
Exposure-Response Analysis of the Efficacy of Tigecycline in Patients with Complicated Intra- Abdominal Infections (cIAI)

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Introduction

Overview of Final Pop PK Model

- Two-compartment model
- Weight, CrCL, and gender were statistically significant predictors of CL
- Empiric Bayesian PK parameters were obtained and tigecycline (TGC) exposure measures were calculated for use in the exposure-response analyses of safety and efficacy
 - 24-hr steady-state AUC

Background Objective

- To develop PK/PD exposure-response models for both microbiological and clinical outcomes of patients with cIAI utilizing individual estimates of TGC exposure (AUCSS and AUCSS/MIC ratio)
 - Using various subsets of infecting pathogen(s)
 - Evaluation of various demographic factors and covariates on the efficacy of tigecycline

Methods

Data Used

- Studies
 - One Phase 2 Study
 - Two Phase 3 Studies
- Endpoints
 - Microbiological and clinical response at test of cure Day 14
- Patients clinically and microbiologically evaluable with PK and baseline MIC values included

Methods

Baseline Pathogen Classification System

Cohort	Baseline Pathogen(s) Included
1	Monomicrobial <i>E. coli</i> infections
2	Other monomicrobial or polymicrobial gram-negative infections (<i>Klebsiella</i> spp., <i>Enterobacter</i> spp. and/or <i>Citrobacter</i> spp. plus or minus <i>E. coli</i>)
3	Infections with at least one gram-negative pathogen plus at least one anaerobic pathogen
4	Infections with at least one gram-negative pathogen plus at least one gram-positive pathogen
5	All other monomicrobial or polymicrobial infections

TGC Exposure Estimates and Covariates

- AUC_{ss}
- AUC_{ss}/MIC
- Breakpoint for AUC_{ss}/MIC
- Demographics: age
- Presence of abscess
- Presence of fecal contaminant
- Baseline APACHE II Score

Methods

Statistical Analysis

- Breakpoint determination using Classification and Regression Tree analysis (CART)
- Logistic regression analyses
 - For microbiological response, Generalized Estimating Equations (GEE) used due to multiple pathogens per patient
 - For clinical response, ordinary logistic regression
 - Backward elimination with $\alpha = 0.05$
 - Goodness-of-fit assessed using graphical displays and the Hosmer-Lemeshow test
 - Predictive ability of the model using area under the ROC curve

Results

Study Population Description

- 123 patients with 216 pathogens
- 37% Female (n = 45)
- 74% White (n = 91); 4% Black (n = 5); 20% Hispanic (n = 25); 2% Other (n = 2)
- 40% from N. America; 50% from Europe; 8% from Latin America; 2% from Other

	N=123	Mean (SD)	Range
Age (years)		45 (18)	18-85
Weight (kg)		77 (17)	45-138
Baseline APACHE II Score		6 (4)	0-25

Results

Response Rates by Cohort

Cohort (Number of Patients/ Pathogens)	Pathogen-Level Microbiologic Response	
	Eradicated N (%)	Persisted N (%)
1 (34/35)	35 (100%)	0
2 (16/24)	22 (92%)	2 (8%)
3 (21/47)	39 (83%)	8 (17%)
4 (21/50)	44 (88%)	6 (12%)
5 (31/60)	54 (90%)	6 (10%)
1 + 2 + 3 (71/106)	96 (91%)	10 (9%)

Results

Response Rates by Cohort, cont'd.

Cohort (Number of Patients)	Clinical Response	
	Cure N (%)	Failure N (%)
1 (34)	32 (94%)	2 (6%)
2 (16)	14 (88%)	2 (12%)
3 (21)	16 (76%)	5 (24%)
4 (21)	18 (86%)	3 (14%)
5 (31)	27 (87%)	4 (13%)
1 + 2 + 3 (71)	62 (87%)	9 (13%)

