PK/PD of Ciprofloxacin in Patients with Cystic Fibrosis

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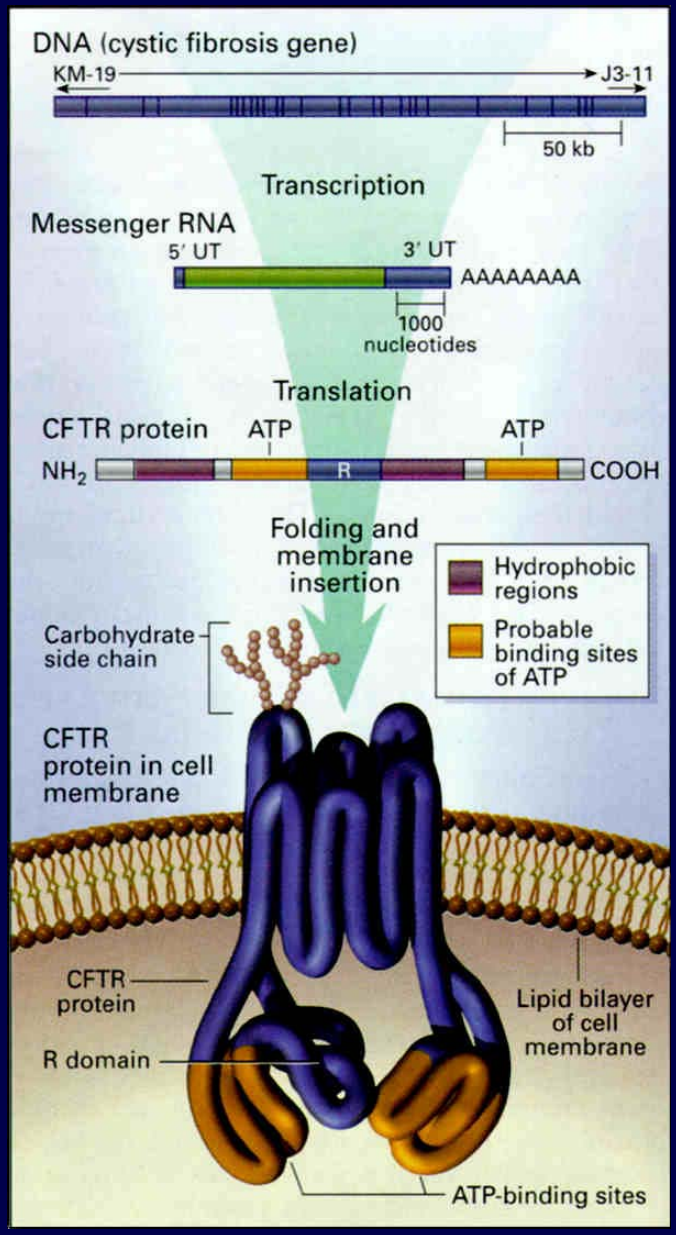
Cystic Fibrosis

- Genetically inherited disease which affects 30,000 individuals in the US
- Mean survival has increased over past 35 years from 10 to 31 years
- Proportion of adult patients with CF has increased from 23% to 35% over a similar period


DNA (cystic fibrosis gene)
KM-19
J3-11
50 kb
Transcription
Messenger RNA
5′ UT
3′ UT
AAAAAAAA
1000
nucleotides
Translation
CFTR protein
ATP
ATP
NH2
R
COOH
Folding and
membrane
insertion
Hydrophobic
regions
Probable
binding sites
of ATP
Carbohydrate
side chain
CFTR
protein in cell
membrane
CFTR
protein
R domain
Lipid bilayer
of cell
membrane
ATP-binding sites

Pathogenesis

- Defective gene on chromosome 7 (identified in 1989)
  - CFTR responsible for transport of CL^- outside cell
  - Abnormally high intracellular Na^+ thickened secretions and obstruction
- Effects exocrine glands: pancreas, lung, GI tract

Why are CF Patients Predisposed to Lung Infections?

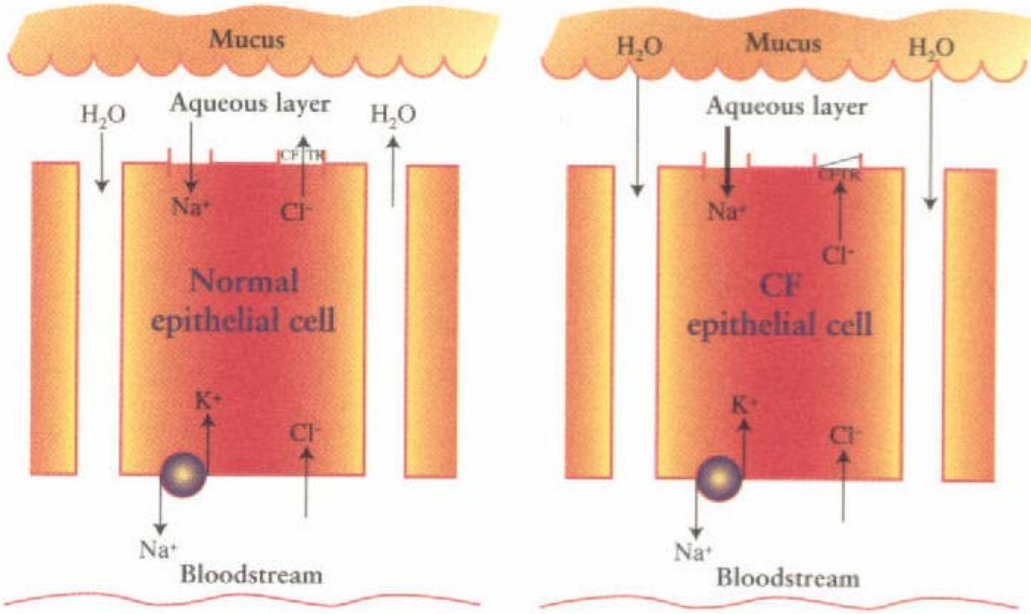


Fig 3.—CFTR function in normal and CF respiratory epithelial cells. Left, Normal CFTR functions as a chloride (Cl^-) channel, which helps to regulate the water (H_2O) content of the mucus in the airways of the lungs. Active transport of sodium (Na^+) into the cells brings water to drive the system. Right, Abnormal CFTR function results in decreased chloride diffusion, limiting the water content of bronchial secretions. (G.W. Fernald, MD, written communication, August 1997).

