Managing Pediatric Poisons: How Important are Accurate Dose Recommendations?

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Conflicts of Interest

- None

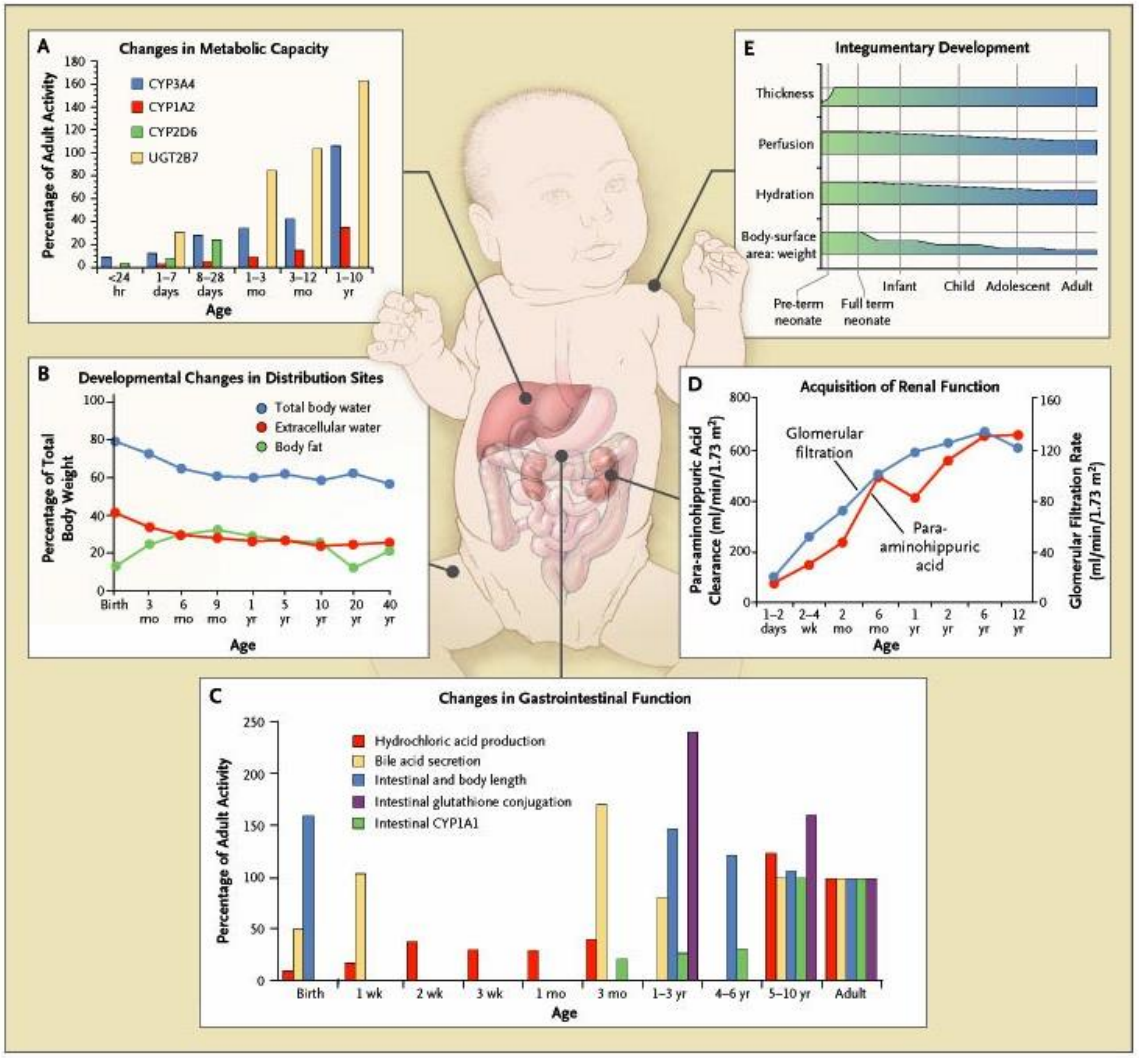
Objectives

- Review barriers to pediatric drug studies
- Discuss the role of modeling and simulation
- Case studies
  - Neonatal sepsis
  - Fungal infection in children on ECMO

Physiologic Differences

Metabolism

Distribution



Body surface area

Renal Function

Absorption

Kearns *N Engl J Med* 2003.

Why are Pediatric PK studies Difficult?

- Limited number of patients with the disease
- No “healthy child/baby volunteer”
- Low rates of parental informed consent
- Perceived study risks
- Limited blood volume and timed sampling
- Sick population – increases variability
- Lack of clinical pharmacology expertise
- Lack of pediatric PK/PD modeling expertise

Modeling and Simulation

- **Disease models**
  - **Understand biomarker(s)/outcome relationship(s)**
  - **Characterize disease processes in the absence of drug**
- **Drug models**
  - **Exposure-response relationships**
  - **Exposure-safety relationships**
  - **Predict differences in PK/PD relationships between healthy, special and diseased populations**
- **Trial Models**
  - **Account for trial dropout and medication adherence**
  - **Explore the importance of patient characteristic**

Gobburu Ann Rev Pharm Tox 2009

Case Study #1

NEONATAL SEPSIS

Neonatal Sepsis

- Infants with sepsis are 3x as likely to die as infants without sepsis
- Up to 20% of extremely premature infant deaths are caused by sepsis
- Survivors often suffer from significant morbidities
  - Bronchopulmonary dysplasia
  - Neurodevelopmental impairment

Stoll *N Engl J Med* 2002, Polin *J Peds* 2008

Empirical Antibiotics

- Majority of infants admitted to the NICU receive empirical antibiotics
- Use of prolonged courses (≥ 5 days) of empirical antibiotics in preterm infants associated with:
  - necrotizing enterocolitis, death, late-onset infection
- Proportion exposed to prolonged courses
  - 27-85% in NICHD Neonatal Research Network