Results

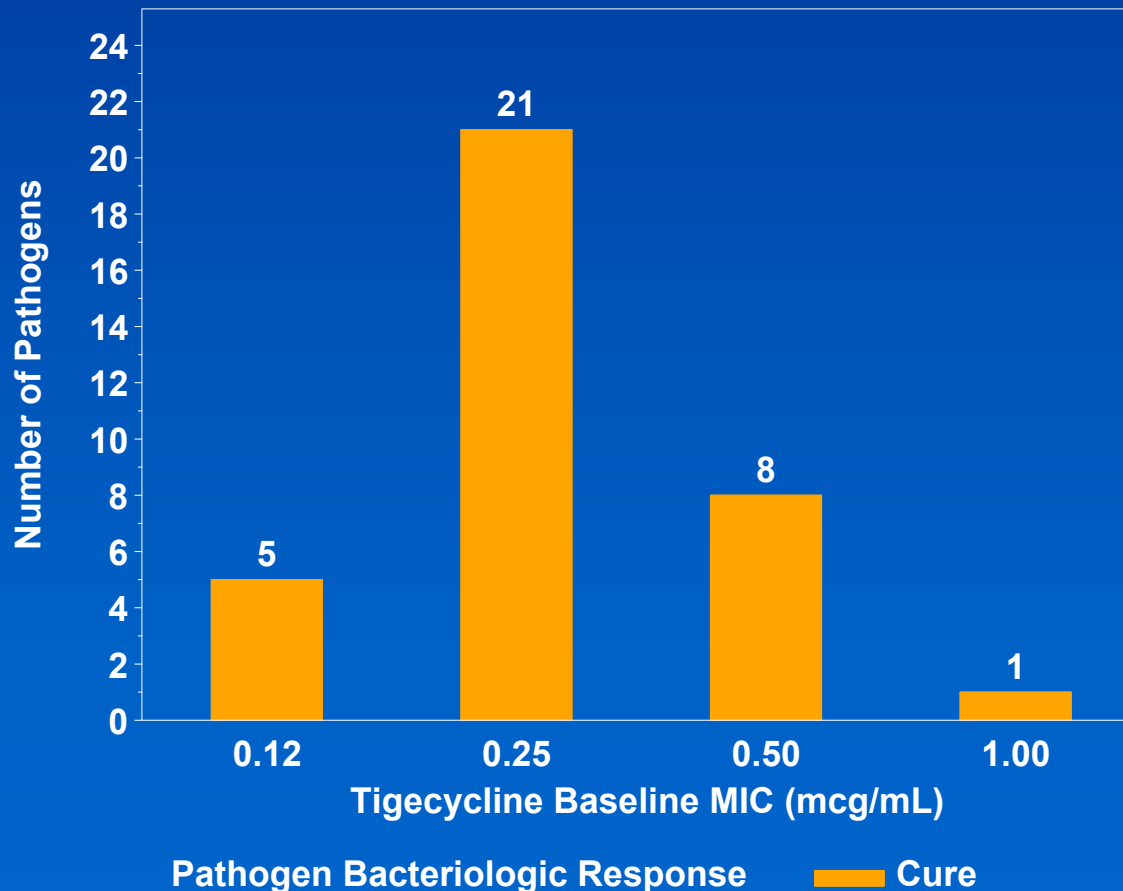
Analysis Steps

- Prospective procedure to look at sample size within cohorts
- Step 1 - Cohort 1 could not be evaluated alone due to small sample size (N = 35)
- Step 2 - Cohort 2 could not be evaluated alone due to small sample size (N = 24)
- Step 3 - Cohort 3 could not be evaluated alone due to small sample size (N=47)
- Step 4 - Analysis began with Cohorts 1, 2, and 3 Combined (N = 106)

Results

MIC Distribution – Cohort 1

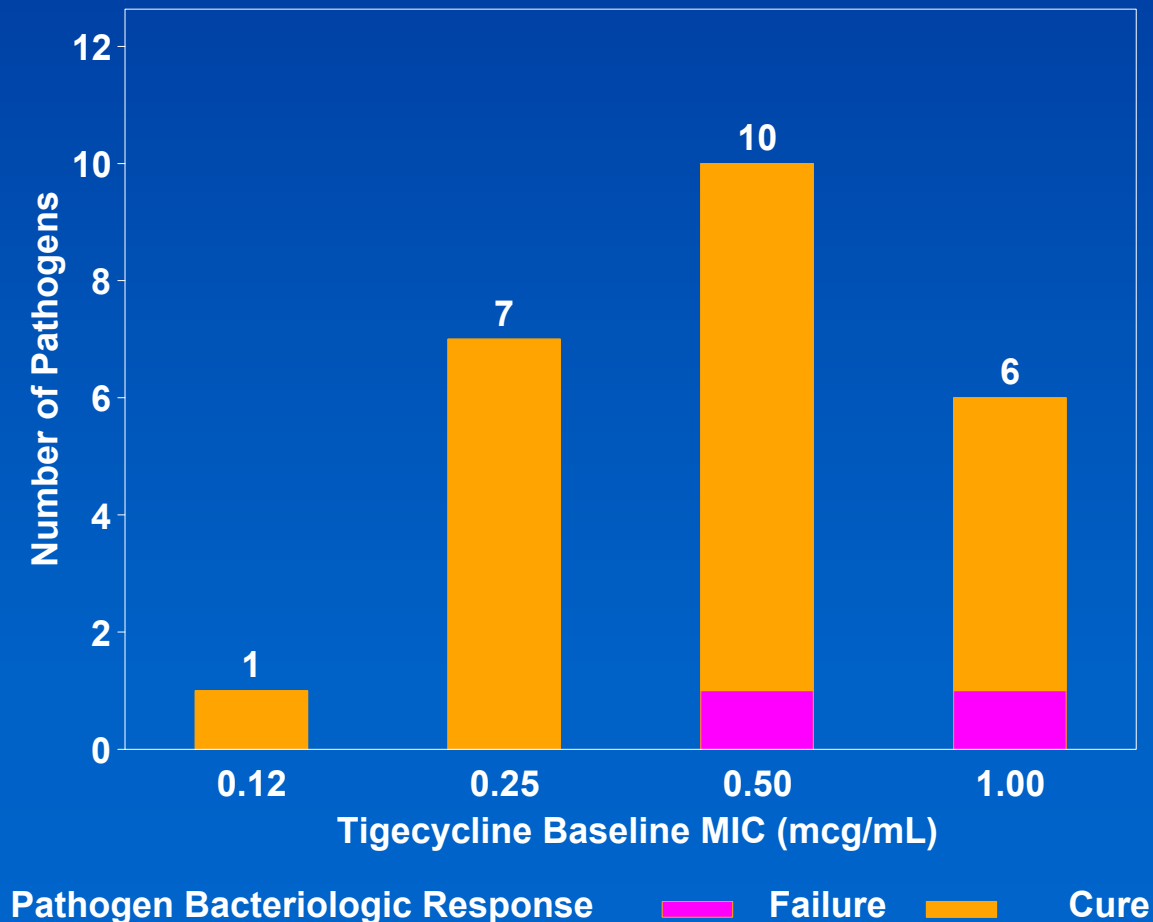
Pathogen Level MIC and Response - Cohort



