

Population Pharmacodynamic Assessment of Linezolid Efficacy in Community Acquired Pneumonia, Skin and Soft Tissue Infections, and Bacteremia

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Analysis Goals

- To develop a PK/PD basis for linezolid dosing regimen selection.
- To evaluate the relationships between linezolid PK, patient covariates, and response in Phase II efficacy trials.

Phase II Studies

Type of Infection	# PK Samples Per Patient	Dosing Regimens (mg)	# Patients Sampled/Enrolled
Community acquired <i>S. Pneumoniae</i> pneumonia (CAP)	12	250 TID 375 BID	22/62
		375 TID 625 BID	50/116
Complicated skin/soft tissue infections (SST)	12	250 TID 375 BID	61/148
		375 TID 625 BID	86/191
Gram positive bacteremia (BAC)	9	600 BID	110/164



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Methods: Pharmacokinetic Analyses

■ PK model

- developed using data from 3 Phase II studies
- one-compartment, first-order absorption and parallel linear and non-linear elimination

■ Bayesian parameter estimates from the PK model were utilized to predict each individual's steady-state C_p -time profile for the last administered dosing regimen.

Methods: Pharmacodynamic Analyses

■ Time above the MIC

- Determined by predicting each individual's steady-state Cp-time profile based on their last administered dosing regimen
- The Cp at each time were compared to the MIC values to estimate the length of time the Cp were above the MIC.

■ AUC:MIC Ratio

- Calculated using the trapezoidal rule on the predicted concentration-time profile
- The ratio was formed by dividing AUC_{0-24} by the MIC value.

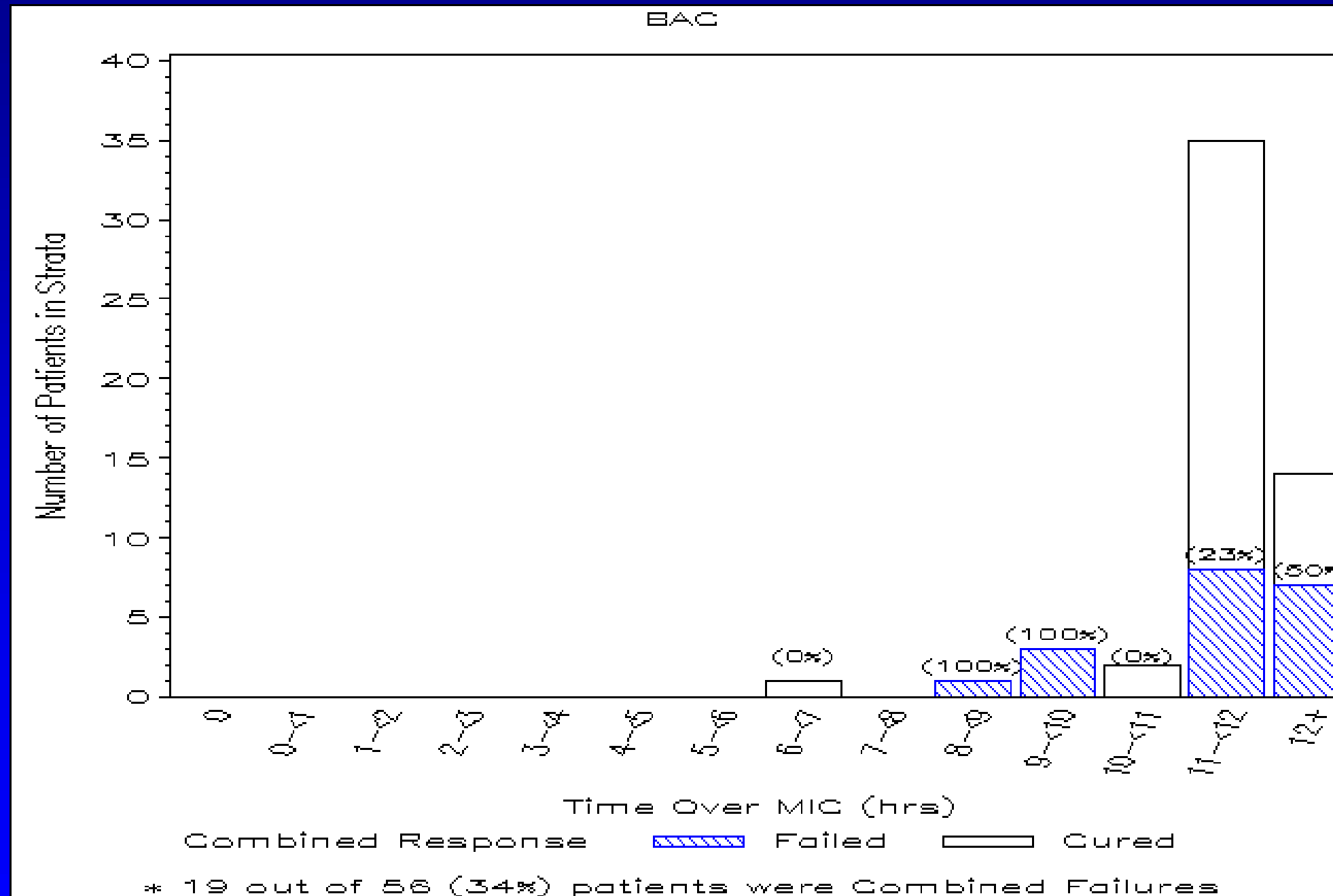
■ Outcome Evaluation - clinical and microbiologic efficacy at the long-term follow-up visit