Cotten *Pediatrics* 2009

Antibiotic Therapy

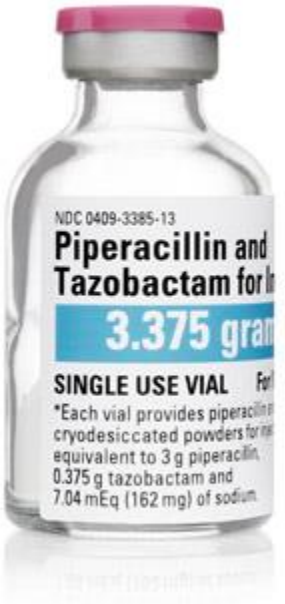
- Clinician has to weigh consequences
  - Short-term – 24 hour mortality
  - Intermediate-term – school age neurodevelopment
  - Long-term – development of resistance and NICU public health

Phase I Trials: Pediatric Surprises

Drug	Preferred adult dosing (mg/kg/day)	Pediatric or infant dosing (mg/kg/day)	Factor Difference
Ampicillin	30–50	50	-
Clindamycin	**10**	**5**	**0.5x**
Piperacillin	**250–340**	**150–480**	**0.6-1.4x**
Metronidazole	**30**	**15**	**0.5x**
Fluconazole	**3–6**	**12**	**2-4x**
Micafungin	**3**	**10–15**	**3-5x**

Piperacillin-Tazobactam

- Piperacillin
  - semisynthetic derivative of ampicillin with enhanced activity against resistant Gram-negative bacteria.
- FDA approved ≥ 2 months
  - Appendicitis and peritonitis



Rahman, PIDJ, 2008.

Piperacillin-Tazobactam Study Design

- NIH sponsored study
- 4 center, 32 infant, open-label, PK, and safety study
- Inclusion Criteria
  - < 61 days of age

    AND ONE OF THE FOLLOWING
  - Suspected systemic infection
  - Receiving piperacillin-tazobactam as standard of care

Piperacillin Model Development

- Population PK analysis and Monte Carlo simulations were performed in NONMEM v. 7.2

- **Model development**
  - One and two compartment models were tested
  - Covariate analysis was performed using a forward inclusion (p=0.05) and backward elimination (p=0.001) approach
  - Model development was guided by goodness of fit plots, plausibility of parameter estimates, VPCs, and parameter precision

$$V\ (L) = 0.4 * Wt$$

$$CL\ (L/h) = 0.08 * Wt * (PMA / 32)^{1.8} * \exp(\eta_{Cl})$$

Demographics

	N=32
Birth weight (kg)	1.43 (0.5, 3.9)
Gestational age (weeks)	30 (23, 40)
Postnatal age (days)	8 (1, 60)
Postmenstrual age (weeks)	32 (25, 48)
Male (%)	63
Serum creatinine (mg/dL)	0.8 (0.3, 2.0)

