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# Clinical Development of Systemic Antifungal Drugs in Pediatrics – Achievements and Challenges

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# Invasive Fungal Diseases in Pediatric Patients

- **Relative to adults, children and adolescents are similarly vulnerable**
- **However, differences exist as to:**
  - **Populations at risk**
  - **Epidemiology**
  - **Usefulness of newer diagnostic tools**
  - **Pharmacology of antifungal agents**

# Pediatric Populations at Risk for Invasive Fungal Diseases

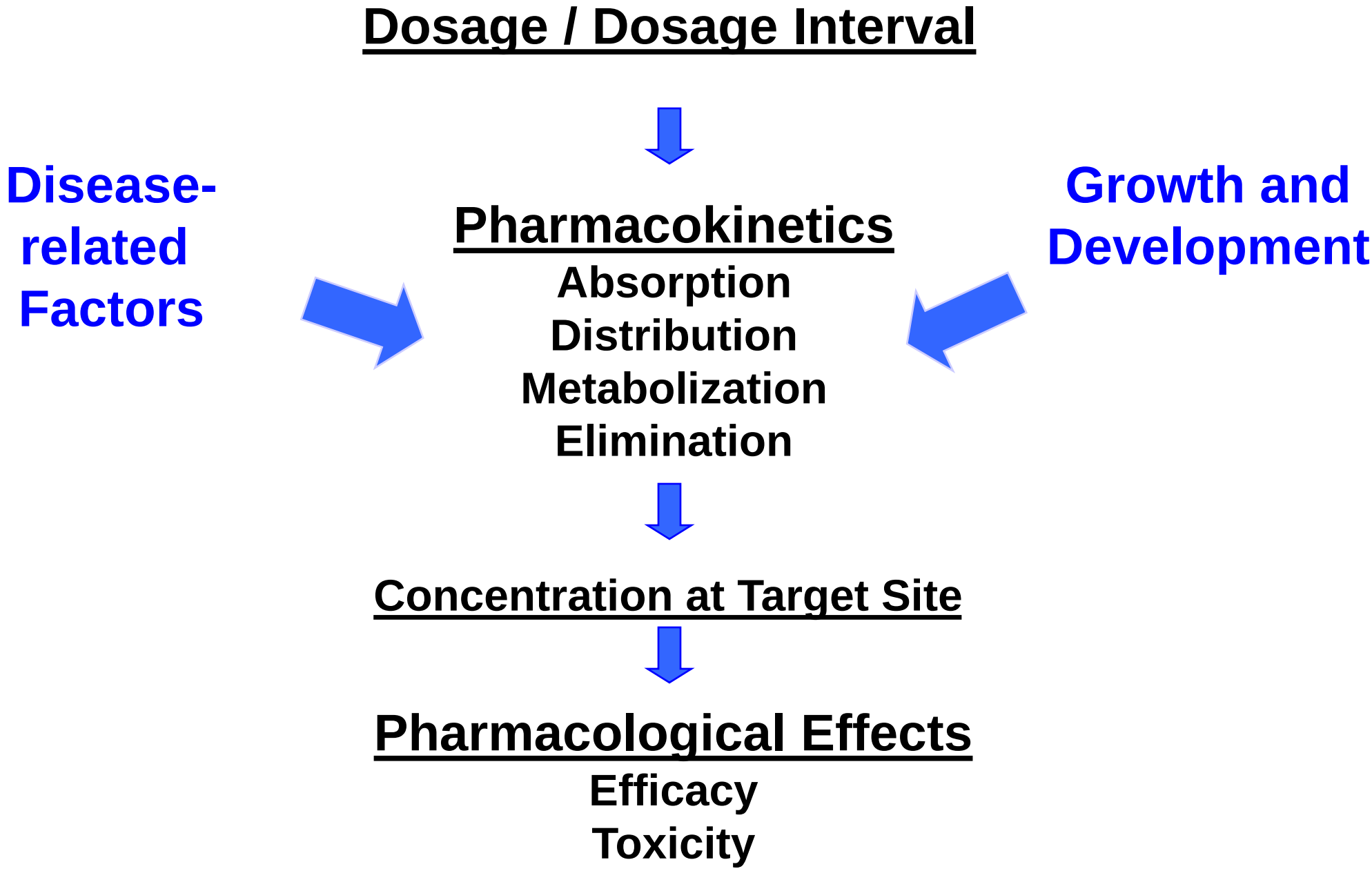
- **AML, ALL during prolonged steroid treatment**
- **Recurrent leukemias**
- **Hematopoietic stem cell transplantation**
  - During granulocytopenia until engraftment
  - During augmented immunosuppression for GVHD

