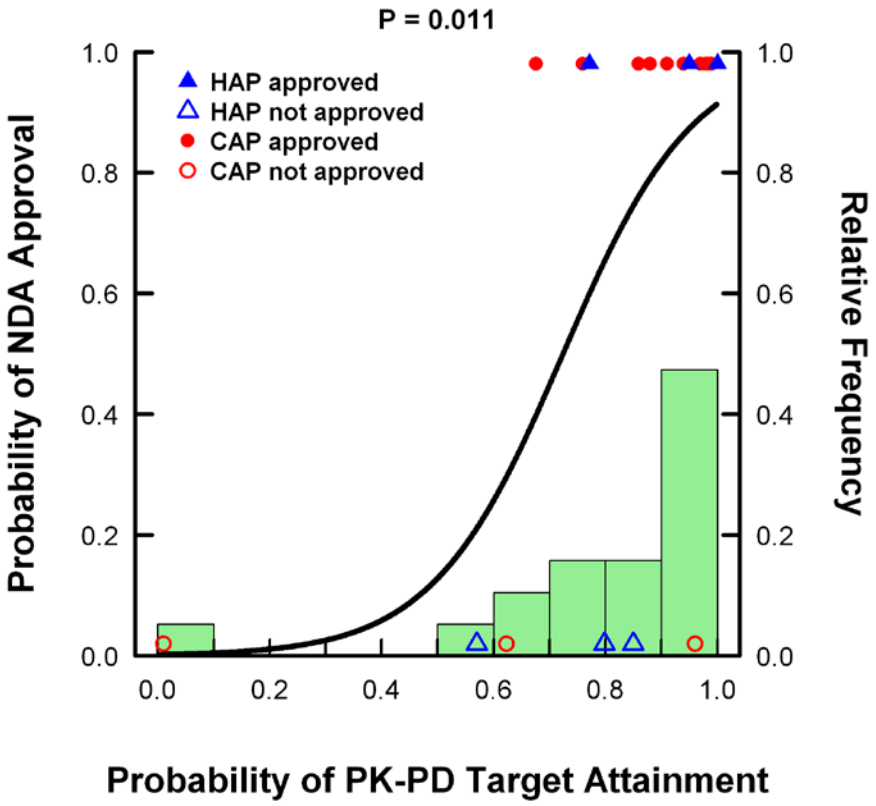
PK-PD INFECTION MODELS
Do They Forecast Regulatory Approval?

- We looked at the relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment
  - The study period was December 1996 through 2011
- Indications included community- and hospital-acquired pneumonia
  - For CAP, *S. pneumoniae* was the index pathogen
  - For HAP, the index pathogen was antibiotic spectrum dependent
  - We identified 14 antibiotics that gained regulatory approval and 6 that failed to gain approval

- Cefditoren
- Ceftaroline
- Ceftobiprole
- Daptomycin
- Doripenem
- Ertapenem
- Faropenem
- Garenoxacin
- Gatifloxacin
- Gemifloxacin
- Levofloxacin
- Linezolid
- Moxifloxacin
- Televancin
- Teilithromycin
- Tigecycline
- Trovafloxacin

PK-PD INFECTION MODELS

Do They Forecast Regulatory Approval?



Quartile	Target Attainment Median (Range)	% NDA Approval (n/N)
1	0.62 (0.01-0.76)	40% (2/5)
2	0.85 (0.77-0.88)	60% (3/5)
3	0.94 (0.88-0.96)	80% (4/5)
4	0.985 (0.97-0.99)	100 % (5/5)