Values are median (range) for continuous variables and percent for categorical

Cohen-Wolkowiez, AAC. 2014

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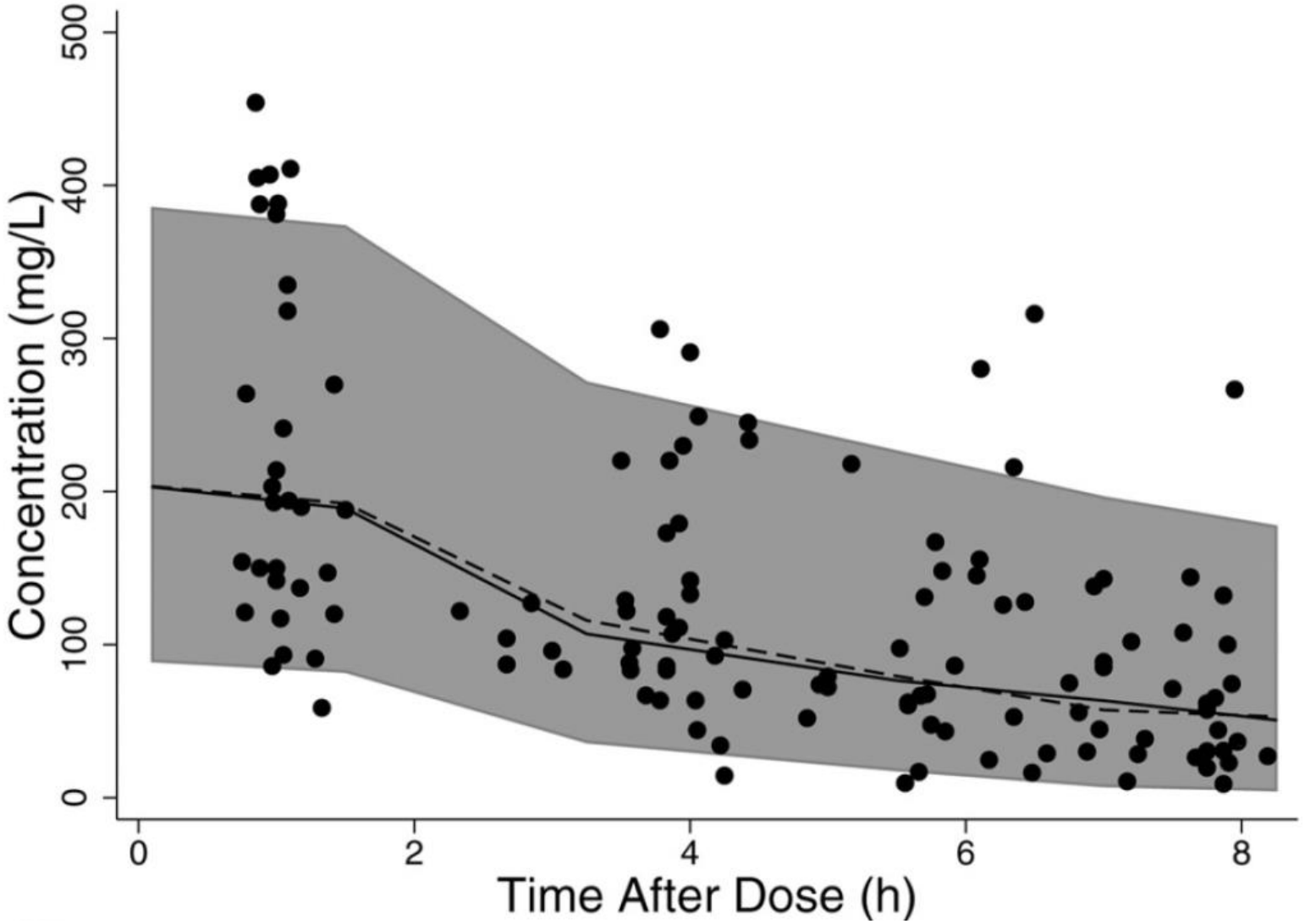
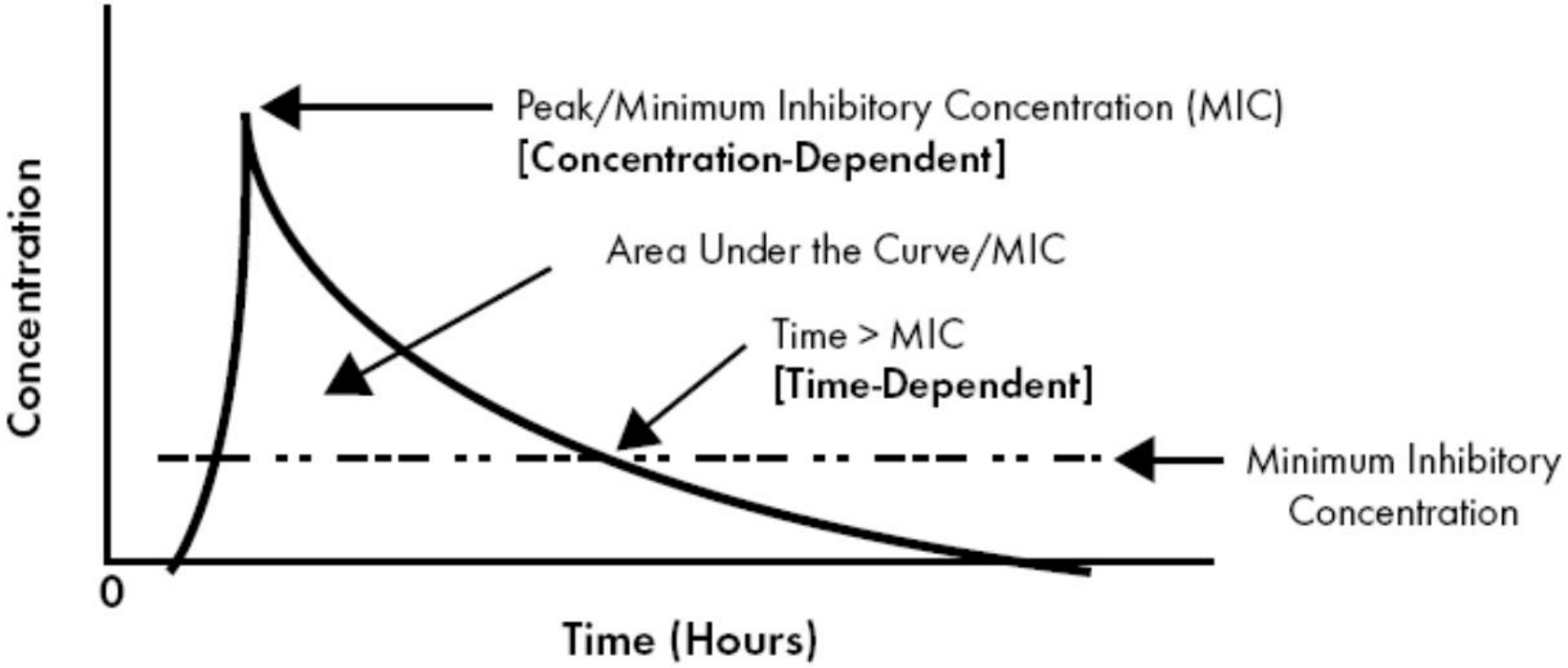
Parameter Estimates

Parameter	Point estimate	% RSE	Bootstrap CI		
			2.5%	Median	97.5%
Fixed Effects					
V (L/kg)	0.4	9.6	0.4	0.4	0.5
CL (L/h/kg)	0.08	7.9	0.07	0.08	0.09
Exponent for PMA on CL	1.8	33.6	0.7	1.8	3.0
Random Effects					
CL interindividual var (CV%)	37.1	27.5	24.5	35.8	48.2
Residual error - prop (CV%)	32.7	9.9	23.1	31.4	37.8
Residual error - add (mg/L)	6.9	42.6	2.2	7.4	17.8