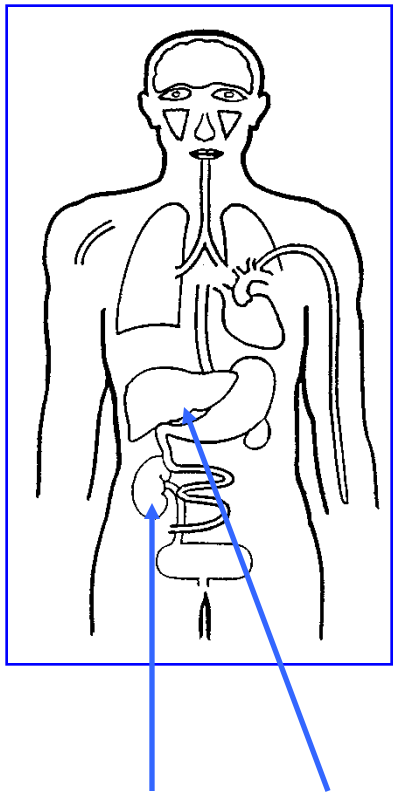
- **Very low and extremely low birth weight infants**
- **Children with life-threatening problems in the ICU**

… chronic granulomatous disease; lung and heart/lung, liver, and pancreas transplantation; metabolic diseases

***Denning 98; Groll et al. 01***

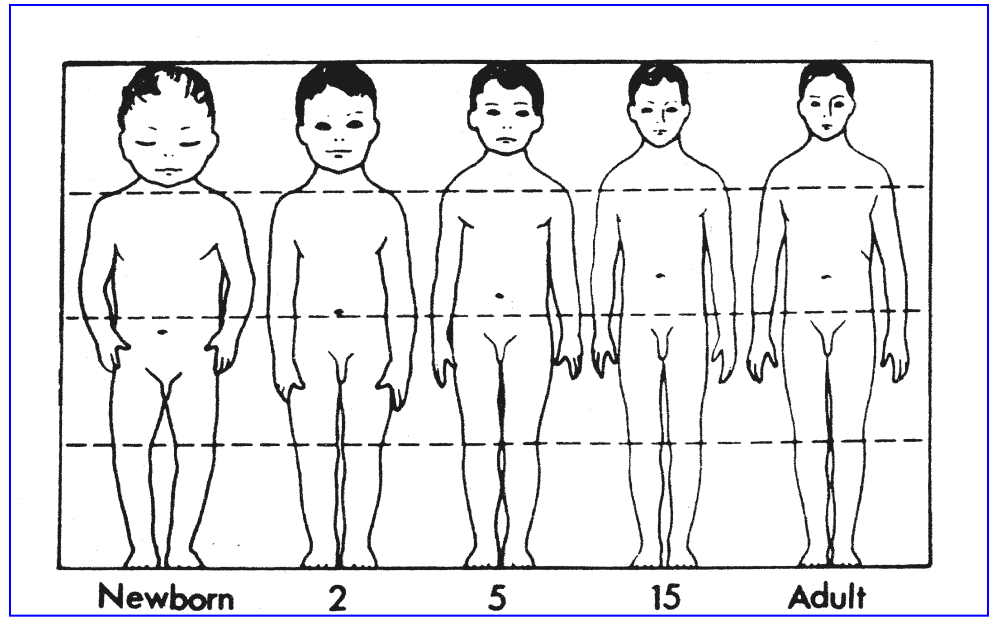
# Antifungal Pharmacology and Pediatric Drug Development


Dosage / Dosage Interval
Disease-related Factors
Pharmacokinetics
Absorption
Distribution
Metabolization
Elimination
Growth and Development
Concentration at Target Site
Pharmacological Effects
Efficacy
Toxicity