Innate Host Defense

- Airway clearance
- Cationic polypeptides
- CFTR as bacterial receptor

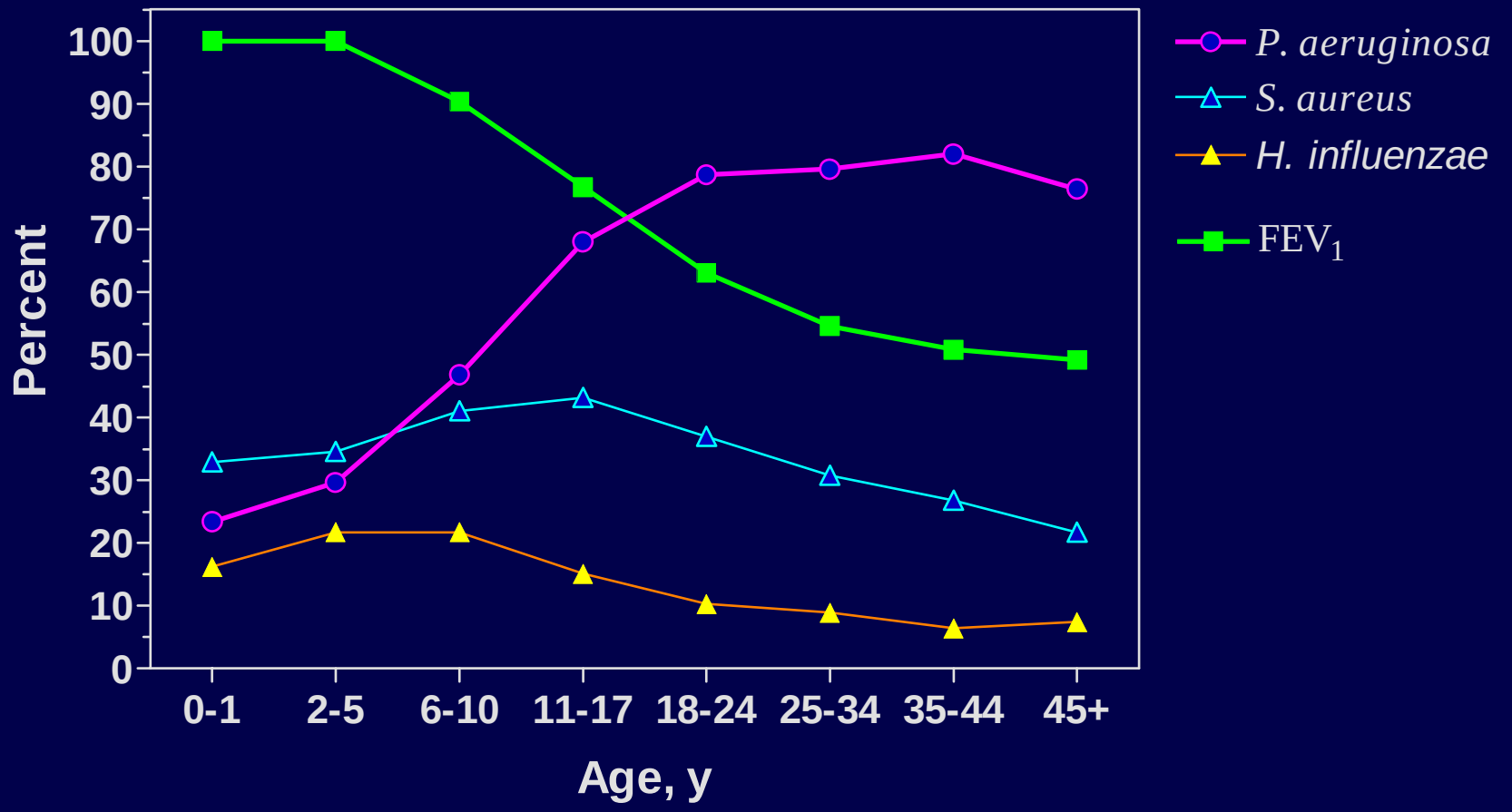
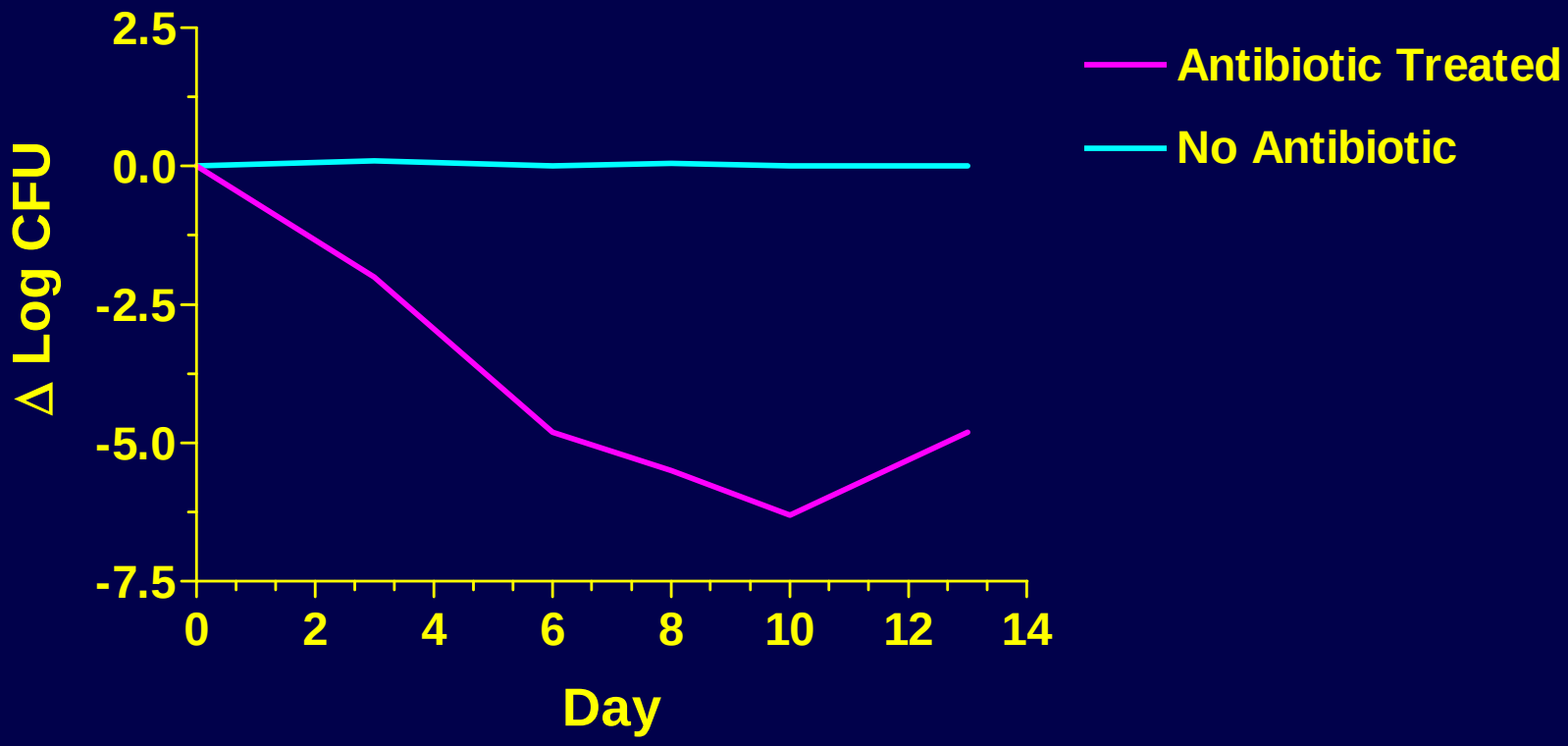


Figure 1. Age related changes in microbiology and pulmonary function in patients with cystic fibrosis. CFF registry data 1996.