Visual Predictive Check



Surrogate PD Target



T>MIC for 75% of the dosing interval

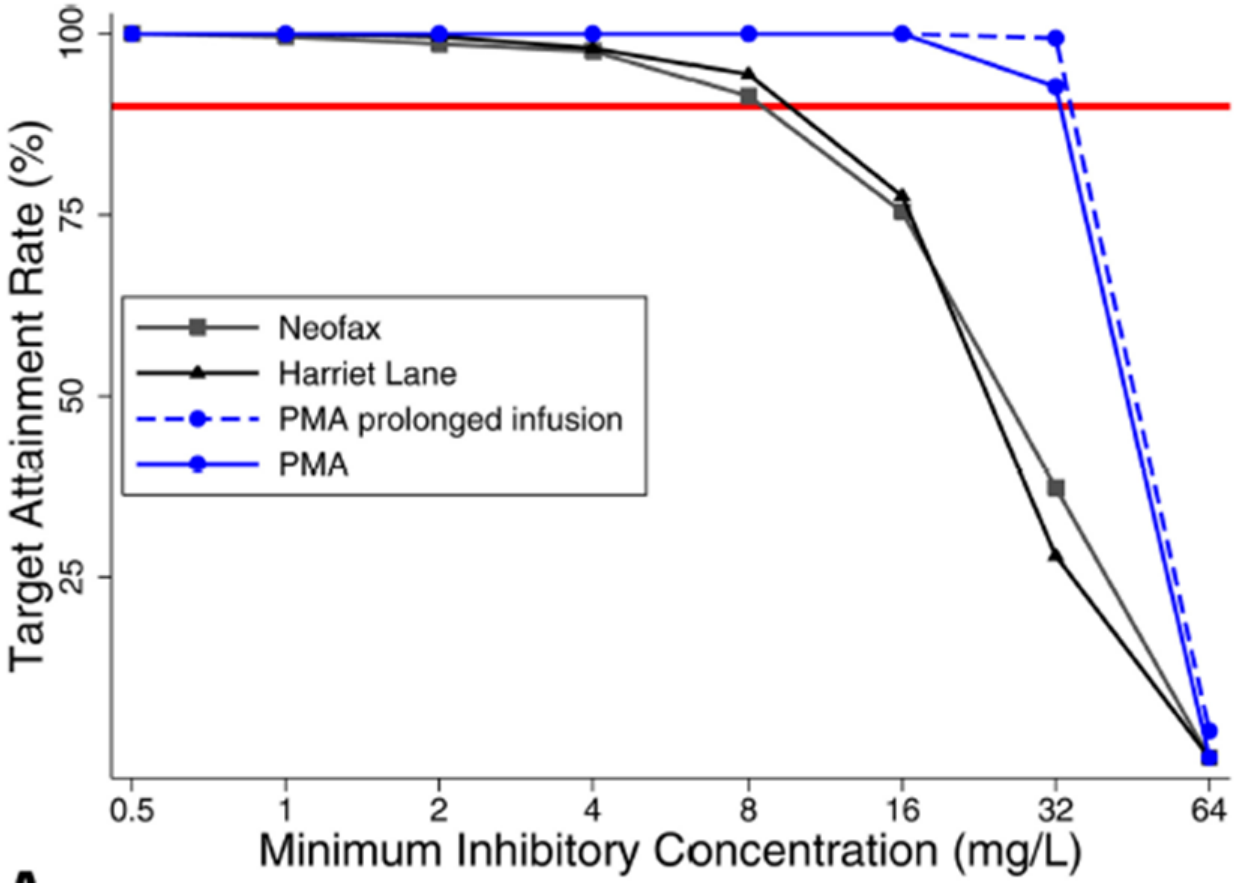
Pseudomonas aeruginosa MIC 16-32 mg/L

Dosing

PMA (weeks)	Maintenance dose (mg/kg)	Dosing interval (hours)
<30	100	8
30-35	80	6
36-49	80	4

Cohen-Wolkowiez, PIDJ 2013

PMA-based Regimen Outperformed Standard Dosing



Cohen-Wolkowiez, PIDJ 2013

Conclusions

- Piperacillin-tazobactam clearance increases with increasing body weight and PMA
- Target concentrations were obtained with a PMA dosing strategy
- A prolonged infusion does not offer benefit over short infusion (0.5 hours) in preterm infants

Future Directions

Establish safety

- SCAMP study
  - Safety of Antimicrobials in Infants with Complicated Intra-Abdominal infections
  - N=350
  - Ampicillin, clindamycin, metronidazole, pip-tazo

Label changes

Case Study #2

FUNGAL INFECTION IN CHILDREN ON ECMO

Extracorporeal Membrane Oxygenation (ECMO)

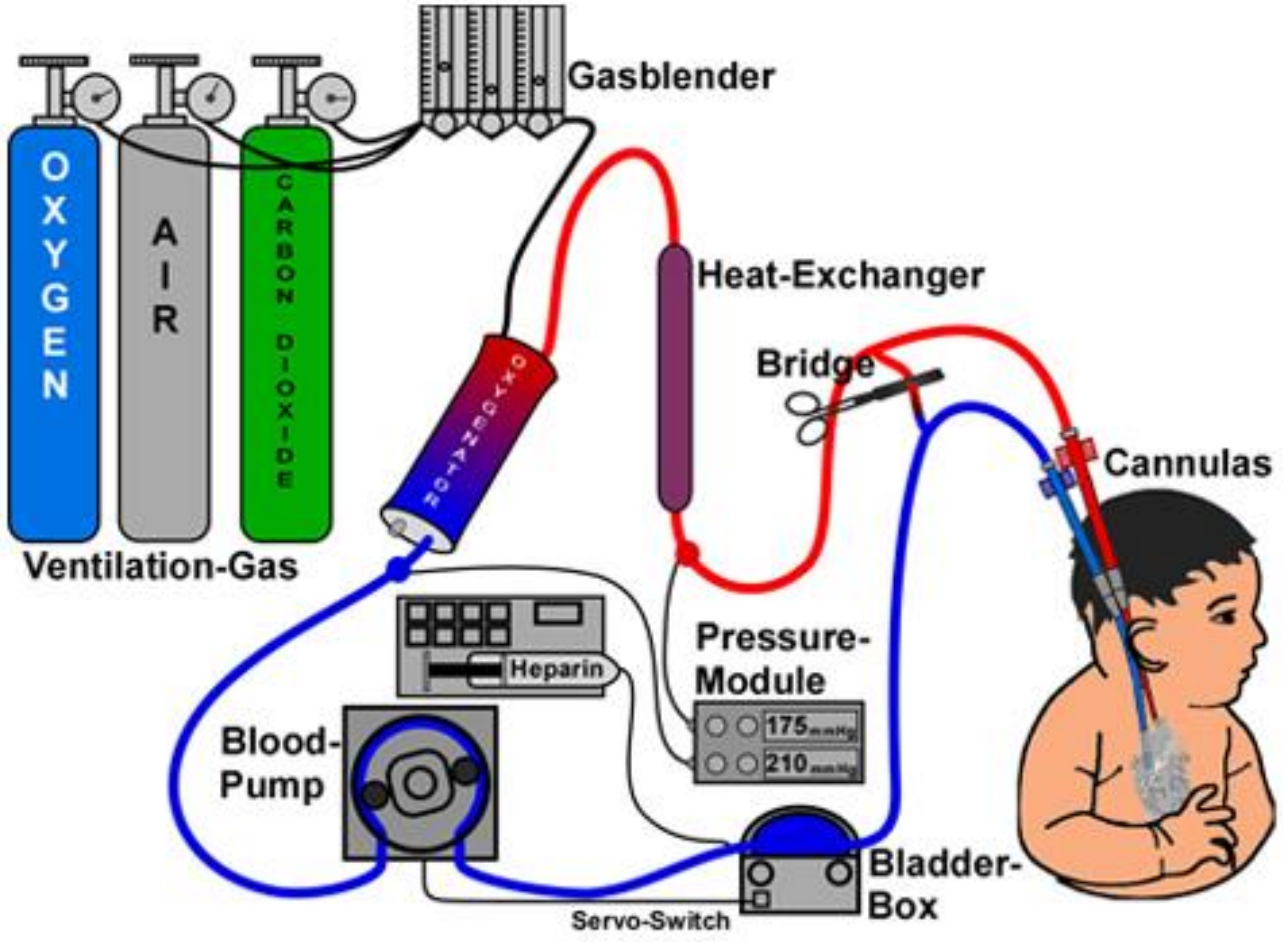
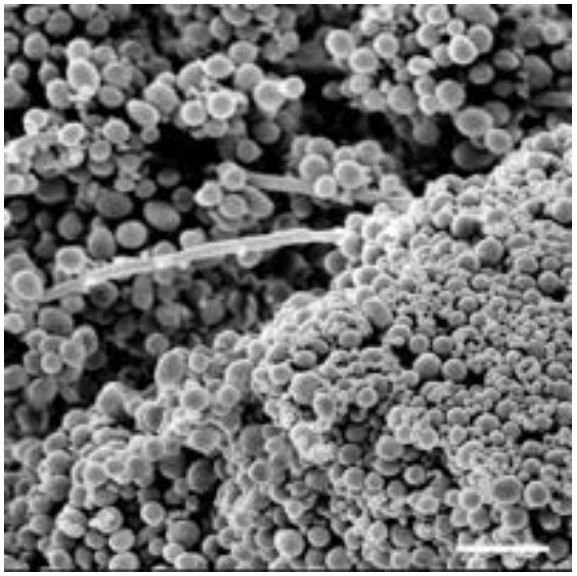