Results

MIC Distribution – Cohort 2

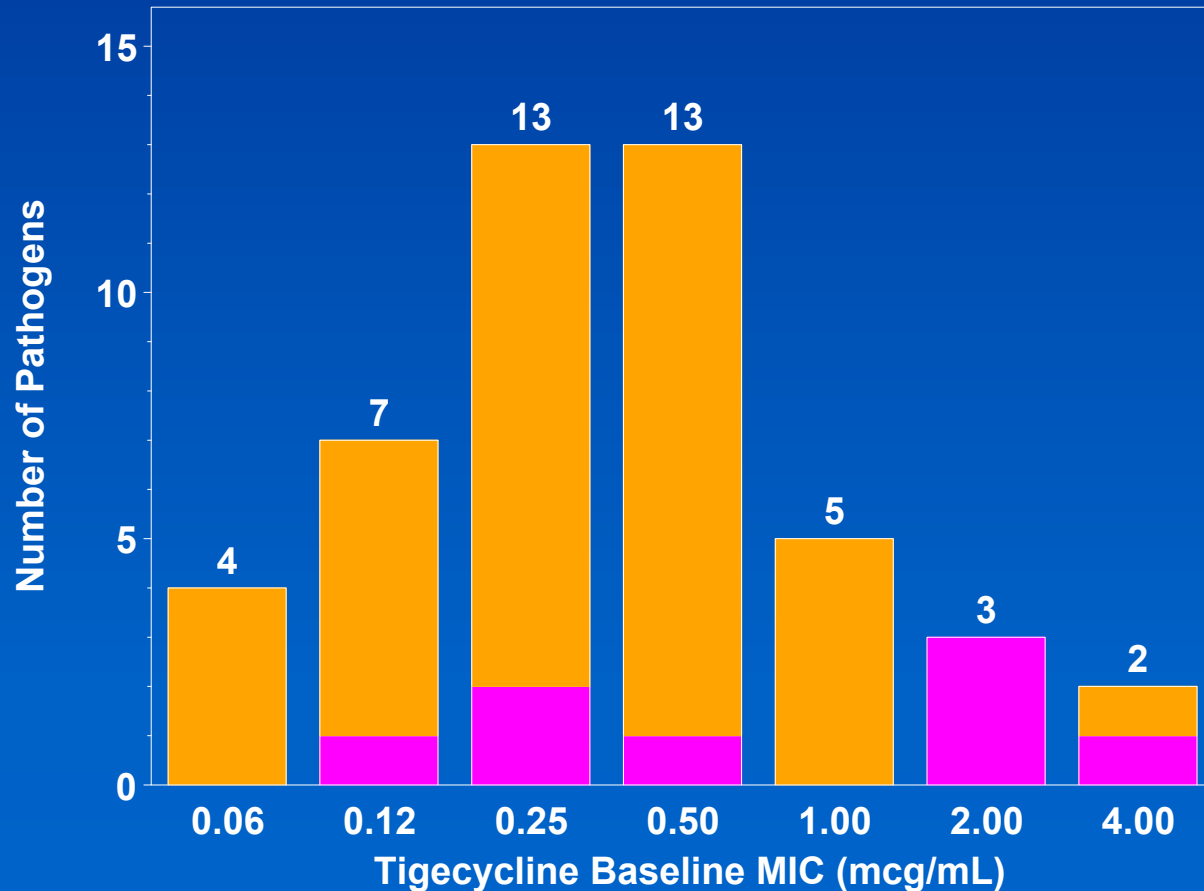
Pathogen Level MIC and Response - Cohort