Treatment of Flare “Tune up”

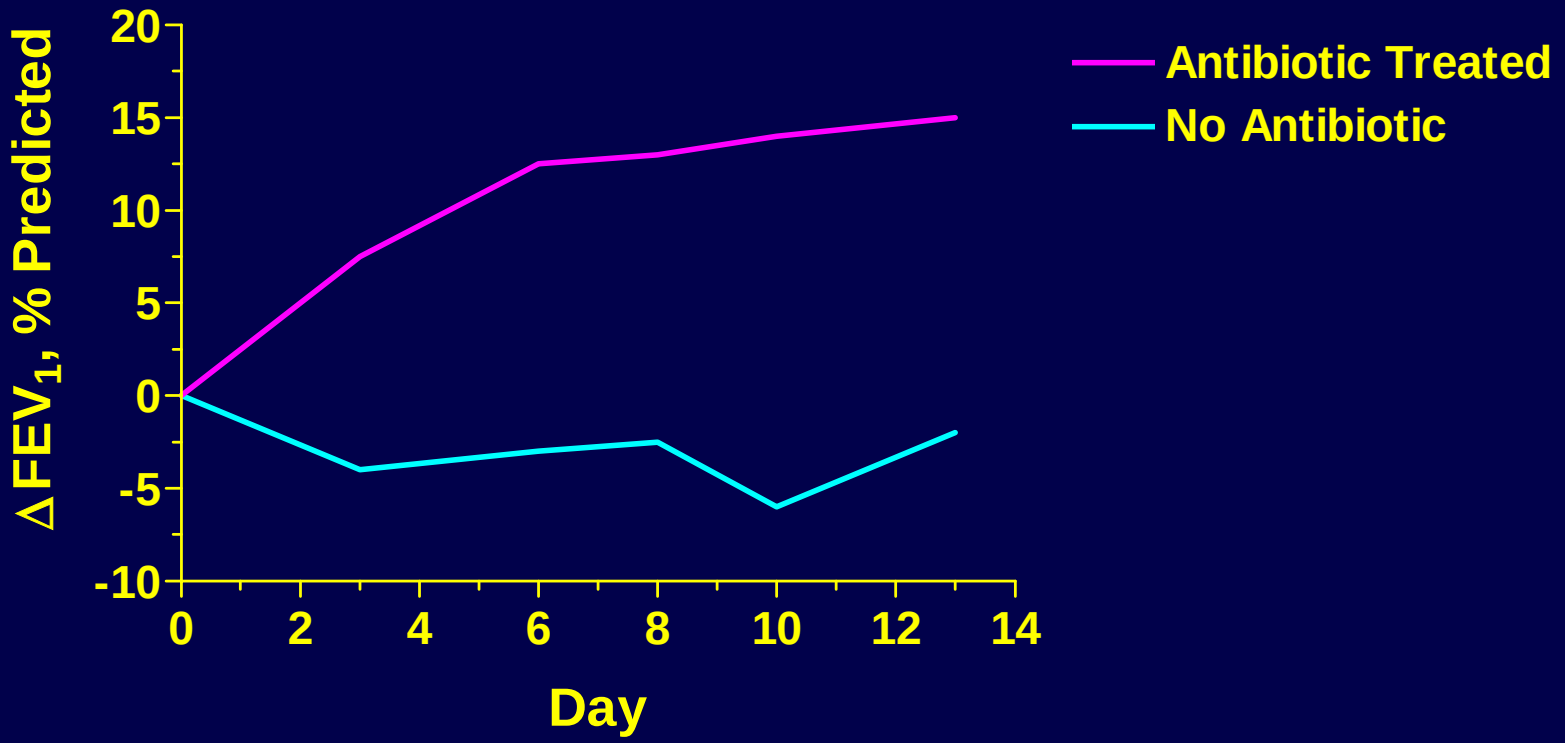
- Airway Clearance
- Nutrition
- Antibiotics
  - Combination of 2 agents
  - 10-21 days

Effect of Antibiotics for Acute Pulmonary Exacerbations



Regelmann et al. Am Rev Respir Dis 1990

Effect of Antibiotics for Acute Pulmonary Exacerbations



Regelmann et al. Am Rev Respir Dis 1990

PK/PD Ciprofloxacin in CF

- Goals:
  - Develop a compartmental pharmacokinetic model which can be utilized for TDM
  - Perform a pharmacodynamic evaluation of recommended dosing of ciprofloxacin

Study Design

- Single dose of 400mg iv administered to 12 adult CF patients
- Multiple serum concentrations obtained at: 0, 15-30 minutes, 1.5, 2.5-3, 7-8, and 10-12 hours following the dose
- Serum concentrations analyzed using HPLC
- Measured concentrations fitted to a 2-compartment model (IT2B)