Illustration by Jürgen Schaub, Creative Commons BY-SA

Infections on ECMO

- Children supported with ECMO are at high risk for infections



- *Candida* species are a common pathogen in this population
- Invasive candidiasis is treated with antifungal drugs and removal of intravascular catheters
- Treatment or prophylaxis on ECMO relies on optimal dosing

Image from Al-Fattani *AAC* 2004

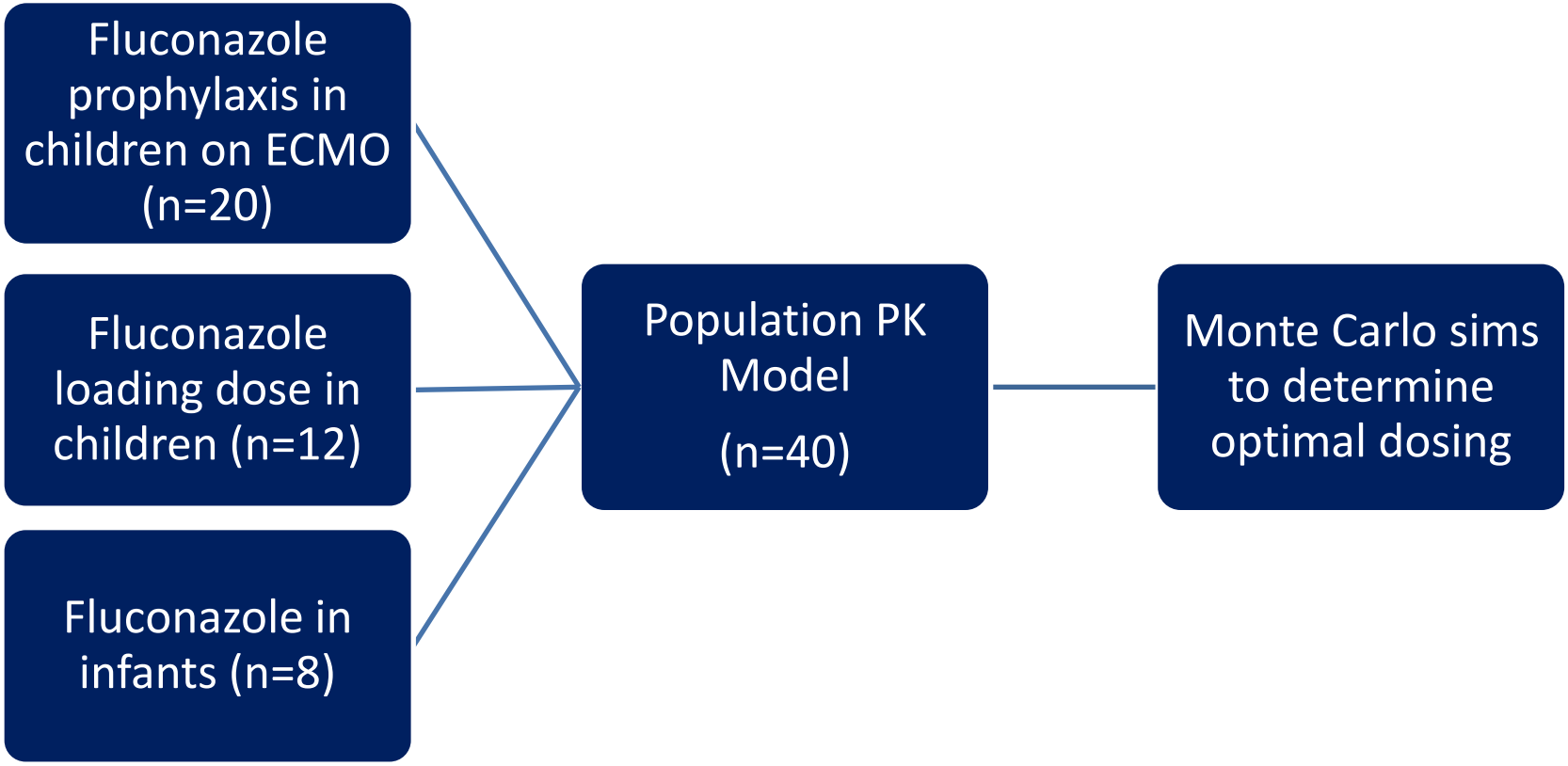
ECMO Can Alter the PK of Drugs

- ECMO increases the volume of distribution (V) of some drugs (e.g., vancomycin, fluconazole)
  - Addition of a large volume of blood to prime the circuit
  - Adsorption of drug by components of the ECMO circuit