Methods: Logistic Regression

- Logistic regression analyses with stepwise selection
- Endpoints evaluated: clinical, microbiologic, and combination (clinically cured or improved and microbiologic success)
- Predictors of failure evaluated
 - AUC:MIC ratio
 - length of time above the MIC
 - age
 - gender
 - weight
 - total daily dose
 - race
- An $\alpha=0.05$ (1 degree of freedom) was used to define statistical significance for the addition of a single parameter and an $\alpha=0.01$ (1 degree of freedom) was used for the deletion of a single parameter.

Combination Response: Histogram of Time Spent Above the MIC Stratified by Response for BAC



Summary of Clinical Response

Study	Number of Patients	Number (%) of Failures
CAP	52	4 (7.7%)
SST	94	14 (14.9%)
BAC	73	17 (23.3%)

Summary of Microbiologic Response

Study	Number of Patients	Number (%) of Failures
CAP	47	2 (4.3%)
SST	82	13 (15.9%)
BAC	56	16 (28.6%)

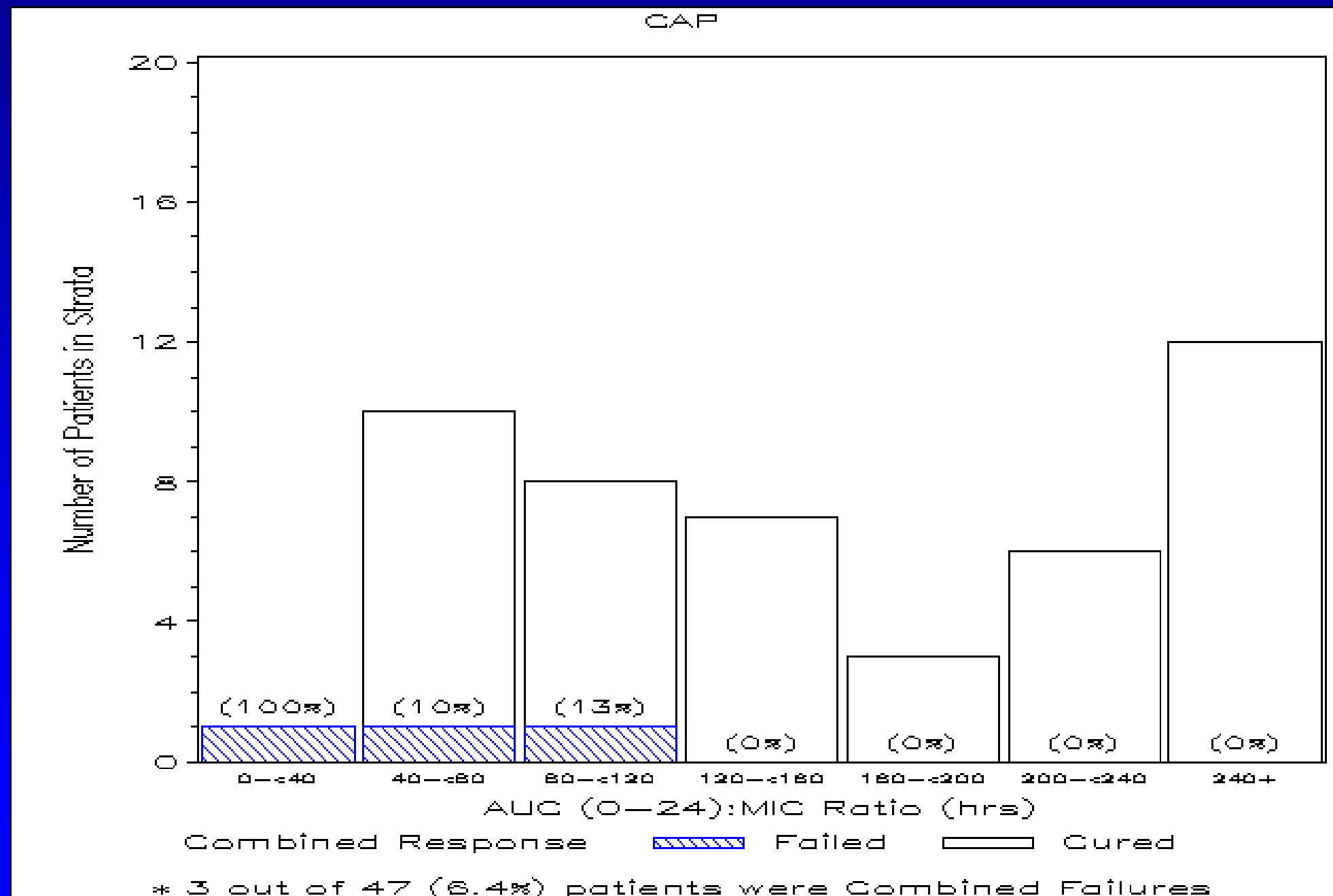
Summary of Combined Response

Study	Number of Patients	Number (%) of Failures
CAP	47	3 (6.4%)
SST	81	14 (17.3%)
BAC	56	19 (33.9%)