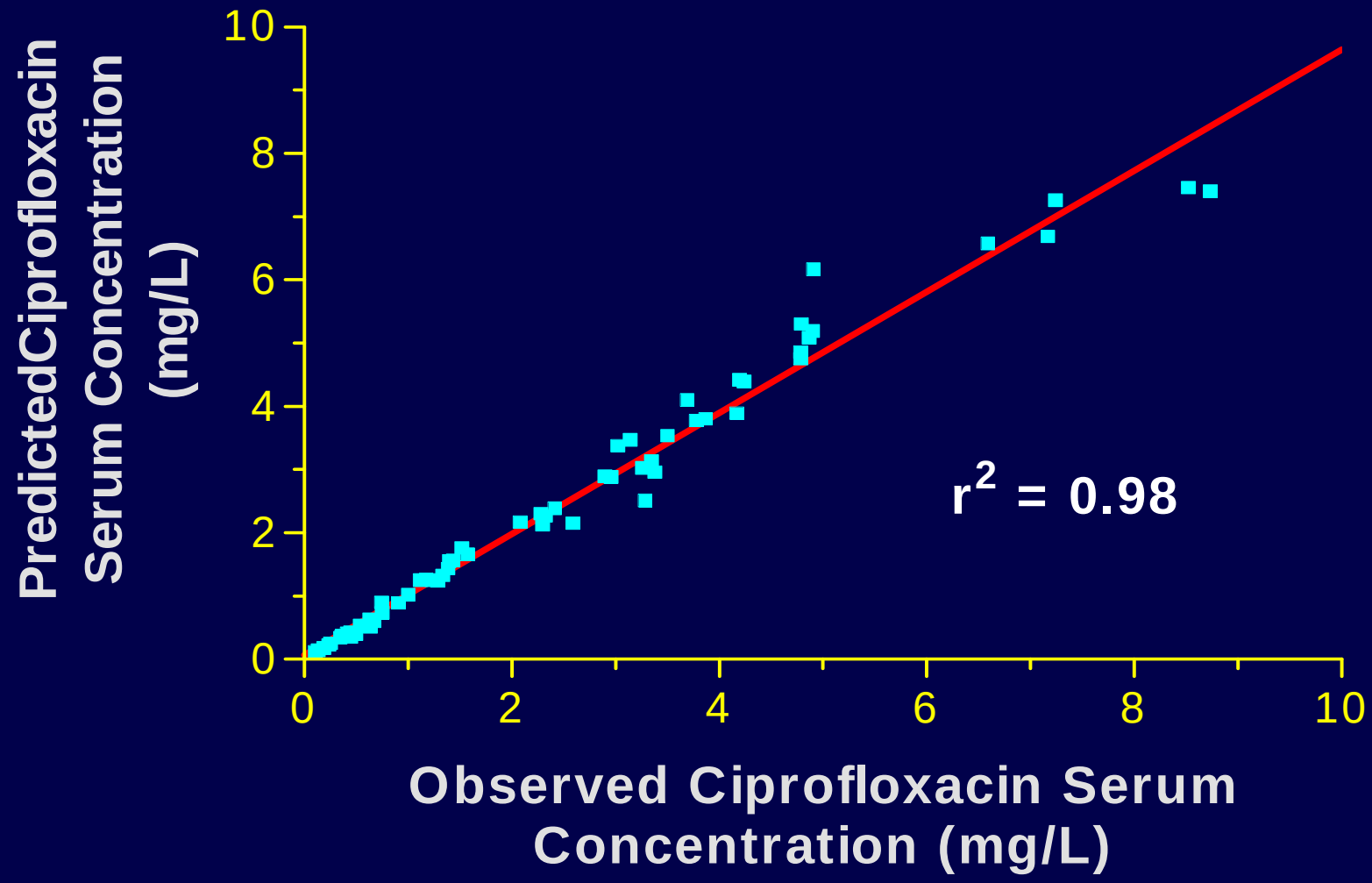
Patient Characteristics

Characteristic	Mean (s.d.)	Range
Age (yr)	31 (6.8)	22-42
Height (in)	66 (3.6)	59-74
Weight (kg)	54.5 (8.9)	41.5-72
CLcr (ml/min/1.73 m^2)	115 (22.7)	86.3-150.4
Genotype		
ΔF508/ΔF508	2	
ΔF508/Other	6	
Other/Other	4	

Pharmacokinetic Parameters

Parameter	Median	Range
V_c (L/kg)	0.39	0.11-0.63
V_{ss} (L/kg)	1.15	0.4-1.9
CL_T (L/h/kg)	0.33	0.24-0.53
CL_D (L/h/kg)	0.77	0.29-1.60
$T1/2_\alpha$ (h)	0.17	0.13-0.25
$T1/2_\beta$ (h)	2.85	2.1-3.7

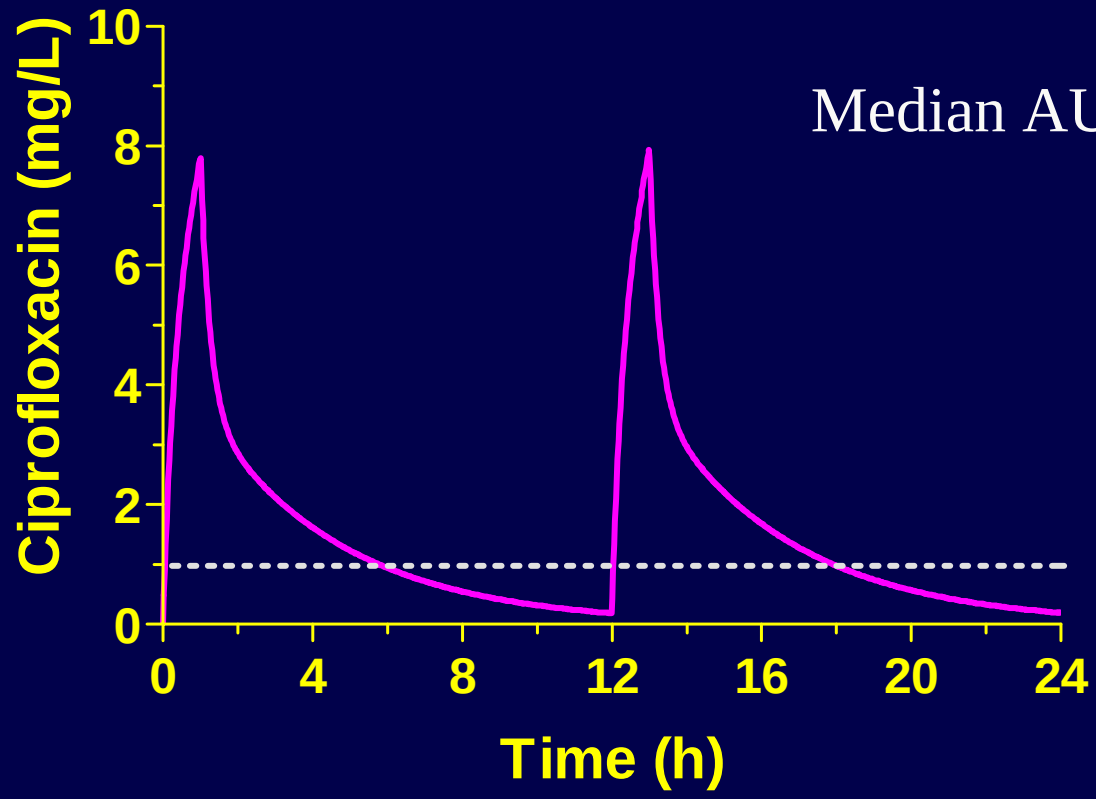
Predicted vs. Observed Ciprofloxacin Serum Concentrations