- Renal insufficiency on ECMO can decrease clearance (Cl)

Mulla *Br J Clin Pharmacol* 2005
Watt *Pediatr Infect Dis J* 2012

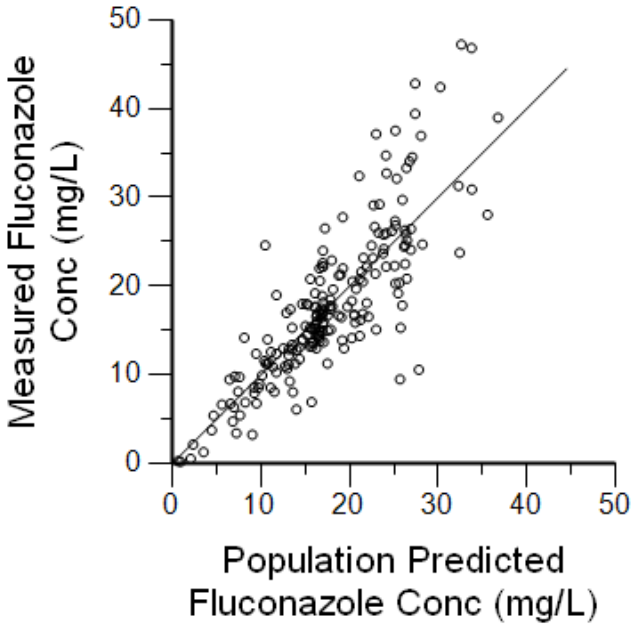
Population PK of Fluconazole in Children on ECMO

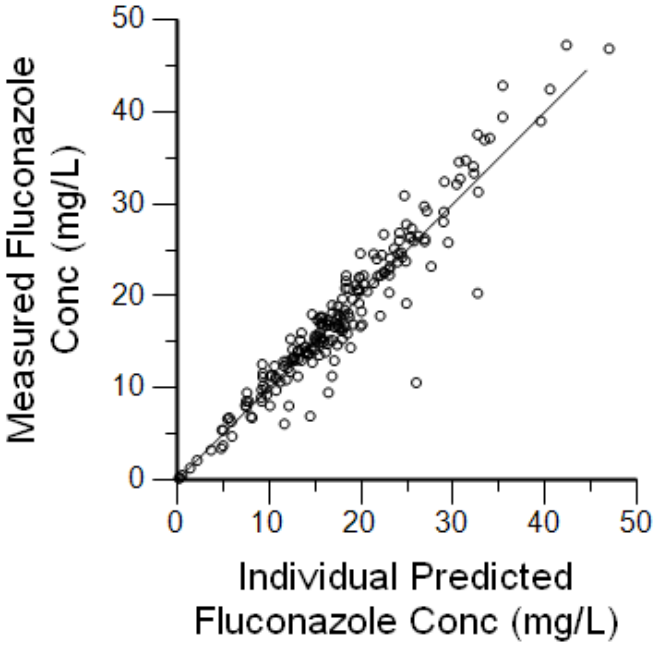


Population PK Final Model

$$CL\ (L/h) = 0.017 * Wt * (creatinine / 0.6)^{-0.44} * \exp(\eta_{Cl})$$

$$V\ (L) = 0.9 * Wt * 1.4^{ECMO} * \exp(\eta_{V}) \qquad ECMO=0/1$$





Watt *Under journal review*

Bayesian Estimates of PK

	ECMO	no ECMO
V (L/kg)	1.4	0.9
	(1.2, 1.6)	(0.8, 1.1)
CL (L/h/kg)	0.018	0.015
	(0.016, 0.020)	(0.011, 0.018)

Values are median (range)

Parameter Estimates

Parameter	Point estimate	% RSE	Bootstrap CI		
			2.5%	Median	97.5%
Fixed Effects					
V (L/kg)	0.9	5.4	0.8	0.9	1.1
CL (L/h/kg)	0.017	5.7	0.016	0.017	0.019
Coefficient for ECMO on V	1.4	7.3	1.2	1.4	1.6
Exponent for SCR on CL	-0.33	9.1	-0.42	-0.33	-0.27
Random Effects					
V interindividual var CV%)	21.8	29.3	14.8	21.0	27.1
CL interindividual var (CV%)	33.0	22.0	24.1	32.1	39.7
Residual error (CV%)	15.8	12.8	13.7	15.8	17.7