Maturation processes
of excretory organs

## Changes in body mass and body composition




**Scaling of dosing regimens based on body weight or body surface area generally inappropriate**

# PK Challenges in Pediatric Patients

- **Distribution: larger Vd**
- **Metabolism/elimination: greater Cl**
- **Oral Bioavailability/Absorption:**
  - **development of a palatable oral solution may be a major challenge to providing oral delivery of an antifungal compound**
- ***Particular challenge: premature neonates***

# EMA Guidance for Pediatric Drug Development

- clinical studies on pharmacokinetics, safety and tolerance are prerequisite
- if underlying conditions, cause of targeted disease and expected response are similar

➡ data generated in adults can be used to support documentation of efficacy

However, the regulations stress the importance of post-marketing surveillance to increase the pediatric database

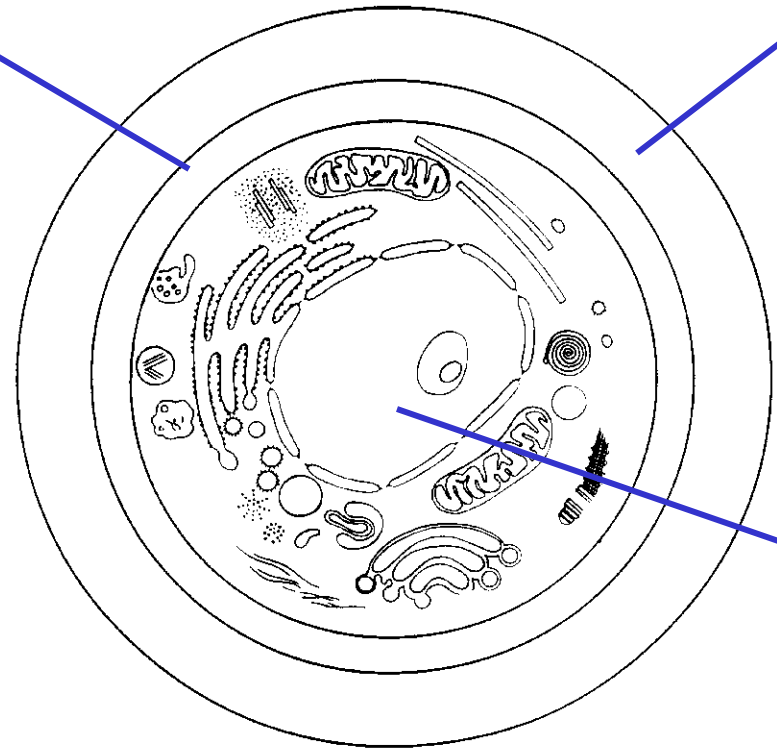
European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION(CPMP/ICH/2711/99).

# Pediatric Antifungal Arsenal

## ***Cell membrane***

- **Polyenes**
  - > DAMB
  - > LAMB
  - > ABLC

- **Triazoles**
  - > Fluconazole
  - > Itraconazole
  - > Voriconazole
  - > Posaconazole



