

**Estimation of *In Vitro*
Susceptibility Breakpoints for
Tigecycline Against
Enterobacteriaceae**

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Introduction

- To define MIC susceptibility breakpoints for Enterobacteriaceae, several key elements were considered
 - Variability in the PK of the drug across a patient population
 - MIC of the target pathogen
 - Distribution of the MIC values of clinical isolates of *E. coli*

Objective

- Estimate the probability of attaining PK/PD target measures (AUC/MIC ratio) associated with the efficacy of tigecycline against *E. coli* and estimating MIC susceptibility breakpoints

Methods

- Individual Bayesian PK parameter estimates from a population PK model were utilized to explore the variability in tigecycline exposure.
- A defined range of PK/PD targets (AUC/MIC) identified in the previously presented exposure-response analysis was used.
- Integration of these results and distribution of *E. coli* from clinical trials were used to estimate MIC susceptibility breakpoints.

Methods

Study Design

- One Phase 2 and two Phase 3 trials of patients with complicated intra-abdominal infections (cIAI)
- 123 patients (216 pathogens) with cIAI
- All patients received tigecycline 100-mg loading dose and 50 mg q12h

Methods

Outcome Evaluation

- Patients with *E. coli* or other Enterobacteriaceae ± anaerobes from intra-abdominal cultures
- Outcome evaluation considered in this analysis was microbiological response
 - Eradication/presumed eradication were considered “successful”
 - Persistence/presumed persistence were considered “failures”

Methods

Pharmacokinetics

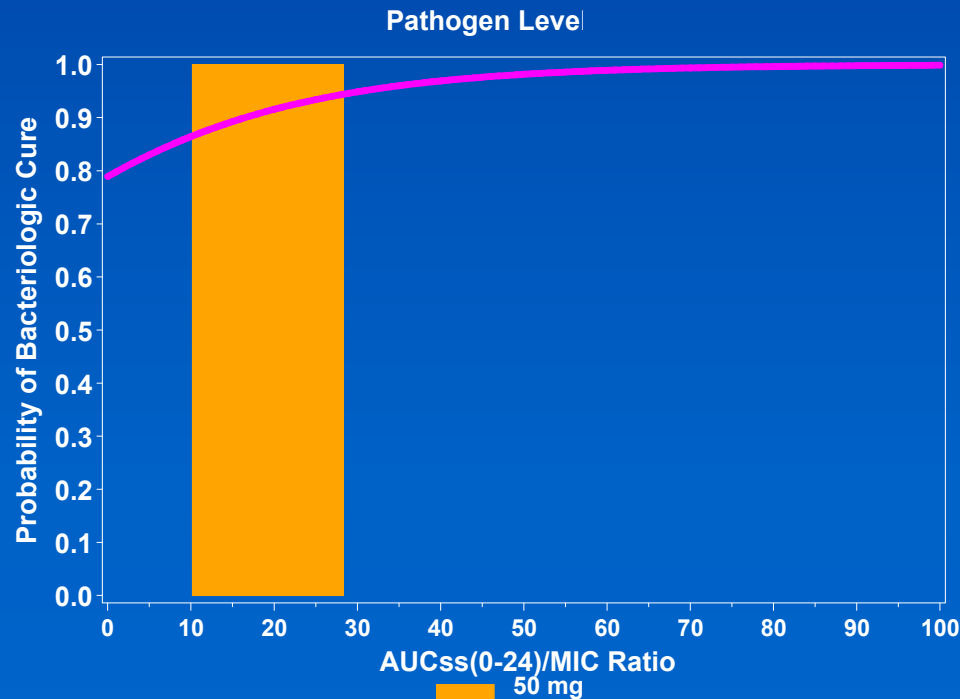
- Two-compartment model with zero-order input and first-order elimination¹
- Using the distribution of predicted 24-hour AUC values, simulated exposure values were generated for 100 trials of 1000 samples each

¹Van Wart, et al. Population PK of tigecycline in Phase 1 subjects. ICAAC 2004.

Methods

PK/PD Analyses

- CART analysis identified two statistically significant breakpoints at 6.96 and 11.07 ($p = 0.0004$ and < 0.0001 , respectively)



The line represents the model-based predicted probability of the pathogen level bacteriologic cure.
The bar represents the 25th to 75th percentiles of the ratio distribution for 50mg dose group.