Results

MIC Distribution – Cohort 3

Pathogen Level MIC and Response - Cohort 3

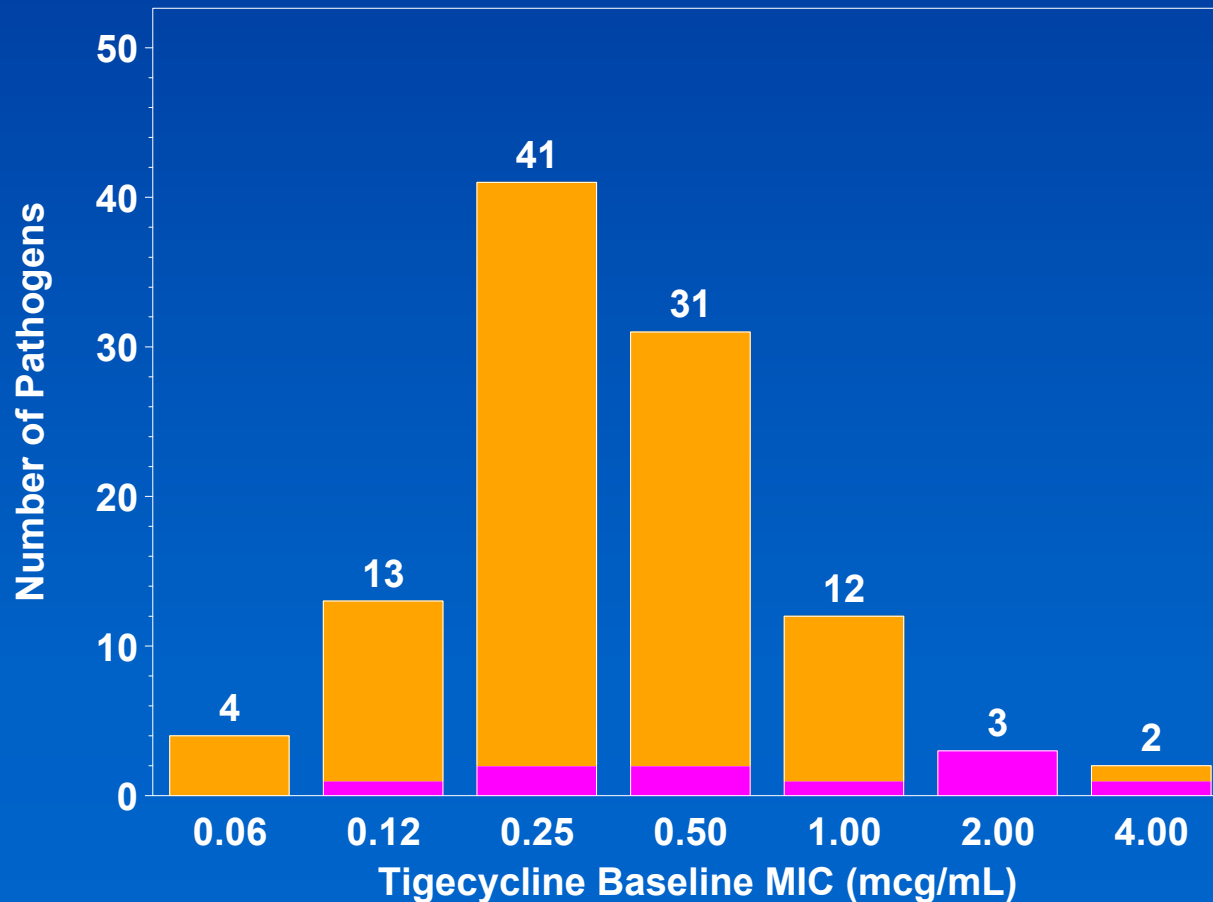


Pathogen Bacteriologic Response Failure Cure

Results

MIC Distribution – Cohorts 1, 2, and 3

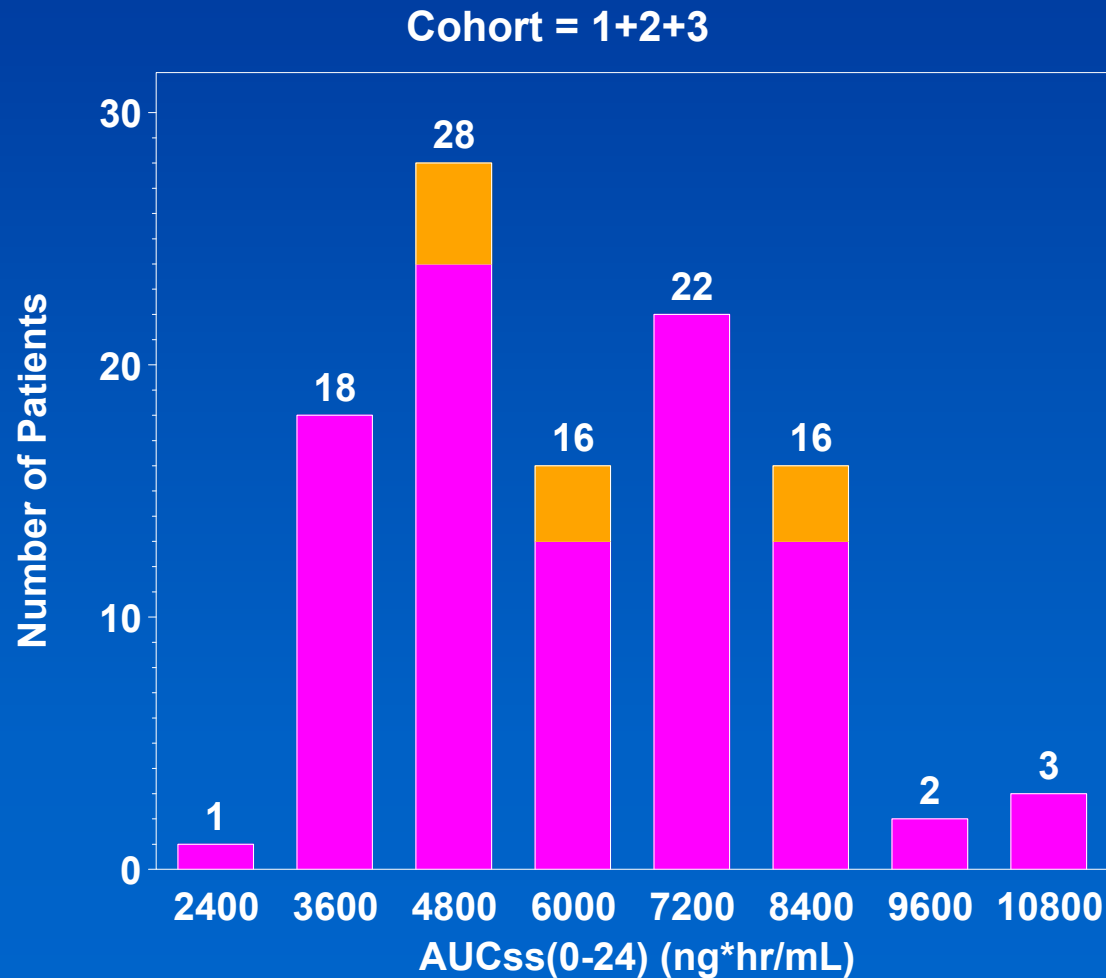
Pathogen Level MIC and Response - Cohorts 1, 2, and