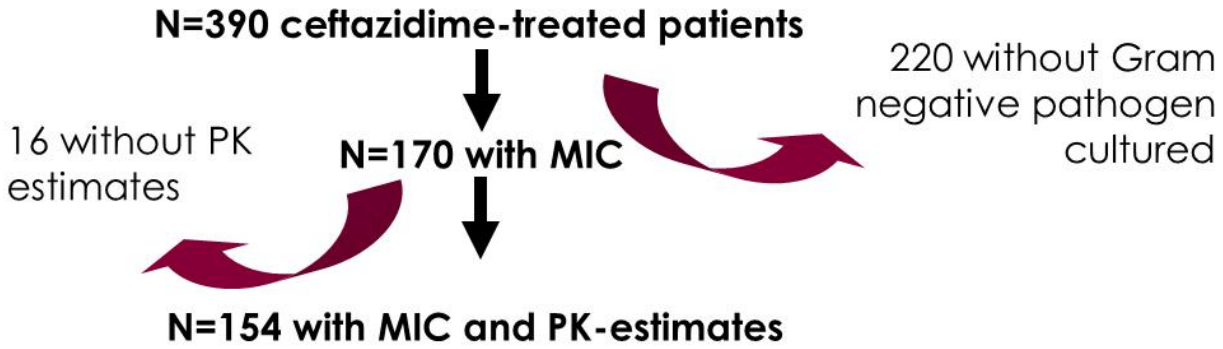
The Answer: Yes! The probability of regulatory approval increases with the probability of PK-PD target attainment

Note: PK-PD target was net-bacterial stasis in neutropenic mice for CAP agents and 1-2 $\log_{10}$ unit reduction in bacterial burden for HAP agents

INFORMATION SOURCE TWO

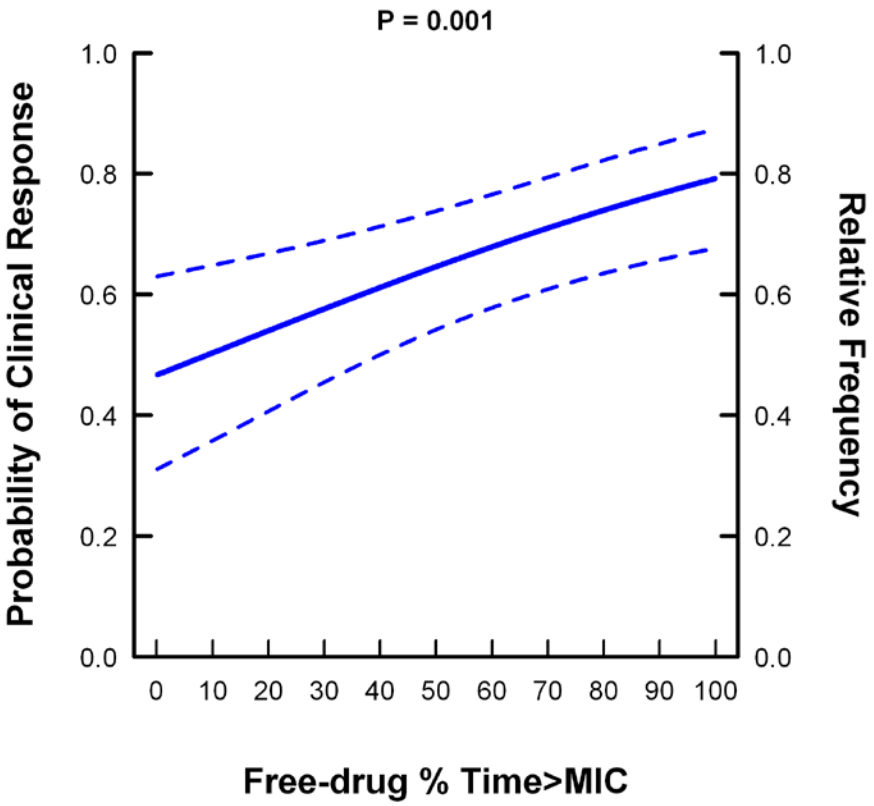
Single Randomized Clinical Trial

- Data from a randomized, double-blind phase 3 clinical trial (NCT-00210964)
  - Study compared ceftazidime versus ceftobiprole in patients with hospital-acquired pneumonia
  - Ceftazidime regimen: 2 grams infused over 2 hrs. every 8 hrs.
  - Blood specimens for drug assay were collected from nearly all (circa 90%) patients



Muller A, Punt, N, Mouton JW. % Free-drug T>MIC of ceftazidime predicts probability of microbiological outcome in the treatment of nosocomial pneumonia caused by Gram-negatives. ECCMID 2011.