Methods

Bootstrap Confidence Interval

- 1000 randomly simulated datasets with replacement (71 patients each) were generated
- Each patient's baseline pathogen composition was preserved
- CART analysis was performed to determine breakpoints in the distribution of the AUC/MIC ratio, based upon microbiological outcomes

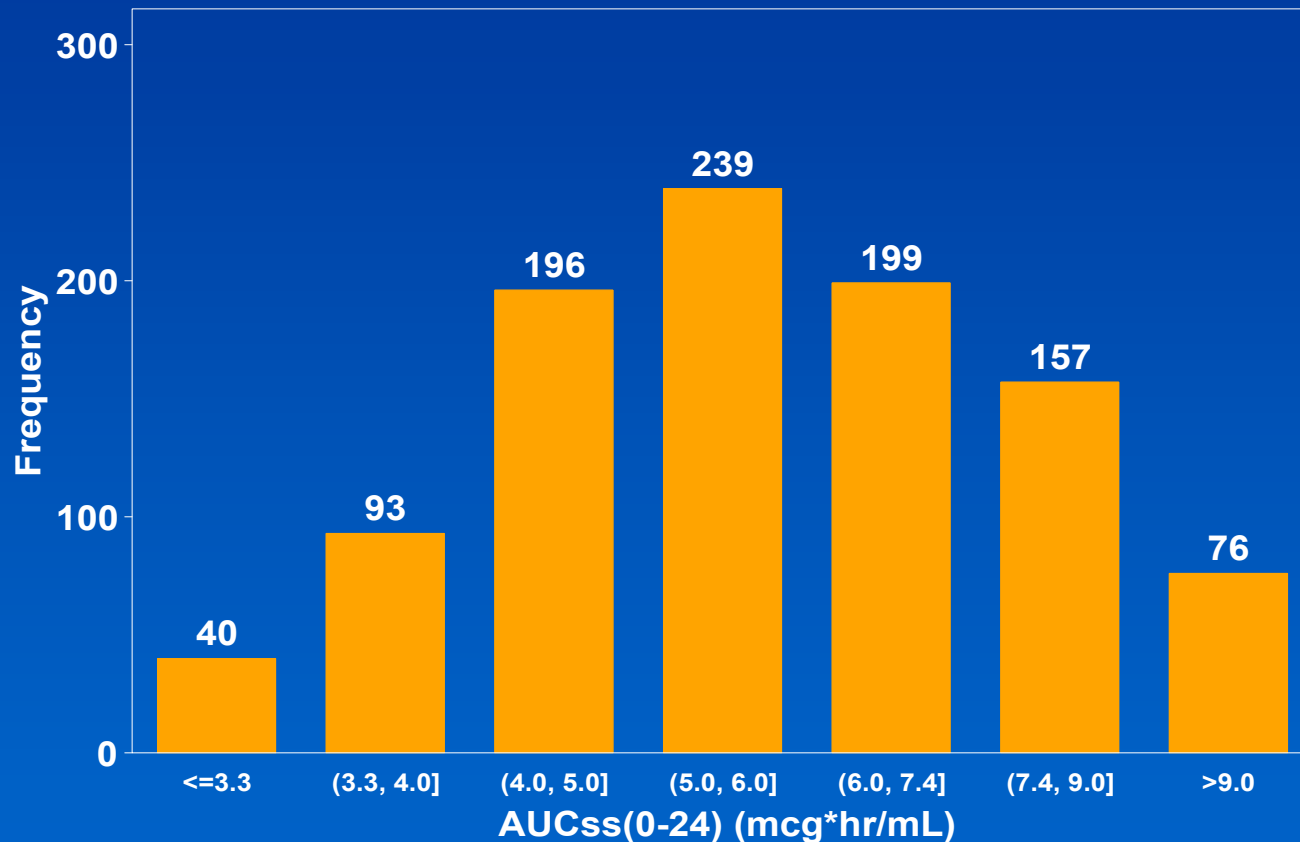
Methods

PK/PD Target Attainment

- Within each simulated dataset, the AUC values were paired with selected MIC values
- AUC/MIC ratios were evaluated with the previously identified PK/PD target values of 6.96 and 11.07 and the median bootstrap breakpoint estimate (8.4)