Pathogen Bacteriologic Response Failure Cure

Results

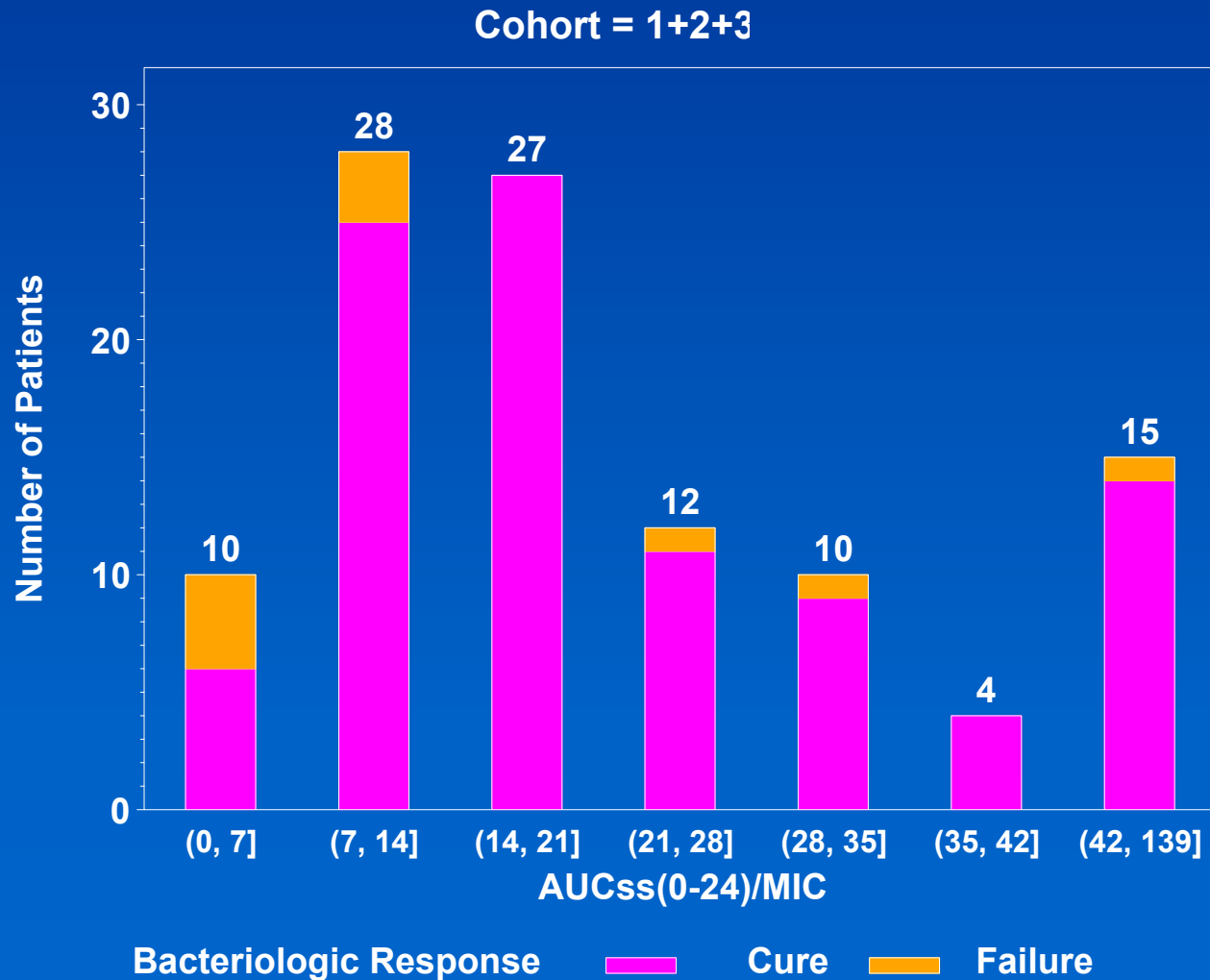
AUCss Distribution – Cohort 1, 2, and 3



Bacteriologic Response ■ Cure ■ Failure

Results

AUCss/MIC Distribution – Cohorts 1, 2, and 3



Results

CART Analysis

- CART identified several possible AUCss/MIC breakpoints including 6.96 and 11.07
- Exploratory evaluation of these and other breakpoints determined 6.96 to be optimal within these data
- 6.96 results in 94% cure rate above the breakpoint and 60% below in Cohorts 1, 2, and 3

Microbiological Response

Univariate Analysis – Cohorts 1, 2, and 3

Parameter	Estimate	SE	OR (95% CI)	p-value
Caucasian ¹	2.1401	0.9801	8.5 (1.24,58.04)	0.0290*
AUC _{ss} /MIC	0.0532	0.0279	1.055 (0.998,1.114)	0.0568
AUC _{ss} /MIC Breakpoint at 6.96	2.3026	0.6548	10.0 (2.77,36.09)	0.0004*

¹ Patients of ethnicities other than Caucasian were used as the reference category.