Comparative Pharmacokinetics

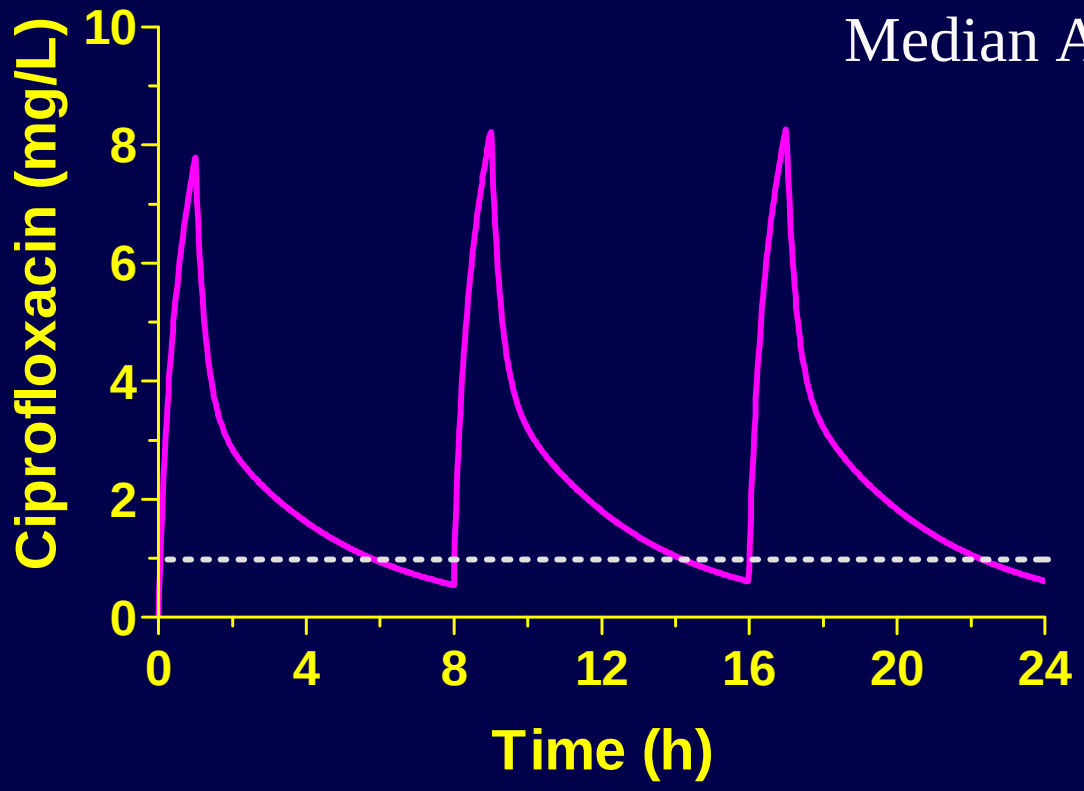
Study	Vd (L/kg)	CL (L/kg/h)	T ½ (h)
Davis et al	2.21 ± 0.38	0.51 ± 0.11	4.5 ± 1.9
Steen et al	2.84 ± 1.59	0.62 ± 0.31	3.2 ± 1.3
Christensson et al	2.71 ± 0.71	0.62 ± 0.10	
Forrest et al.	1.2	0.24	6.5
Current	1.2 ± 0.43	0.33 ± 0.12	2.9 ± 0.55