CEFTAZIDIME
Hospital-Acquired Pneumonia



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INFORMATION SOURCE THREE

Small Non-Comparative Study

- Data from a retrospective analysis evaluating the relationship between cephalosporin MIC and clinical outcome[1]
  - 35 patients with bacteremia associated with ESBL-producing Enterobacteriaceae
  - Patients treated with mono-therapy with either cefepime, ceftrixone, cefotaxime or ceftazidime
- Now, I realize this is not an ideal dataset, but I think it will be instructive

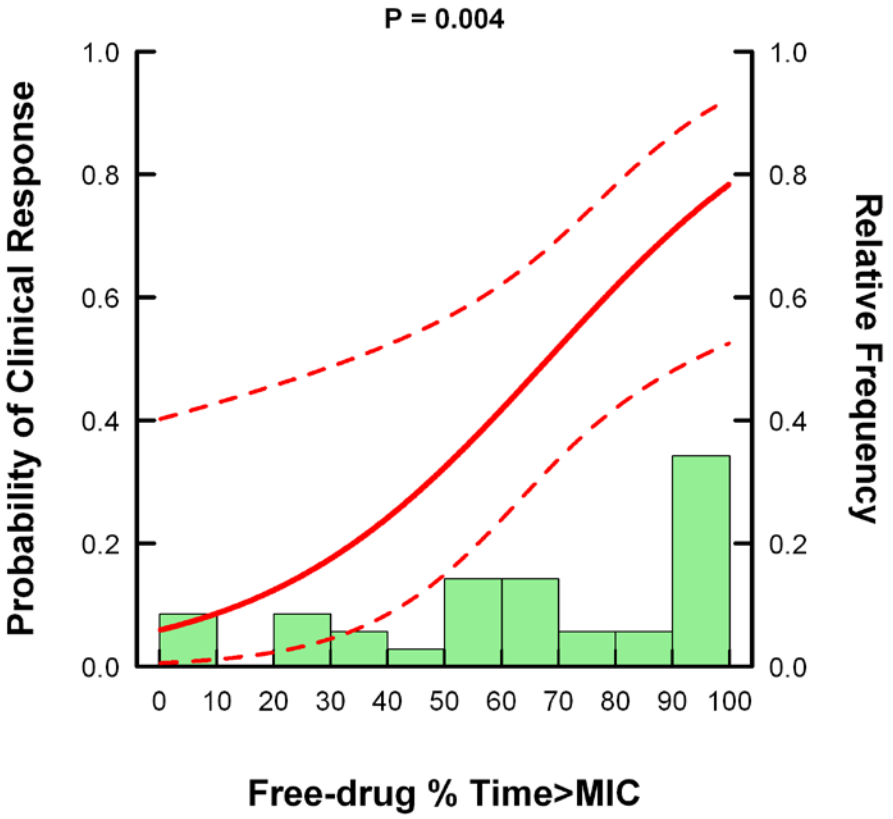
Craig WA Bhavnani SM, Ambrose PG, Dudley MN, Jones RN. Evaluation of clinical outcome among patients with ESBL-producing Enterobacteriaceae treated with cephalosporin mono-therapy. 45th ICAAC. 2005; Abstract K-1291.

CEPHALOSPORINS

Bacteremia Associated with ESBL-Elaborating Enterobacteriaceae

Key Question: In patients, can one overcome the presence of resistance determinants with adequate drug exposure?

The Answer: Yes! Just like in animal infection models, drug exposure indexed to MIC predicts outcome



SEWING THE THREE TOGETHER

Un Pour Tous, Tous Pour Un[1]