* Represents statistical significance at an $\alpha = 0.05$

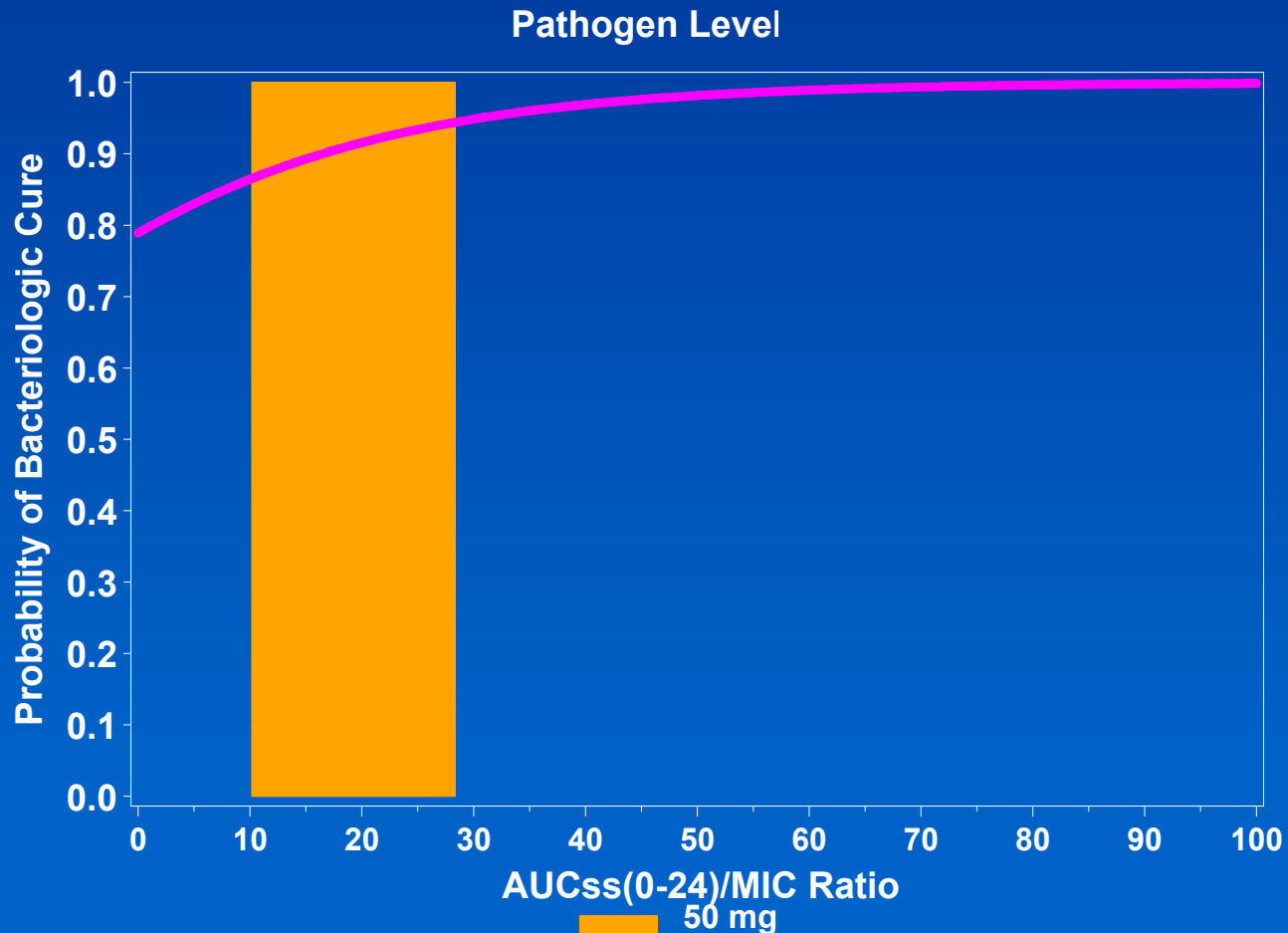
Microbiological Response

Final Model – Cohorts 1, 2, and 3

Parameter	Estimate	SE	OR (95% CI)	p-value
AUC _{ss} /MIC	0.0532	0.0279	1.055 (0.998,1.114)	0.0568
Hosmer-Lemeshow Goodness-of-Fit Test = 9.78 with 7 Degrees of Freedom (p-value = 0.2016)			Area Under the ROC Curve = 0.70	

Microbiological Response

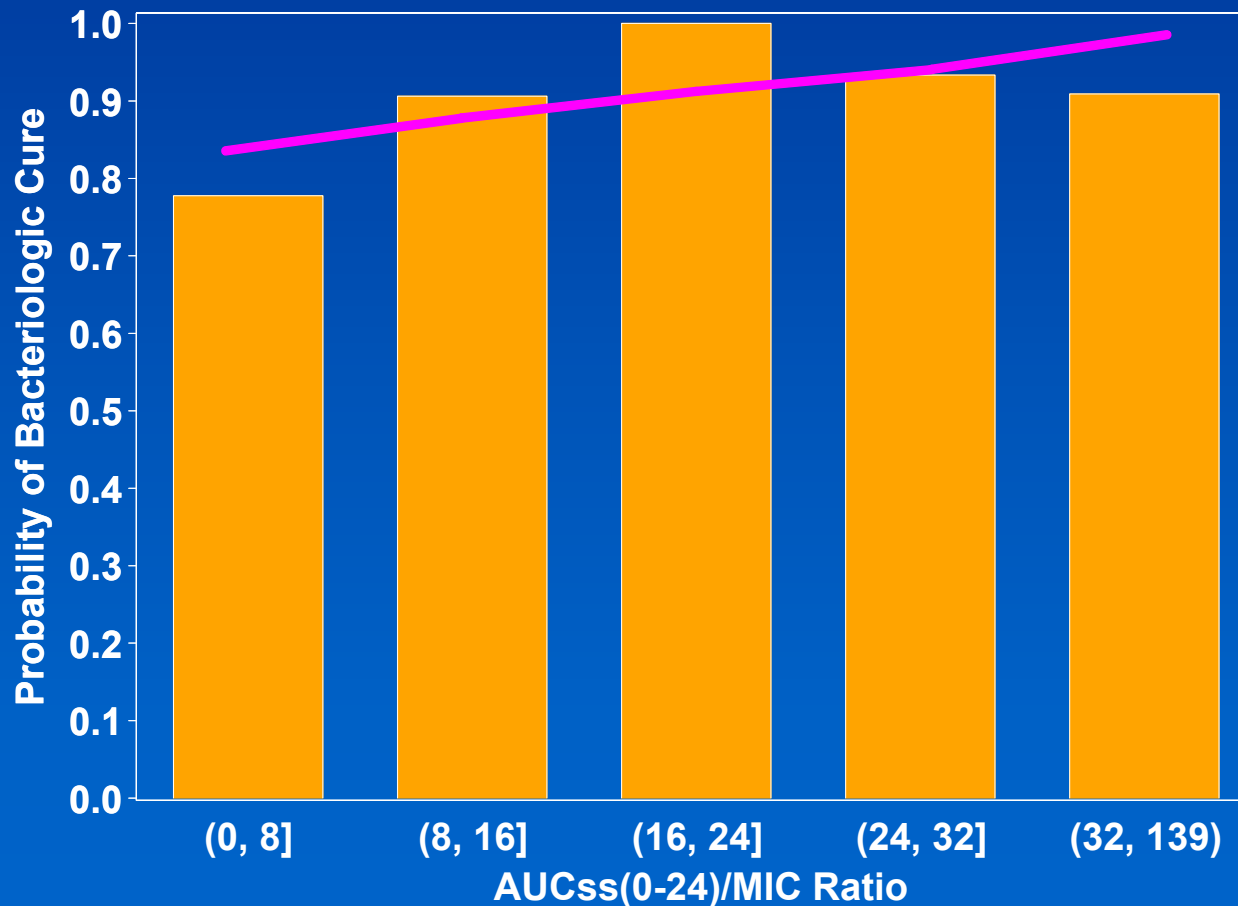
Cohorts 1, 2, and 3



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.