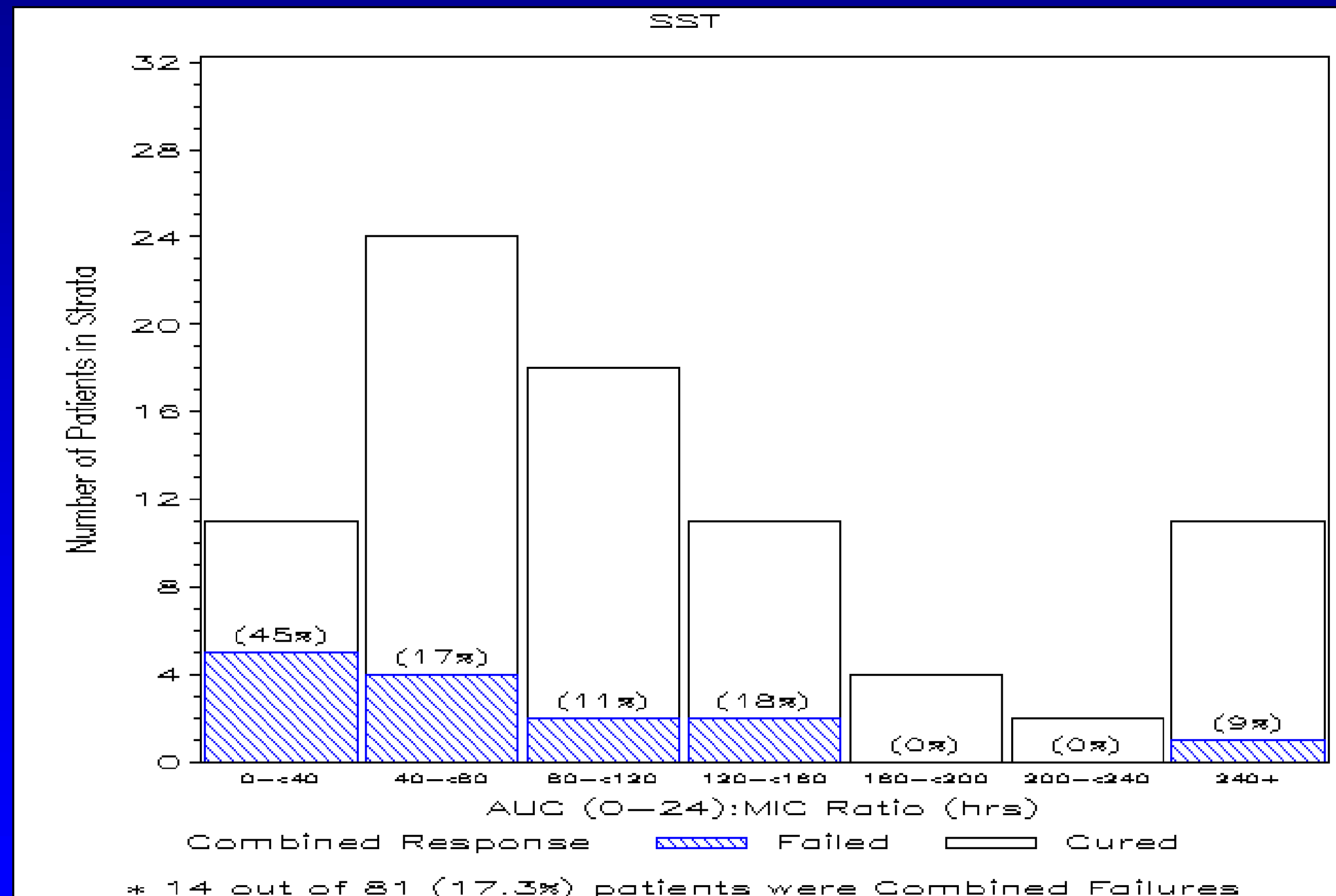
Study Design Considerations

- Exclusion criteria allowed enrollment of patients with infected devices (not removed) or severe infections such as osteomyelitis, endocarditis, gram negative sepsis, septic arthritis, and meningitis.
- These patients would be expected to:
 - Require prolonged antibacterial therapy
 - Have high clinical and microbiologic failure rates
- Enrollment occurred predominantly in BAC study, with a few in SST study.