Results

Pharmacokinetics

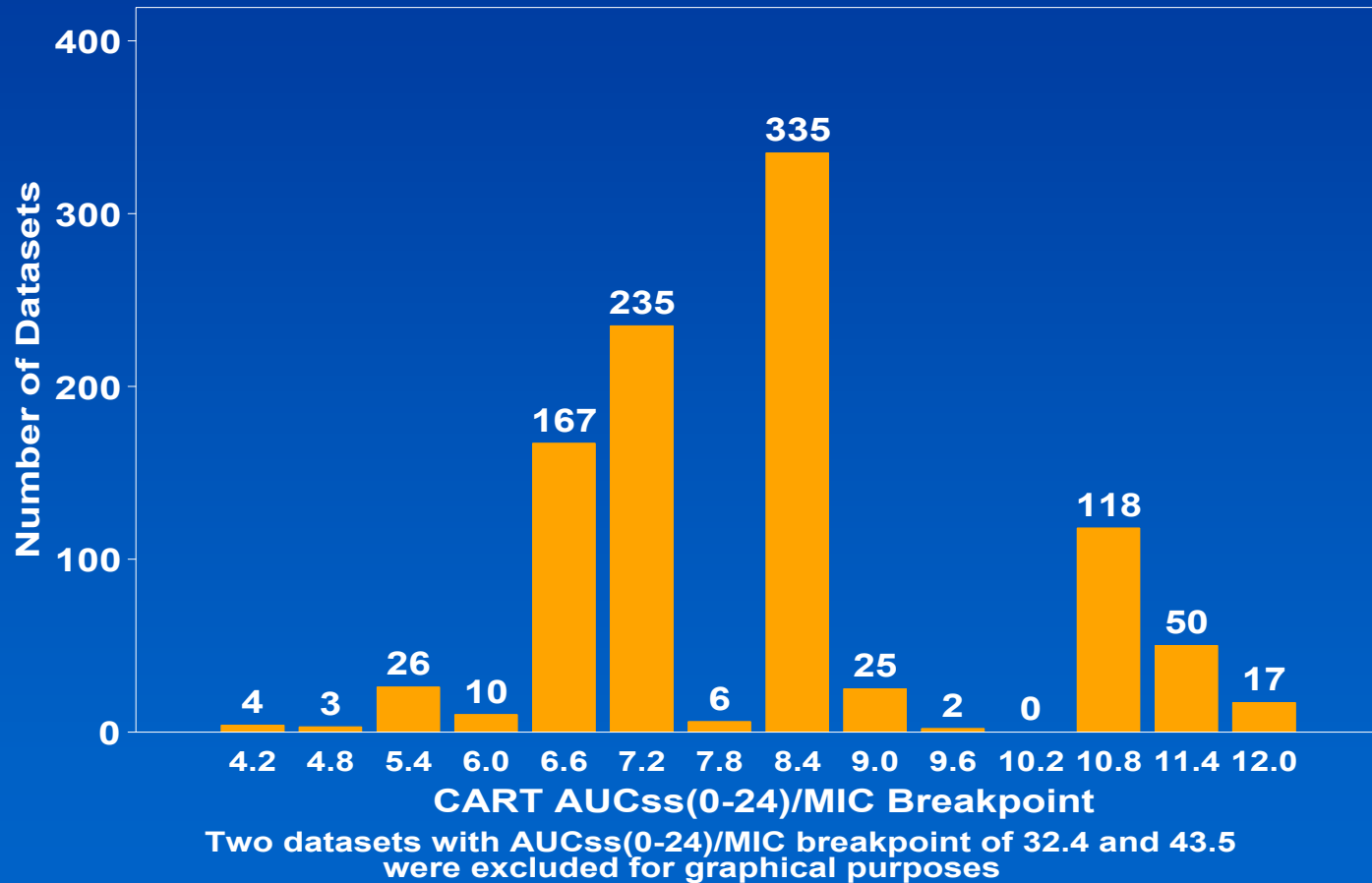


Mean (SD) observed AUC was 6.02 (2.2) $\mu\text{g}\cdot\text{hr}/\text{mL}$ (2.6 to 22.58 $\mu\text{g}\cdot\text{hr}/\text{mL}$)

Mean (SD) simulated AUC was 6.02 (1.99) $\mu\text{g}\cdot\text{hr}/\text{mL}$ (1.5 to 26 $\mu\text{g}\cdot\text{hr}/\text{mL}$)