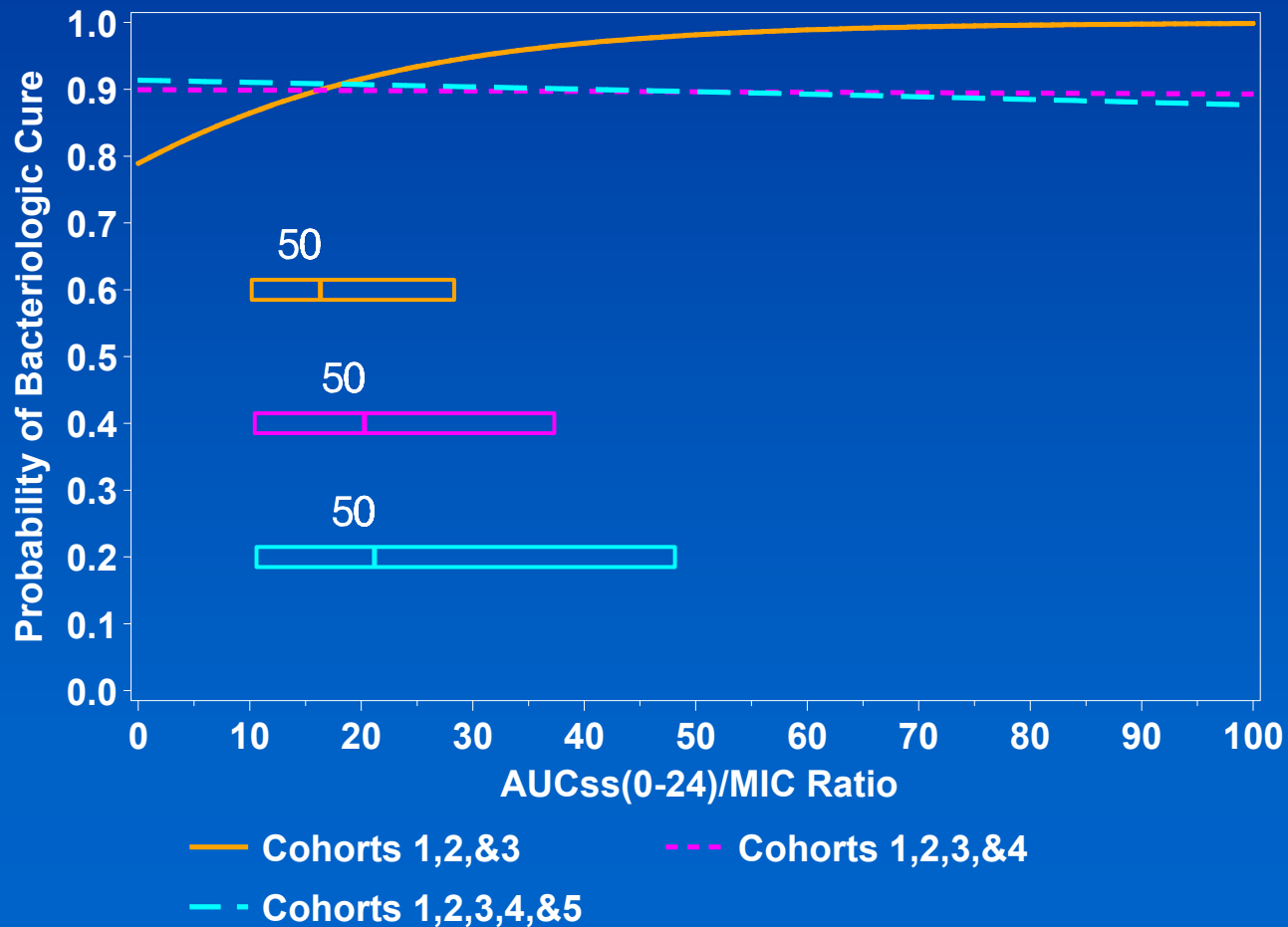
Microbiological Response

Cohorts 1, 2, and 3, cont'd



The line represents the model-based predicted probability of bacteriologic cure

Microbiological Response All Cohorts



The Boxes represent the 25th, 50th and 75th percentiles for each group of Cohor

Clinical Response

Univariate Analysis – Cohorts 1, 2, and 3

Parameter	Estimate	SE	OR (95% CI)	p-value
Baseline APACHE II Score - Continuous	-0.1704	0.0775	0.843 (0.724,0.982)	0.0279*
AUC _{ss} /MIC	0.0936	0.0524	1.098 (0.991,1.217)	0.0740
AUC _{ss} /MIC Breakpoint at 6.96	0.8702	0.4235	5.70 (1.084,29.99)	0.0399*