## ***Cell wall***

- **Echinocandins**
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

## ***Nucleic acid synthesis***

- > Flucytosine

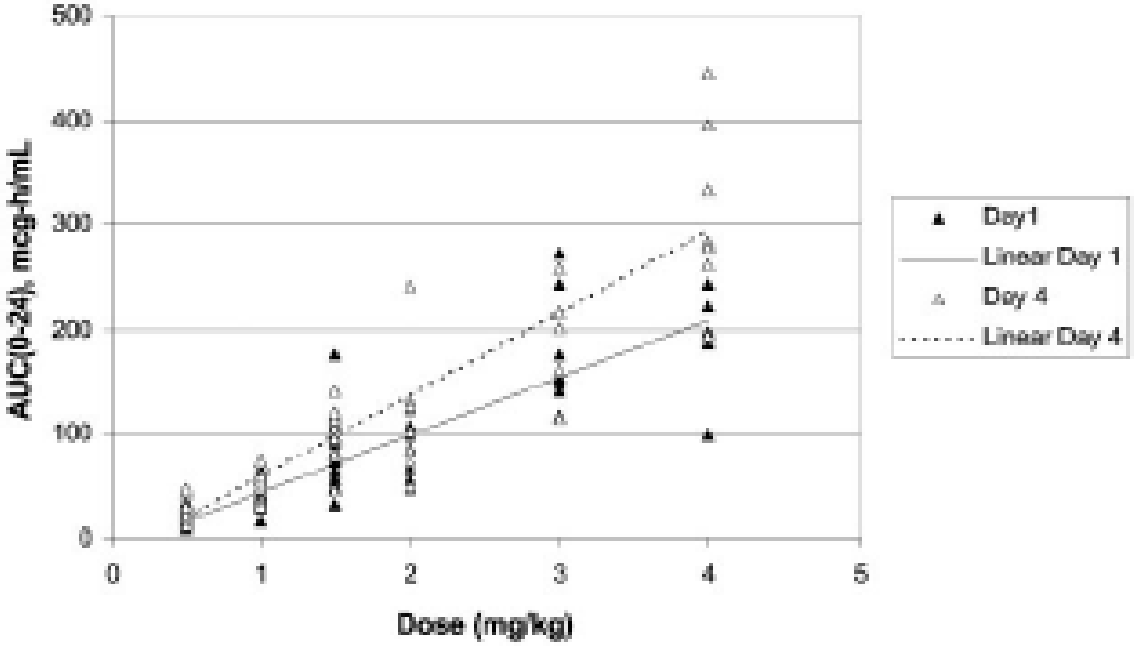
# Micafungin

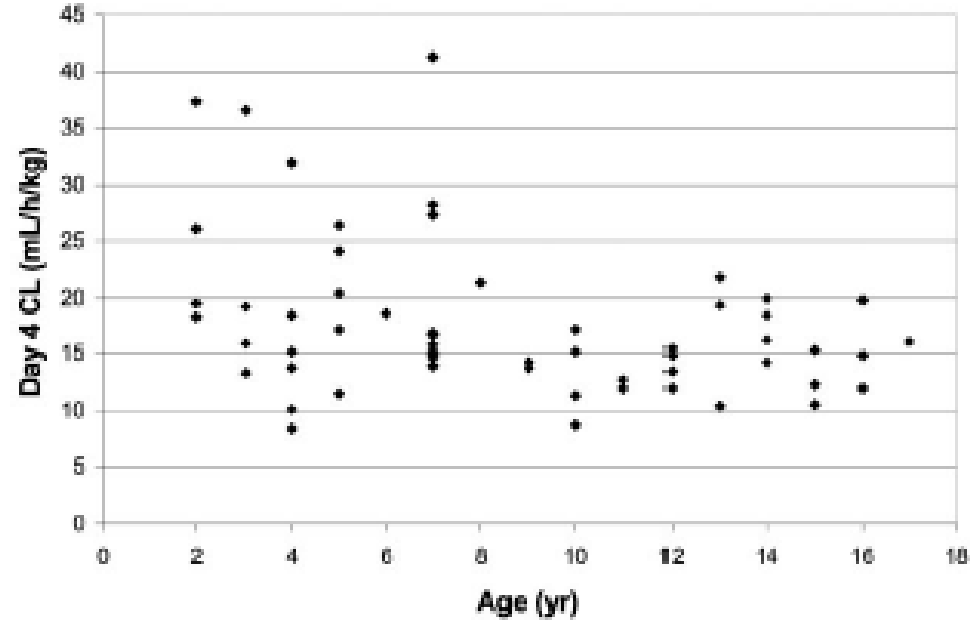
# Micafungin: Pk-Study in in Children 2-17 Years

- **Open-label, sequential, dose-escalation study in 78 patients with neutropenia requiring antifungal therapy**
  - **Six dose levels of MICA (0.5–4.0 mg/kg); 1-hour infusion once daily**
  - **Two age groups (2–12 and 13–17 years)**
  - **Samples for PK analysis taken on d 1 and 4**