Serum Concentration Time Curve: Ciprofloxacin 400mg Q12h



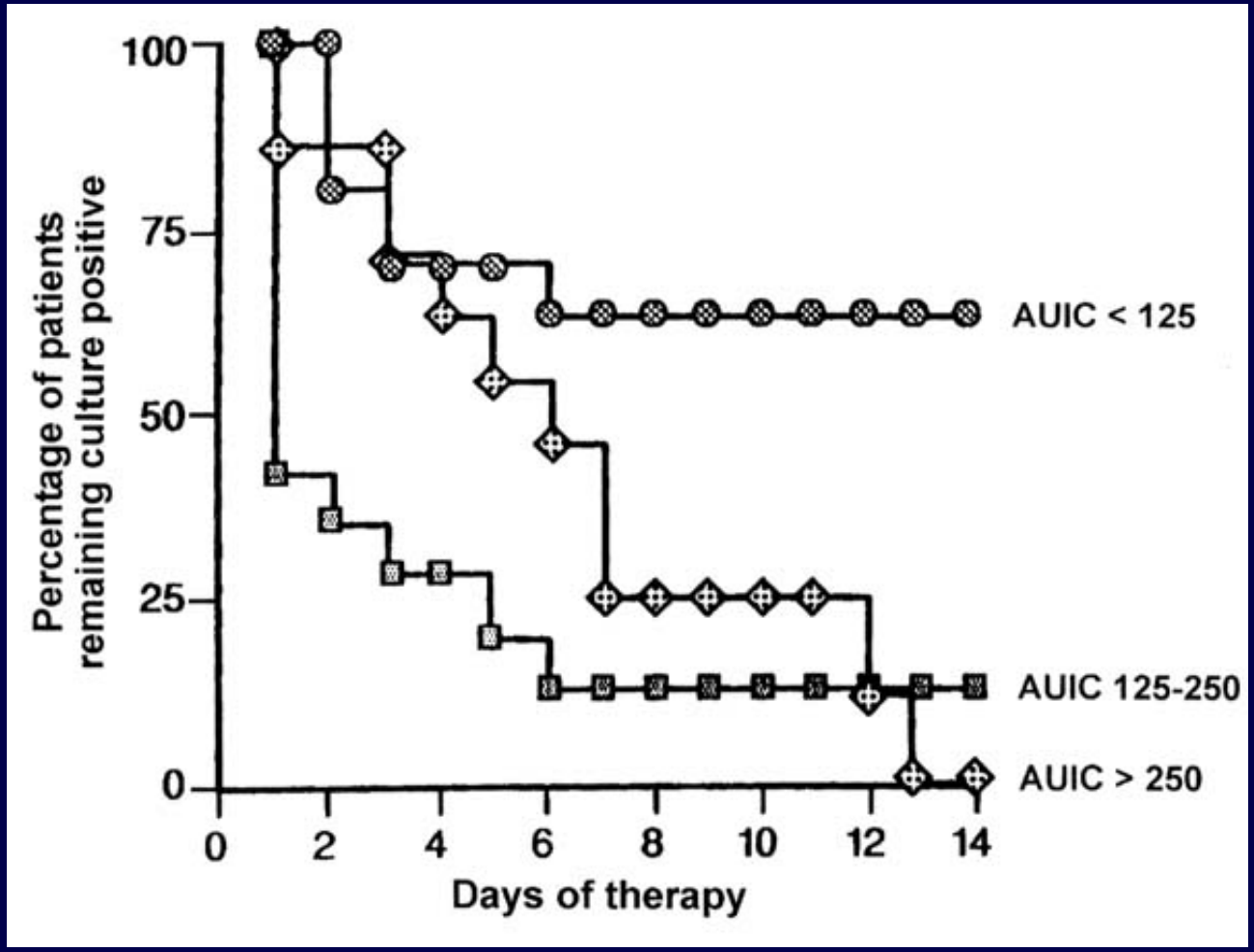
Median AUC 39.3

Serum Concentration Time Curve: Ciprofloxacin 400mg Q8h



Median AUC 58.9

PK/PD of Ciprofloxacin

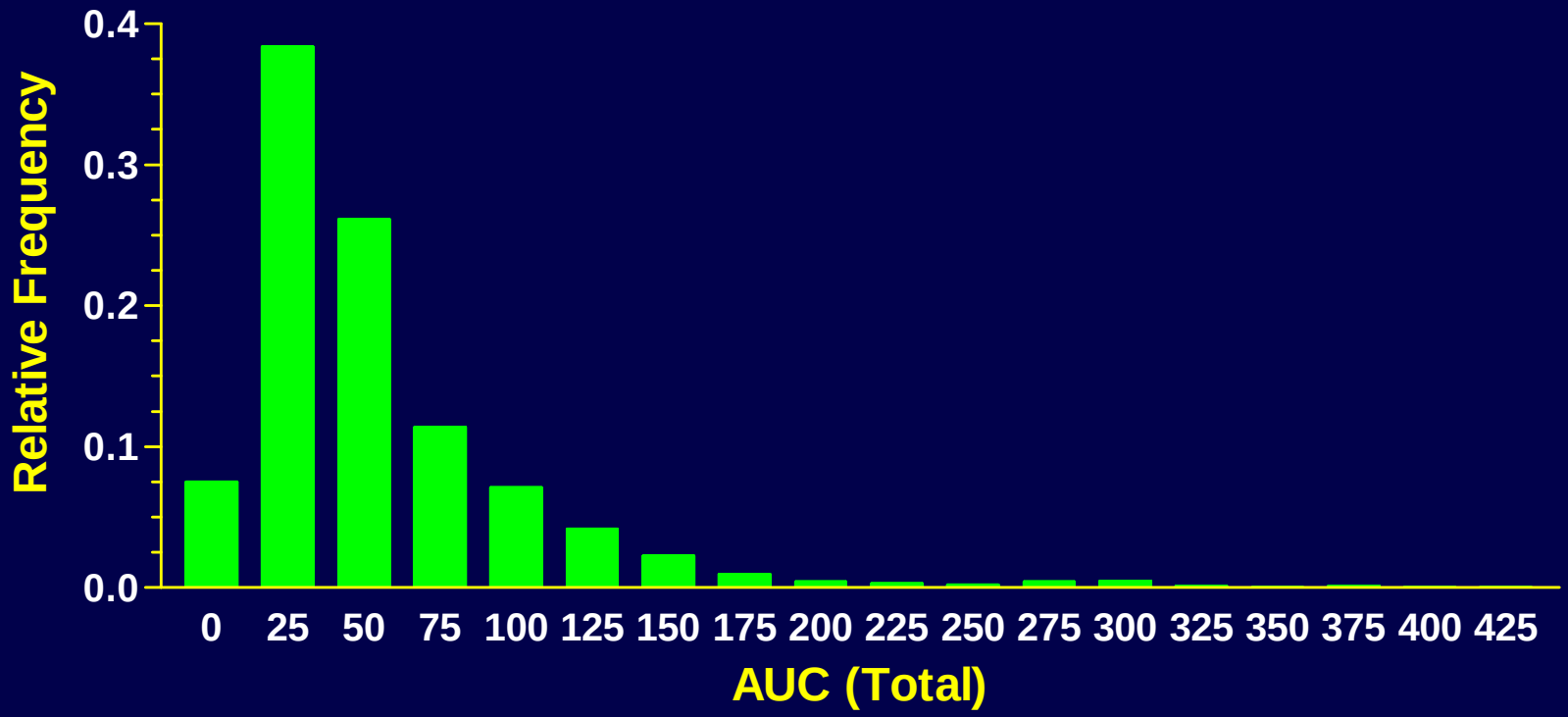


Forrest et al. AAC 1993

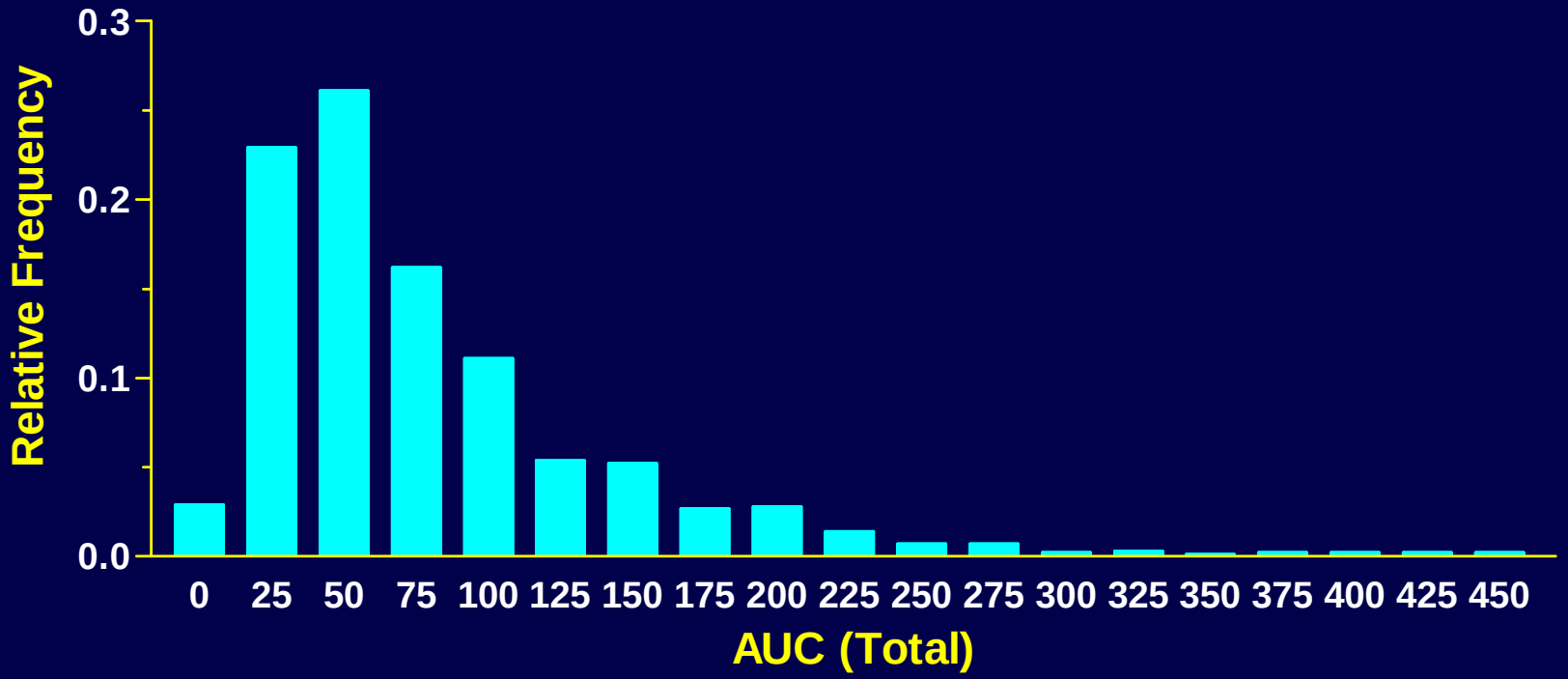
Monte Carlo Simulation

- 1000 random data vectors were sampled. Each consisted of AUC values simulating 400mg q12h and 400mg q8h and an MIC value
- AUC values sampled from a lognormal distribution (AdaptII)
- MIC values sampled from a discrete distribution modeled on 1213 observed values