* Represents statistical significance at an $\alpha = 0.05$

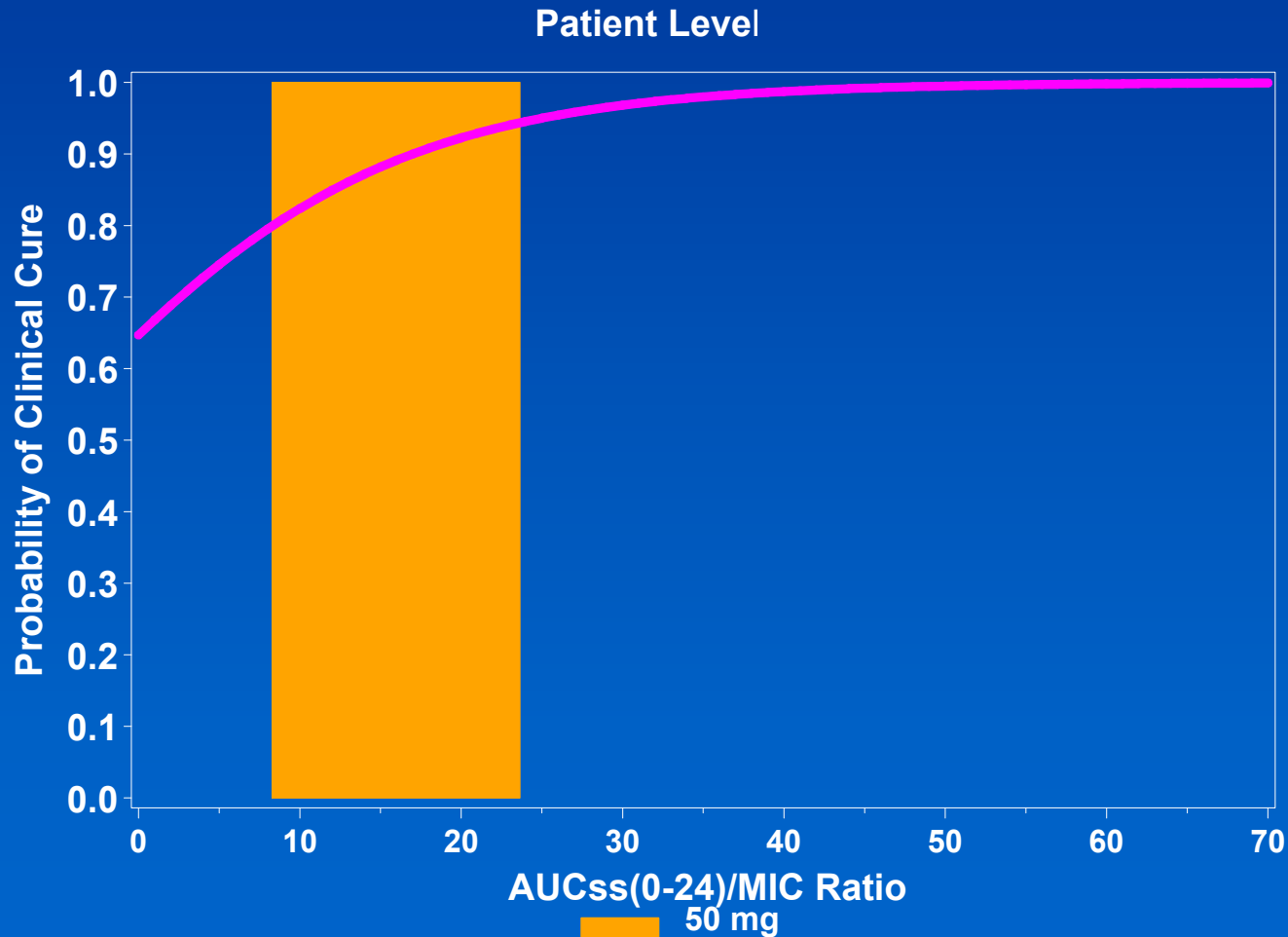
Clinical Response

Final Model – Cohorts 1, 2, and 3

Parameter	Estimate	SE	OR (95% CI)	p-value
AUC _{ss} /MIC	0.0936	0.0524	1.098 (0.991,1.217)	0.0740
Hosmer-Lemeshow Goodness-of-Fit Test = 10.66 with 8 Degrees of Freedom (p-value = 0.2214)			Area Under the ROC Curve = 0.71	

Clinical Response

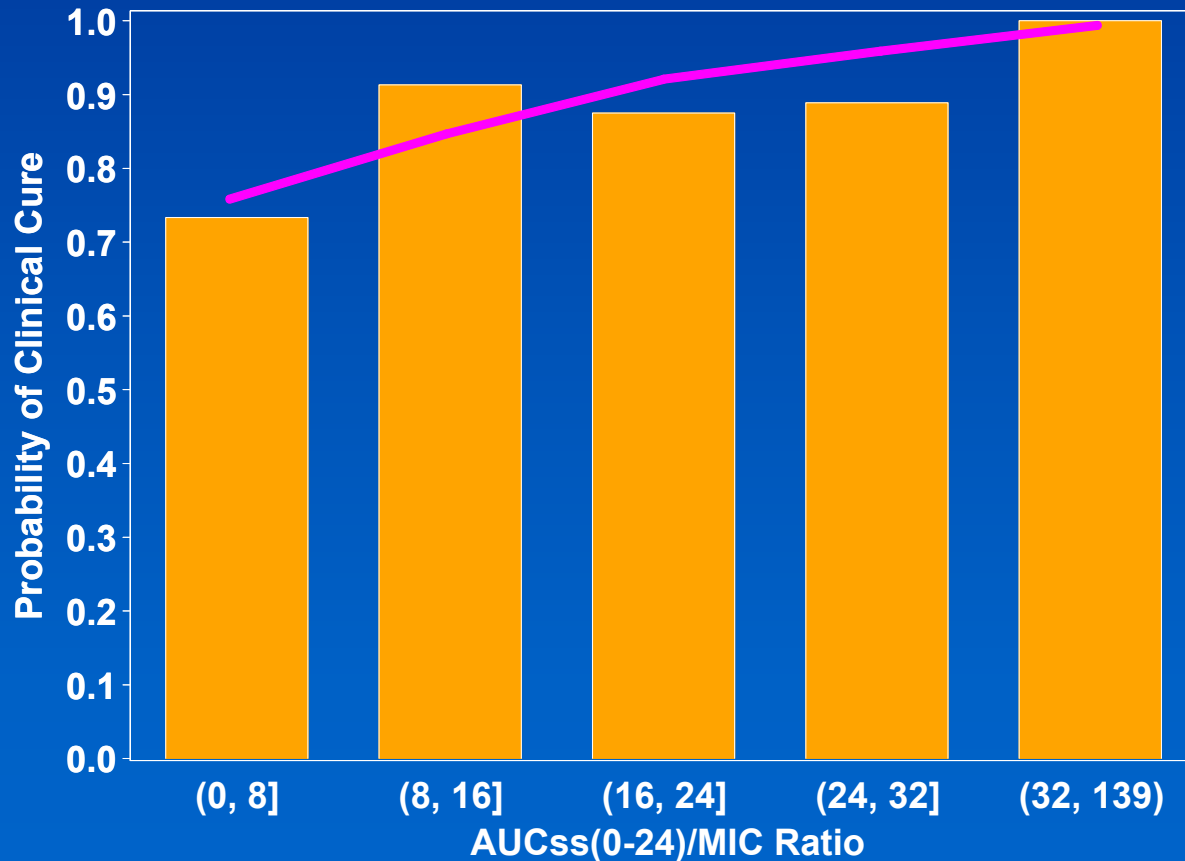
Cohorts 1, 2, and 3



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

Clinical Response

Cohorts 1, 2, and 3, cont'd.



The line represents the model-based predicted probability of clinical cure.

Results

Statistical Assessment

- Small sample size
- Caution should be used when interpreting model results evaluating the breakpoint due to small number of failures above the breakpoint
- The continuous AUC/MIC models are better for predicting probability of response
- All-pathogen approach added variability (noise) to the analysis making the exposure-response relationship undetectable

Results

Conclusions

- AUCss/MIC ratio was borderline significant and the breakpoint was significant with p-value = 0.0004 ($\alpha = 0.05$) when evaluating Cohorts 1, 2, and 3.
- Age, gender, and baseline APACHE II score were not statistically significant predictors of microbiological response.
- Baseline APACHE II score and the breakpoint were significant when evaluating clinical response in Cohorts 1, 2, and 3.
- Age, ethnicity, and AUC/MIC ratio were not statistically significant predictors of clinical response.
- **The exposure-response relationship was undetectable when analyzing all pathogens.**

Thank You