Results

Bootstrap Confidence Interval



Median of 8.4 served as bootstrap estimate for 95% CI interval of 5.7 to 11.5

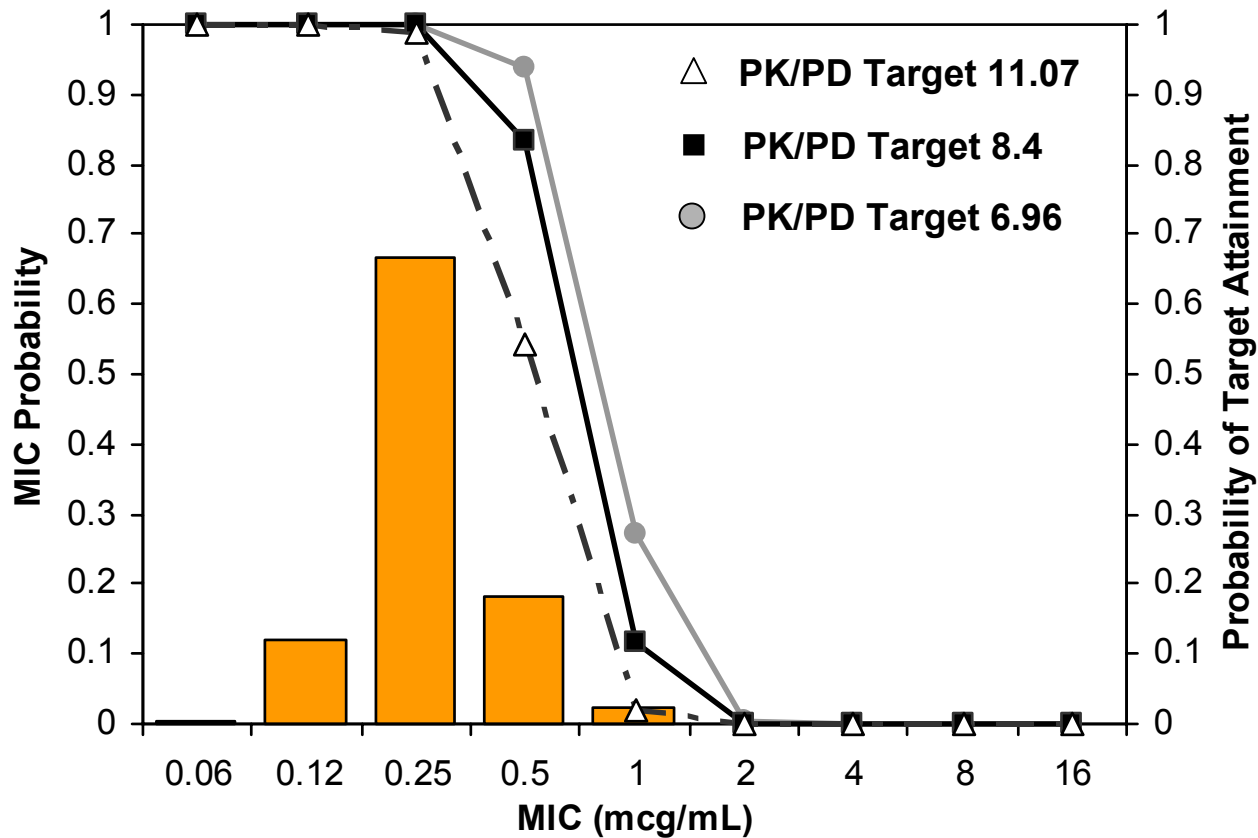
Results

PK/PD Target Attainment

MIC ($\mu\text{g/mL}$)	AUC/MIC Breakpoint		
	6.96	8.4	11.07
0.06	100	100	100
0.12	100	100	100
0.25	99.99	99.91	98.80
0.5	93.89	83.41	54.2
1	27.12	11.76	20.3
2	0.34	0.12	0.1
4	0	0	0

Results

PK/PD Target Attainment



Conclusions

- Integration of PK from population models, results from exposure-response analyses, and clinical distributions of MIC values is a valuable means of assessing susceptibility breakpoints.
- By this method, we were able to estimate susceptibility breakpoints for tigecycline against Enterobacteriaceae.
- These analyses, in conjunction with clinical outcomes, may be an important consideration in the evaluation of tigecycline breakpoints.

Discussion

- *E. coli*, which is highly susceptible to tigecycline, was the predominant organism in this analysis.
- Other members of the Enterobacteriaceae group, with higher MIC values, may not have been adequately represented.
- Given the extensive distribution of tigecycline, future exploratory PK/PD work with tissue concentrations may be informative in setting susceptibility breakpoints.