***Seibel AAC 05***

# Micafungin:
# Pk in Children 2-17 Years




➡ 1) linear PK; 2) age-dependent weight-normalized CL

***Seibel AAC 05***

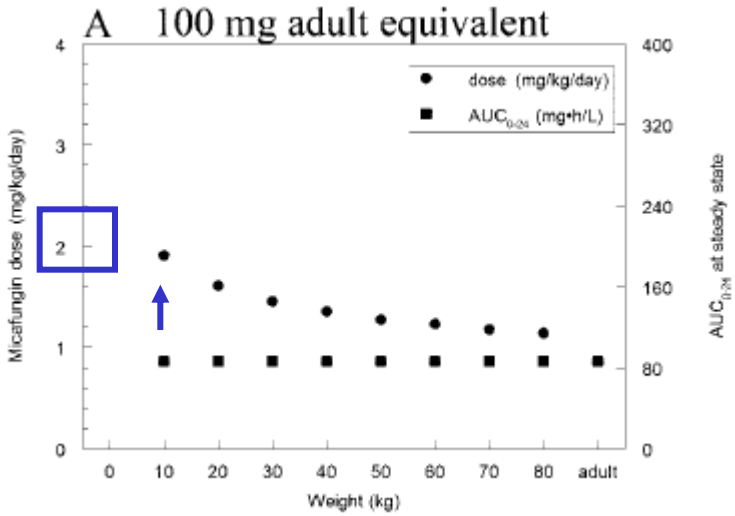
# Micafungin:
# PK Study in Children 2-17 Years

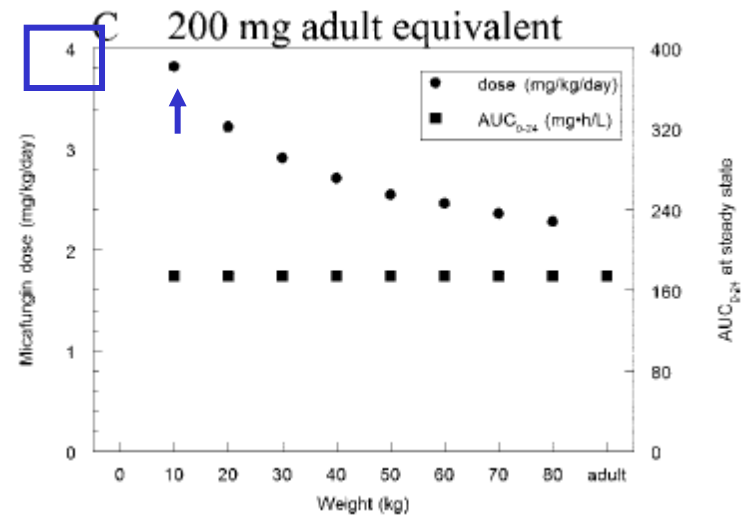
| | Pediatric pts (2-17 yr) | | | Adults | |
|---|---|---|---|---|---|
| **Dosage** | **1 mg/kg** | **2 mg/kg** | **4 mg/kg** | **50 mg** | **100 mg** |
| | | | | | |
| **Cmax (ug/mL)** | 10.8 | 15.3 | 30.3 | 3.6 | 7.1 |
| **AUC 0-24h (ugxh/mL)** | 40.3 | 83.0 | 191.4 | 33.9 | 59.9 |
| **T ½ beta (h)** | 12.5 | 13.2 | 11.6 | 12.5 | 13.0 |
| **CL (L/h/kg)** | 0.021 | 0.020 | 0.017 | 0.017 | 0.018 |
| **VDss [L/kg]** | 0.33 | 0.31 | 0.28 | 0.31 | 0.32 |

***Seibel AAC 05; Hiemenz AAC 05***

# Micafungin: Population Pk in Children 2-17 Years

- **Allometric power model:** ***Clearance in smaller children is higher than predicted on the basis of weight alone, requiring a relative dosage increase to ensure exposure comparable to older children***