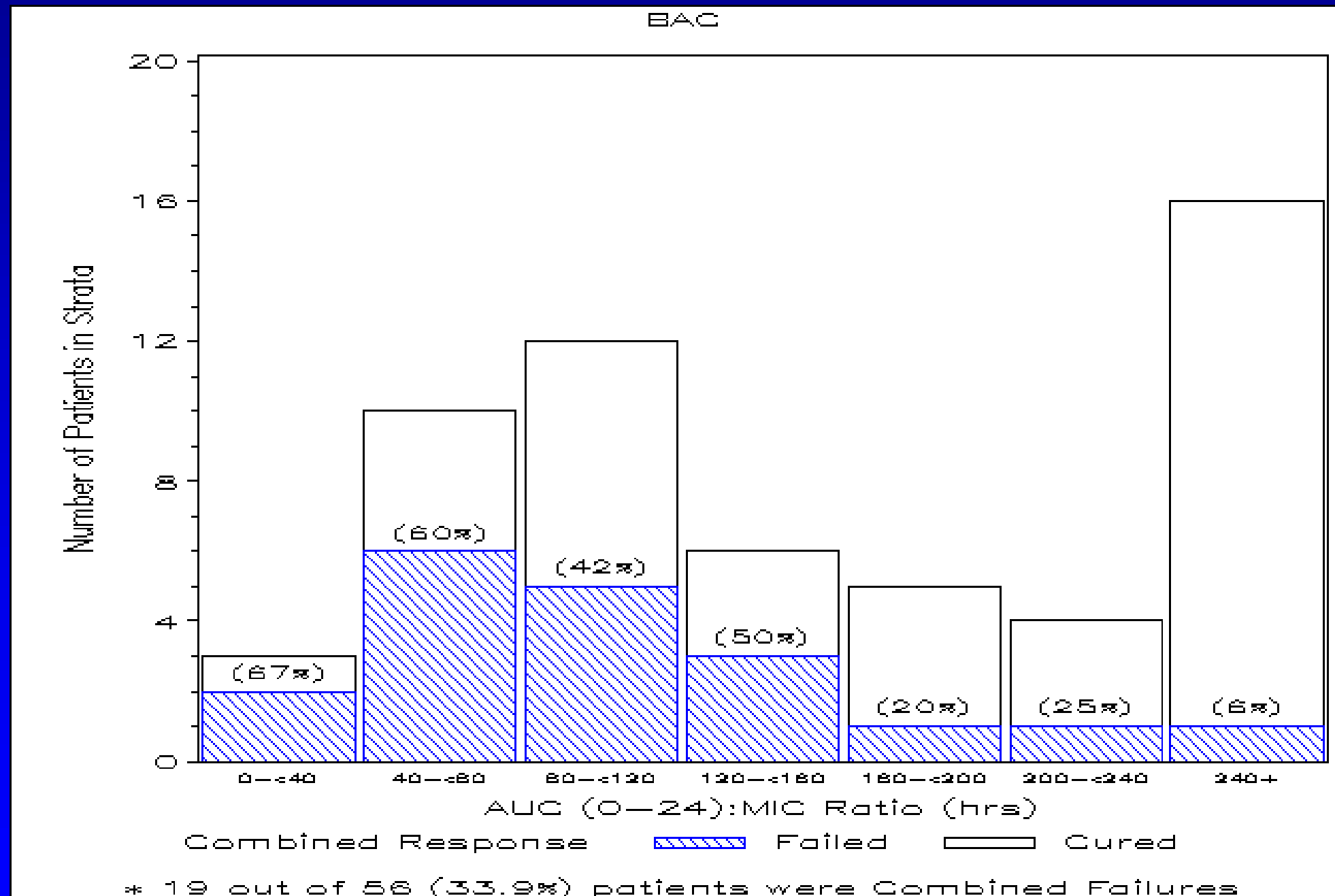
Combination Response: Histogram of AUC:MIC Ratio, Stratified by Response for CAP