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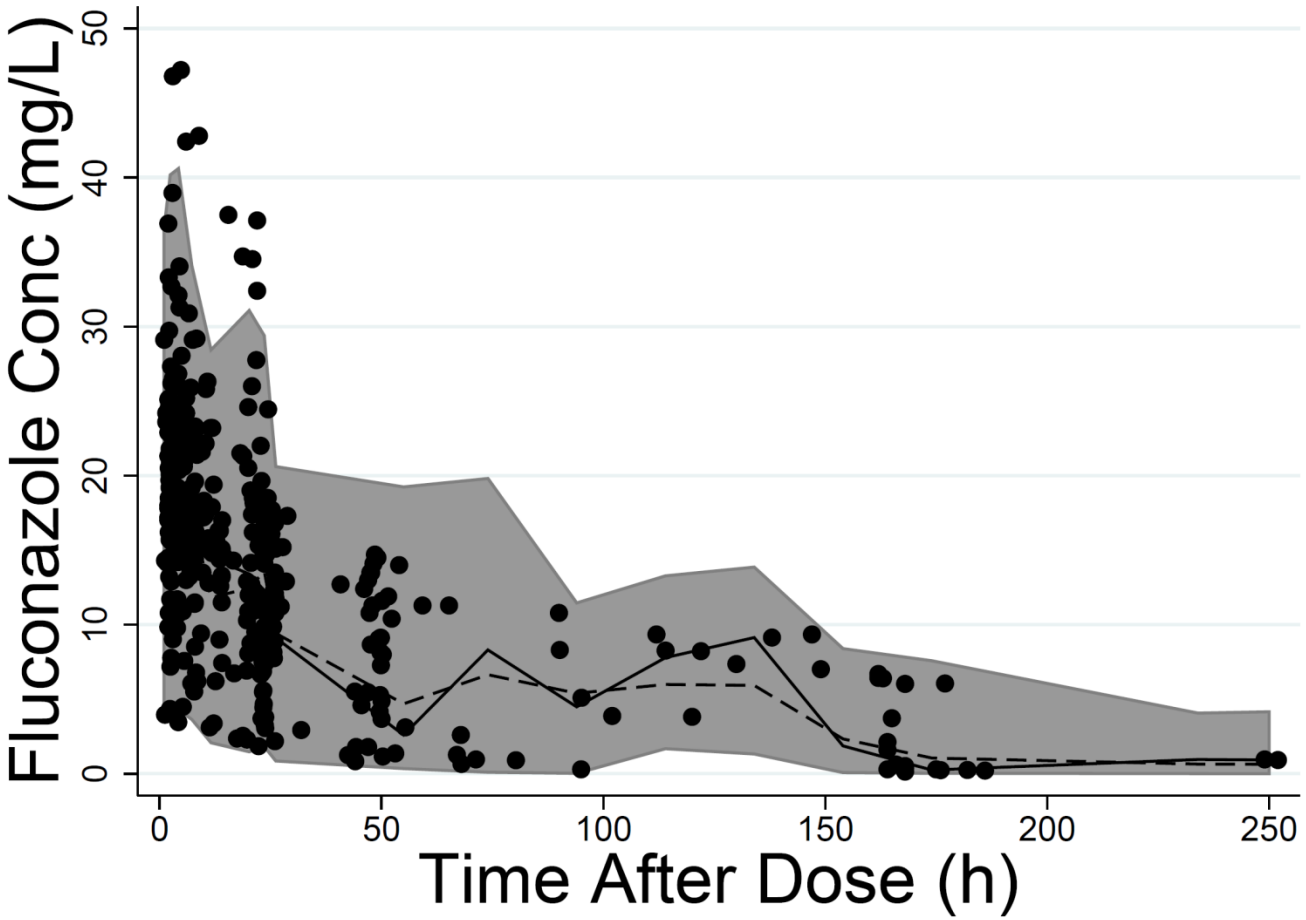
Visual Predictive Check



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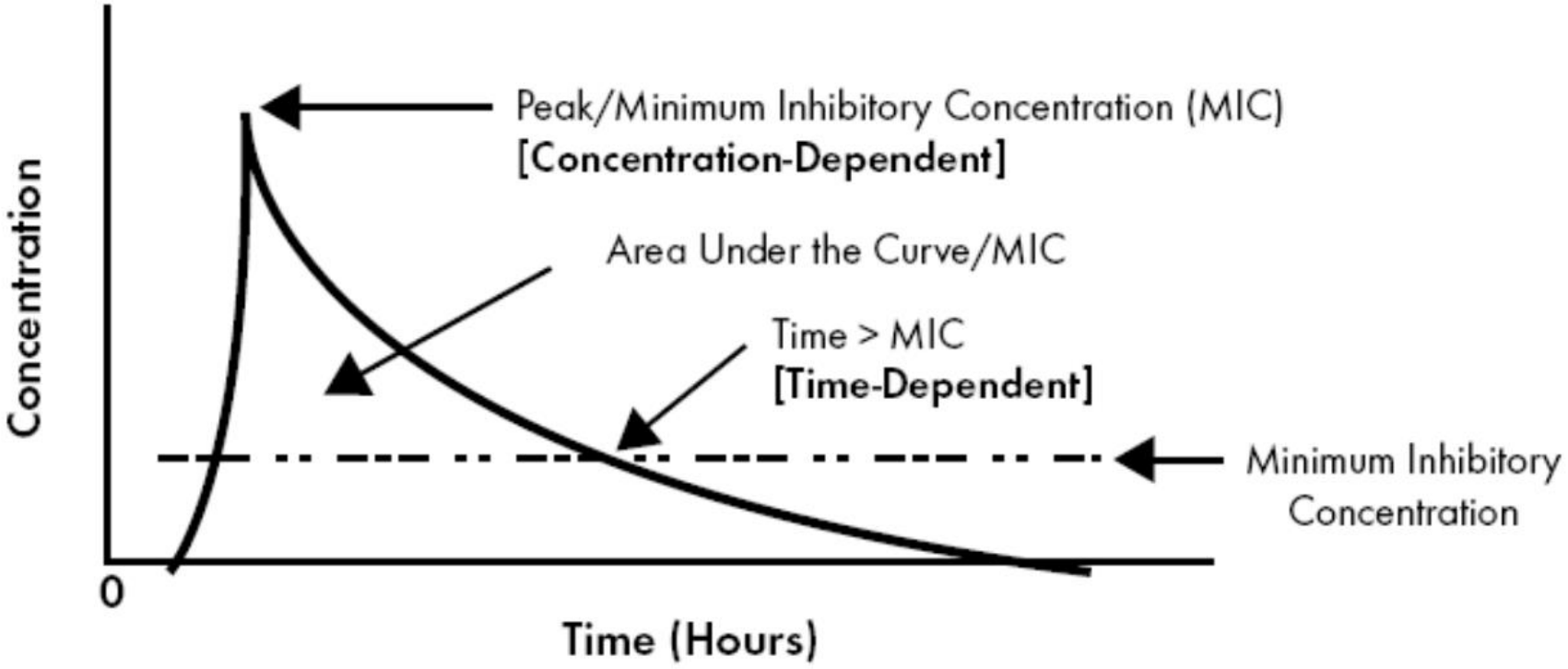
Surrogate PD target for treatment