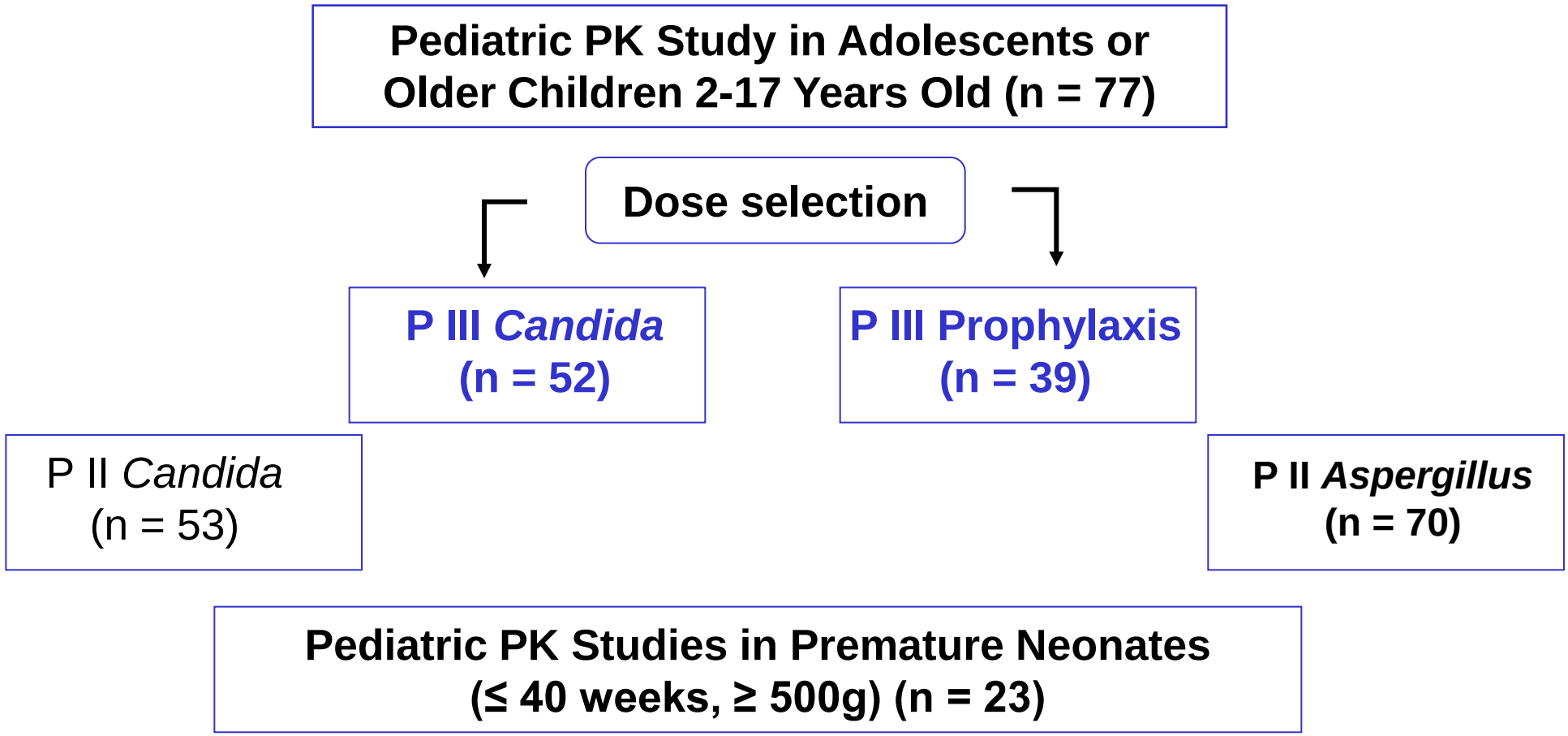



Monte Carlo simulations in 9,999 simulated pts showing micafungin dosages in children 10 to 80 kg required to produce a mean AUC 0-24 equivalent to the AUC0–24 observed in adults receiving 100 mg (A) and 200 mg (C) at s/s

***Hope et al. AAC 07***

# Micafungin Pediatric Program



# Micafungin: Pk-study in Premature Infants

- Phase I, single-dose, multicenter, open-label trial
  - Post-gestational age ≤40 weeks and body weight ≥500 g
  - MICA doses of 0.75, 1.5 and 3.0 mg/kg; single 30-minute infusion
- A total of 23 patients were included; five weighed 500–1000 g, 18 weighed >1000 g
- Micafungin safe and well tolerated
- No serious drug-related AEs