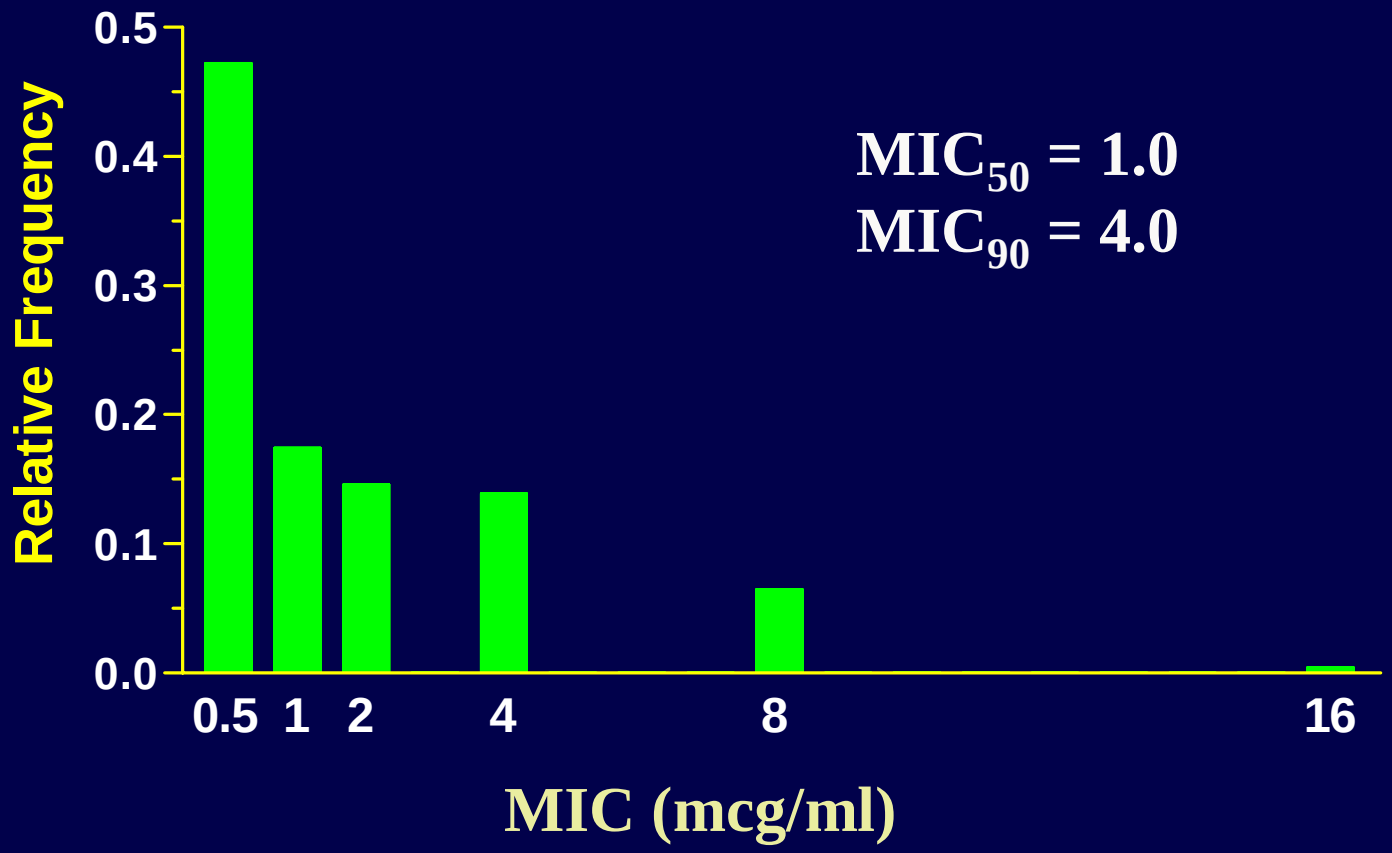
PD Simulation: Ciprofloxacin 400mg Q12h



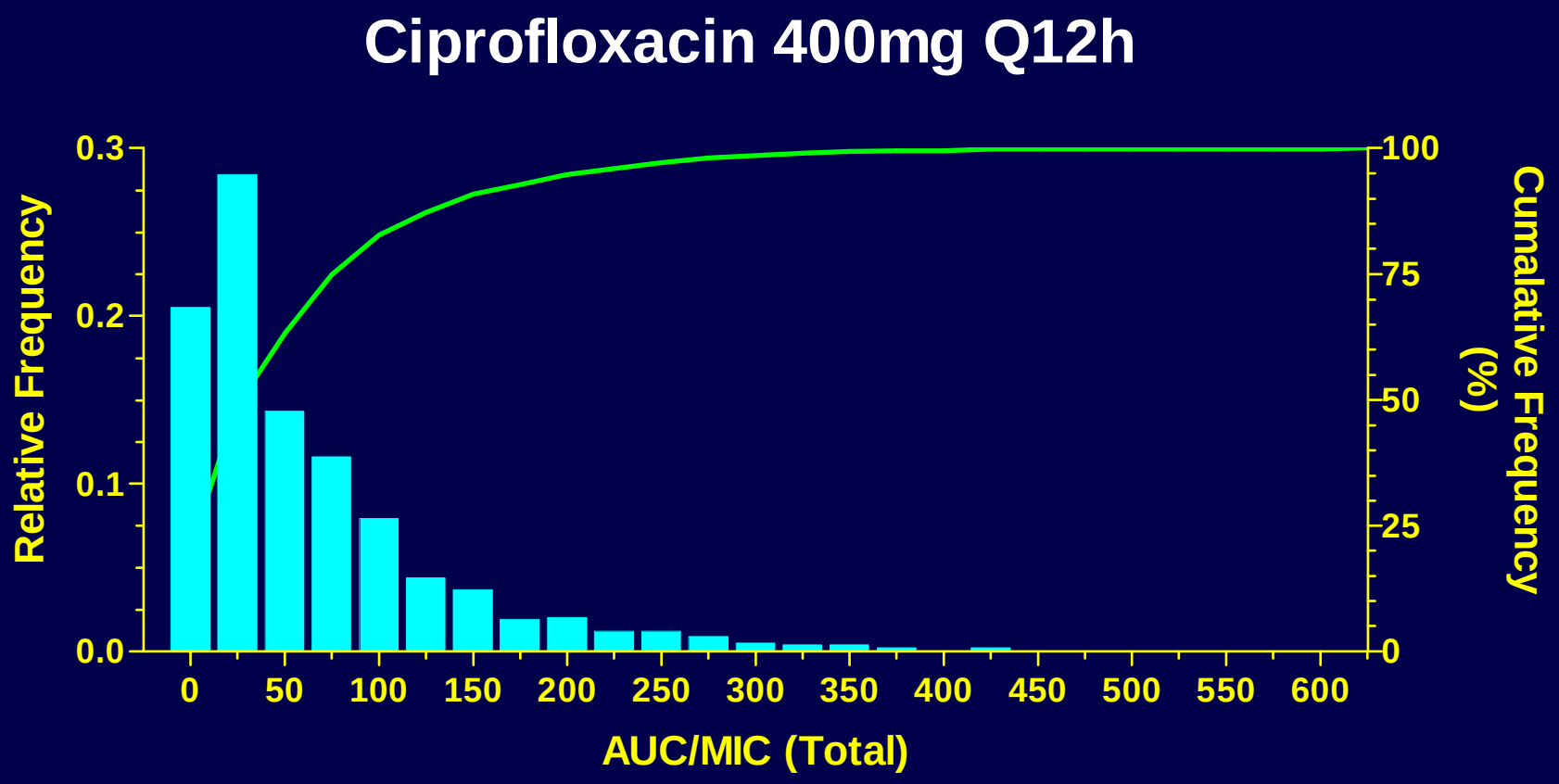
PD Simulation: Ciprofloxacin 400mg Q8h



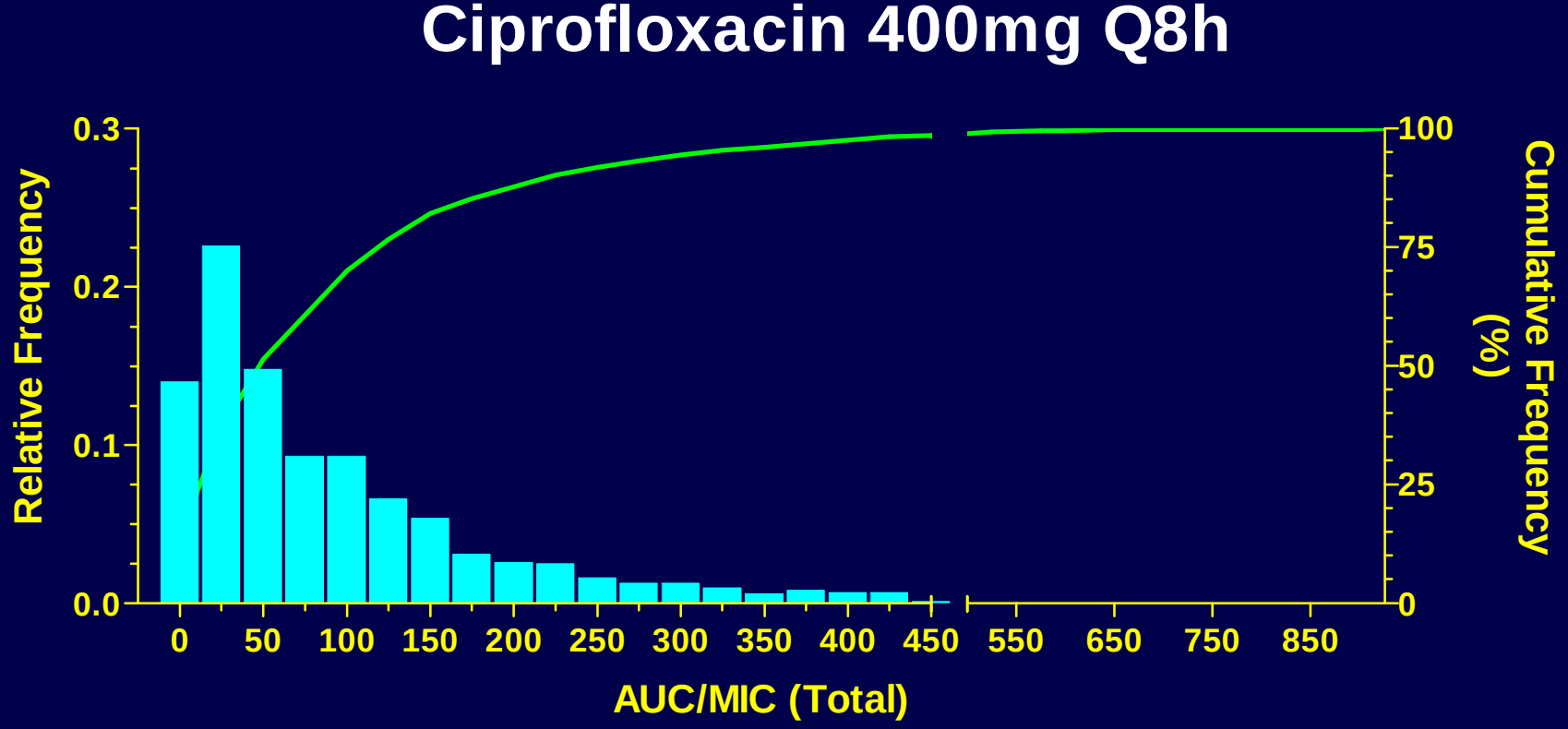
Distribution of MICs



PD Simulation: AUC/MIC



PD Simulation: AUC/MIC



Conclusions

1. The pharmacokinetics of ciprofloxacin in adult CF patients are well described using a 2-compartment model
2. The recommended doses of 400mg q8-12h may be inadequate to treat an acute exacerbation when given as monotherapy

Study Contributors

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