AUC/MIC >50 (AUC>400 mg*h/L) in first 24h

Median AUC 600-800 mg*h/L at steady state

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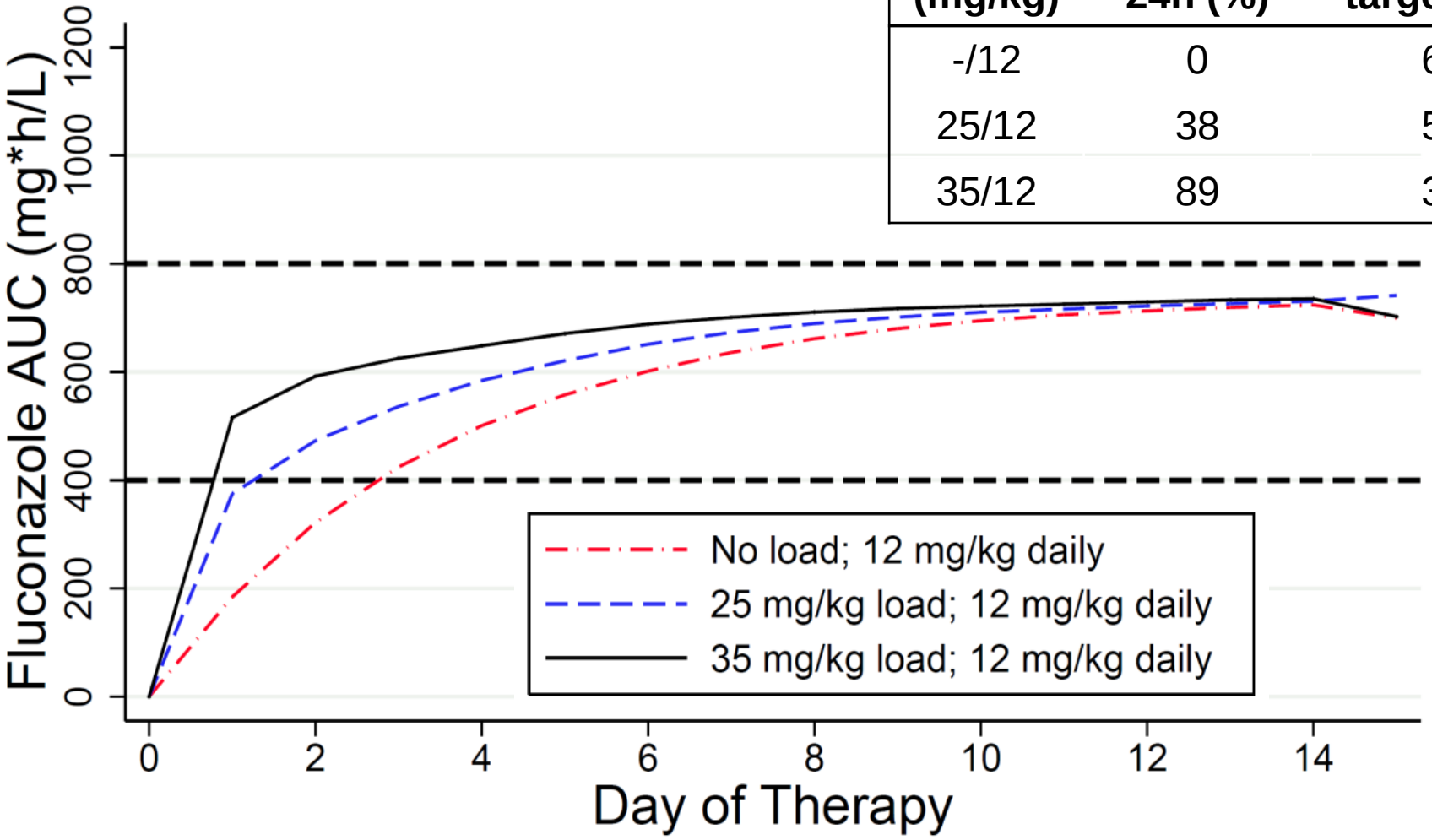
Fluconazole Treatment: Simulated Exposures

LD/MD (mg/kg)	PD Target 24h (%)	Time to SS target (d)
-/12	0	6
25/12	38	5
35/12	89	3



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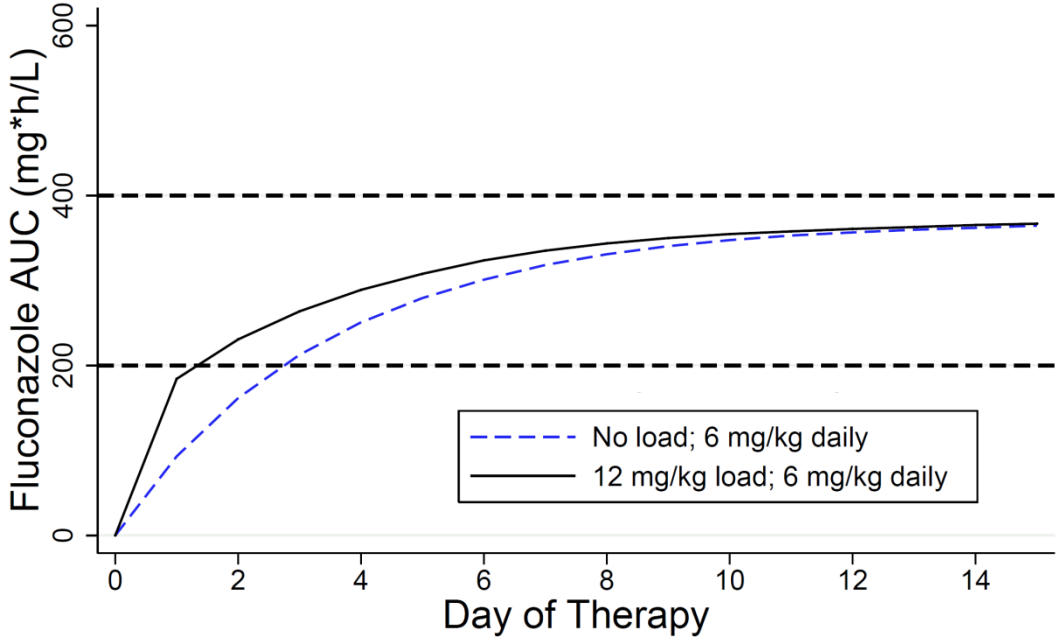
Fluconazole Prophylaxis: Simulated Exposures

Median AUC 200-400 at steady state

T>MIC 4 mg/L for 50% of dosing interval



LD/MD (mg/kg)	PD Target 24h (%)	Time to SS target (d)
-/6	17	4
12/6	99	2

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Next Steps

Use PBPK models to evaluate the impact of physiologic derangements on drug dosing in children on ECMO

- Determine relationship between drug physicochemical properties and interaction with ECMO circuit
- Develop PBPK models of fluconazole and micafungin in children on ECMO
- Evaluate PBPK models with clinical trials

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