Combination Response: Histogram of AUC:MIC Ratio, Stratified by Response for SST



Combination Response: Histogram of AUC:MIC Ratio, Stratified by Response for BAC

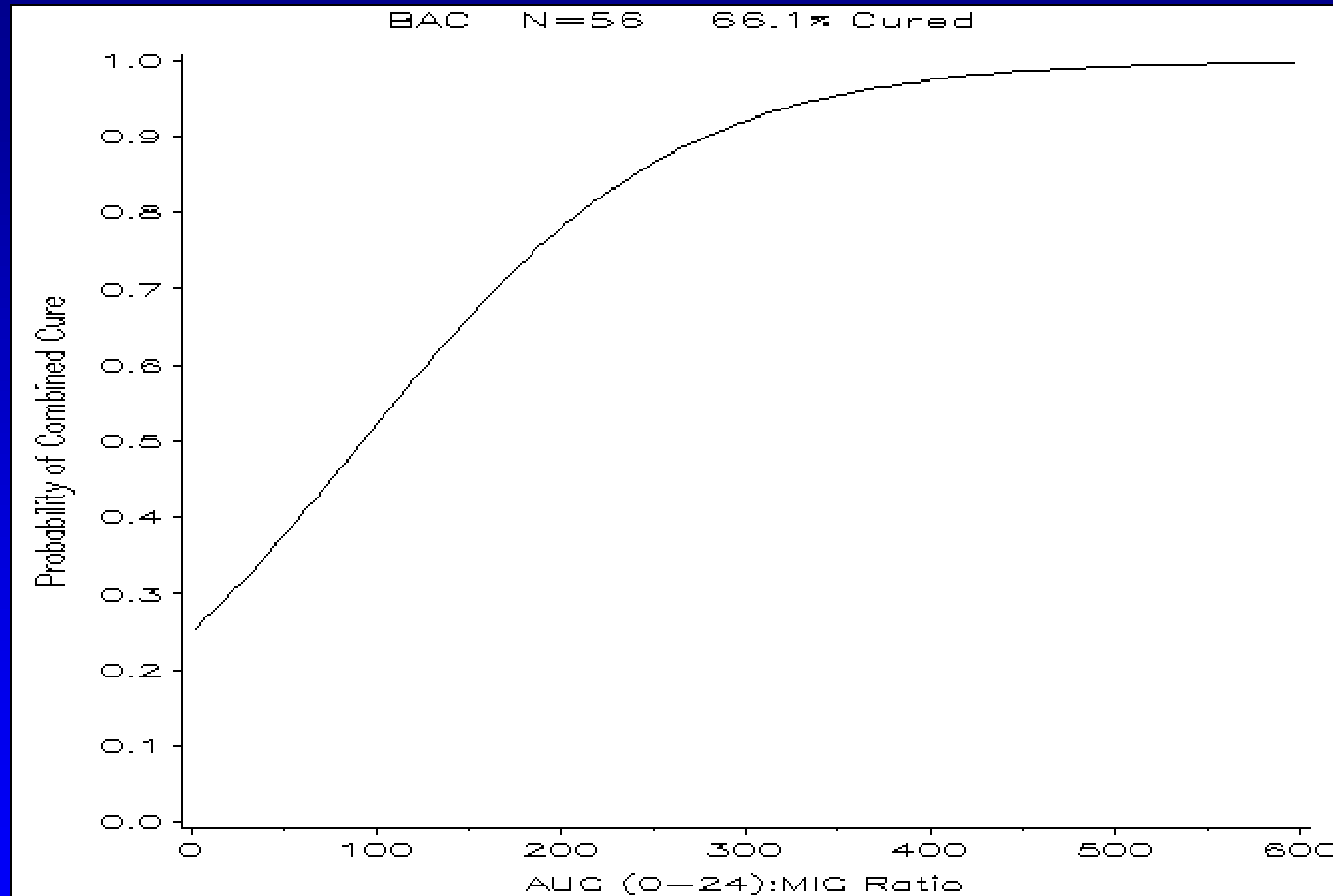


Results of Logistic Regression Analyses For Combination Failure in BAC

Study	Variable	Parameter Estimate	p-value	Odds Ratio (95% CI)
BAC	Intercept	1.09 (0.61)	0.075	
	AUC ₀₋₂₄ : MIC Ratio	-0.01 (0.00)	0.005	0.988 (0.980, 0.996)

- Logistic regression analysis of the CAP study could not be performed due to small number of failures.
- Logistic regression analysis of the SST study did not identify significant covariates.

Probability of Combined Cure for BAC



Mean (SD) Values of AUC:MIC Ratio Stratified by Dose Level and Study

Study	Dose Level	
	Low (750 mg/day)	High (1125-1250 mg/day)
CAP	106.0 (59.1)	241.5 (239.0)
SST	77.9 (56.9)	140.8 (125.9)
BAC	NA	188.8 (163.9)

Cure Rates Stratified by Response, Study, and the Median Value of the AUC:MIC Ratio

Response	CAP		SST		BAC	
	% Cure ≤Median	% Cure >Median	% Cure ≤Median	% Cure >Median	% Cure ≤Median	% Cure >Median
Clinical	84.6	100.0	83.0	87.2	63.9	89.2
Microbiologic	91.3	100.0	80.5	87.8	57.1	85.7
Combined	87.5	100.0	78.0	87.5	46.4	85.7

Conclusions

- The analysis of the time above the MIC was not informative; the majority of patients were above the MIC for the majority of their dosing interval.
- Logistic regression analysis of the CAP study could not be performed due to the small number of failures.
- Logistic regression analysis of the SST study did not identify significant predictors of failure.

Conclusions

- Logistic regression analysis of combined response in the BAC study concluded that AUC:MIC ratio was a significant predictor of failure.
- Pharmacodynamic analysis of efficacy response in BAC studies suggests that patients at the lower end of the AUC:MIC ratio distributions experience a greater risk of failure; trends were noted for CAP and SST.
- Patients receiving low doses had a greater probability of low AUC:MIC ratios.
- Currently recommended doses for linezolid are expected to yield AUC:MIC ratios which will be associated with good response.



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