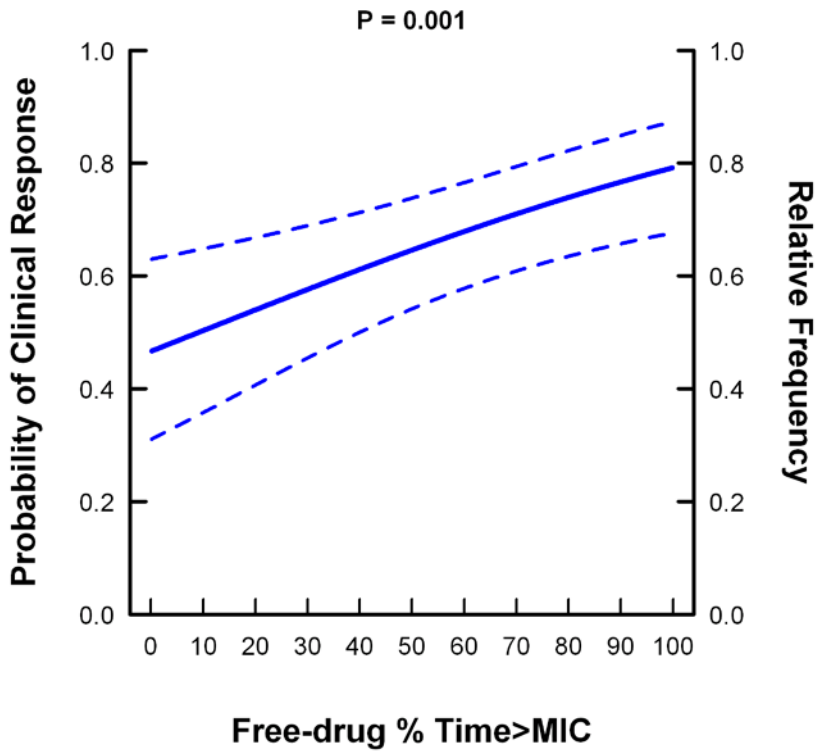
- What did the 3 distinct data sets teach us?
  - The pre-clinical infection model demonstrated:
    - Response to cephalosporin therapy was related to %T>MIC
    - The MIC is key—The relationship between % T>MIC and response was not different for wild-type, ESBL-elaborating isolates, or isolates having a high MIC for other reasons
  - The single randomized clinical trial demonstrated:
    - Response to cephalosporin therapy was related to %T>MIC in patients infected with *predominantly wild-type* isolates
  - The small non-comparative study demonstrated:
    - Response to cephalosporin therapy was related to %T>MIC in patients infected with ESBL-elaborating isolates
- A pharmacologically-based data package balances unmet medical need with data quality and quantity

1: All for one, one for all. *The Three Musketeers, Alexandre Dumas, 1844.*

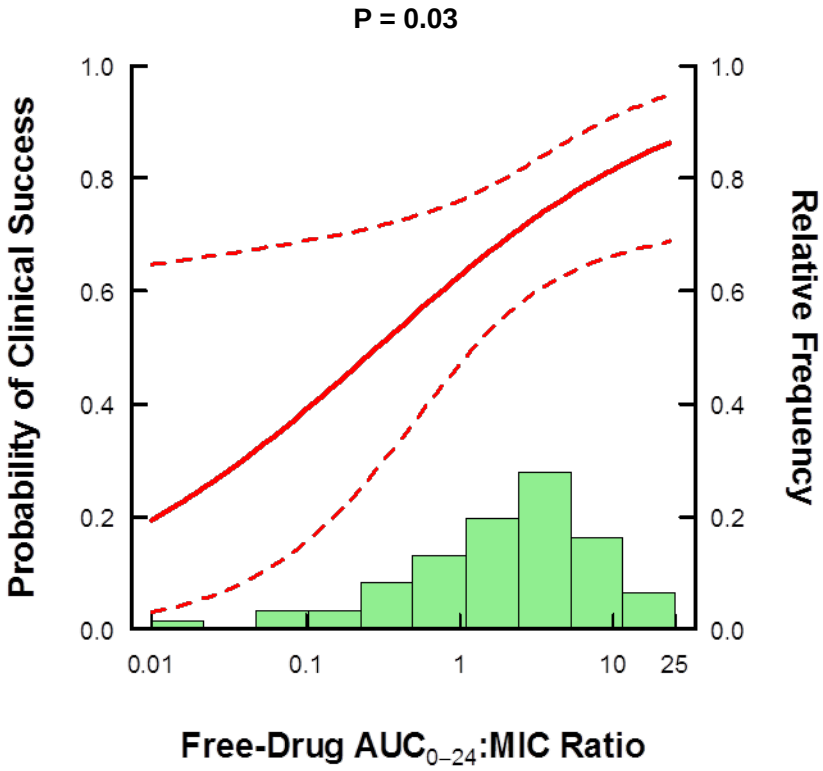
ONE MORE THING

Concordance Between HAP Analyses

CEFTAZIDIME



TIGECYCLINE



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THANK YOU FOR YOUR ATTENTION

Questions, Comments or Wise Remarks?

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