# Micafungin: Pk-study in Premature Infants

| Population | $t_{1/2}$ (h) | $K_e$ (1/h) | $Vd_{ss}$ (L/kg) | Cl (mL/h/kg) |
|---|---|---|---|---|
| Neonates >1000 g (n = 15) | | | | |
| Mean | 8.3 | 0.088 | 0.435 | 38.9 |
| SD | 1.8 | 0.02 | 0.111 | 12.1 |
| 95% CI | 7.4–9.2 | 0.08–0.1 | 0.378–0.491 | 32.8–45.0 |
| Children 2–8 years old (n = 33)[14] | | | | |
| Mean | 11.5 | 0.064 | 0.335 | 22.5 |
| SD | 2.9 | 0.016 | 0.16 | 8.6 |
| 95% CI | 10.5–12.4 | 0.059–0.069 | 0.28–0.39 | 19.6–25.4 |
| Children 9–17 years old (n = 32)[14] | | | | |
| Mean | 13.4 | 0.056 | 0.243 | 15.1 |
| SD | 3.8 | 0.018 | 0.074 | 6.3 |
| 95% CI | 12.1–14.7 | 0.05–0.062 | 0.216–0.271 | 12.87–17.24 |
| Adults (n = 48)[8] | | | | |
| Mean | 13.1 | 0.055 | 0.256 | 14.6 |
| SD | 3.0 | 0.01 | 0.052 | 3.4 |
| 95% CI | 12.2–13.9 | 0.052–0.058 | 0.241–0.271 | 13.6–15.5 |

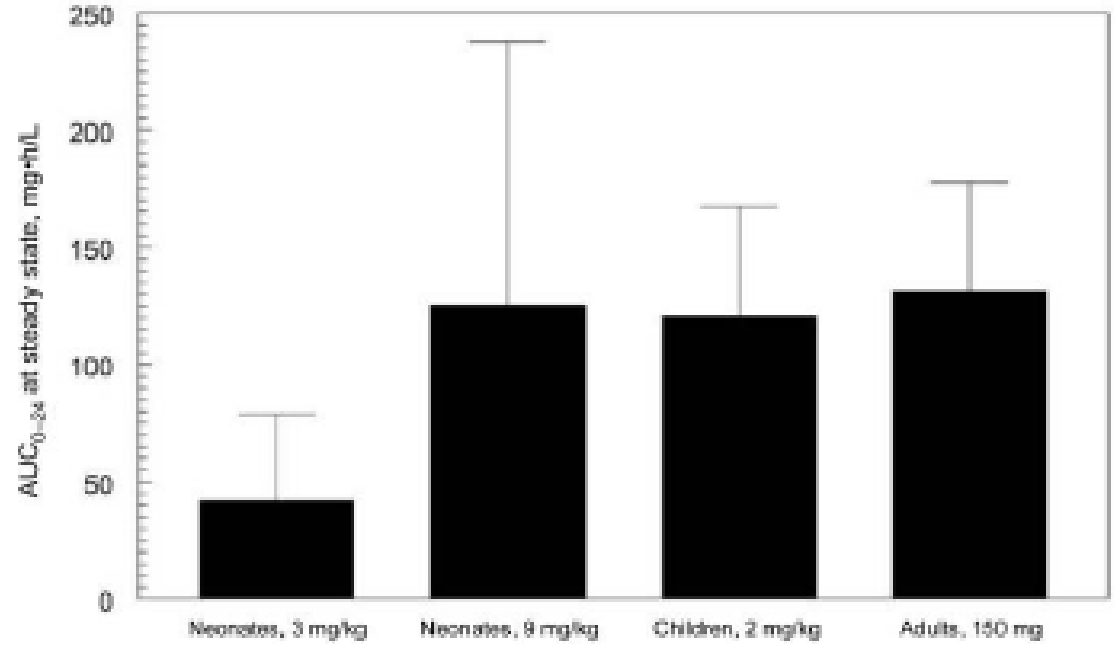
$t_{1/2}$ indicates half-life; $K_e$, elimination rate constant; $Vd_{ss}$, steady-state volume of distribution; Cl, clearance; SD, standard deviation; 95% CI, 95% confidence interval.

*Heresi PIDJ 06*

# Micafungin: Population Pk in Premature Neonates

**Population PK modeling of the neonatal PK data and Monte Carlo Simulation:**

- **a larger neonatal dose is required to produce drug exposure comparable to those predicted on the basis of weight in children and adults**
- **Additional population PK based on open label PK studies with doses of 7- 15 mg/kg/d support the use of 10 mg/kg for neonates**




*age-dependent serum protein binding – 8-fold higher unbound fraction (f(u)) in neonatal serum*

***Hope et al. JID 08; Benjamin et al. AAC 10; Smith et al. PIDJ 09; Hope et al. AAC 10; Yanni et al. BDD 11***

# Micafungin: Antimicrobial Bridging

- **Characterization of pharmacokinetics and pharmaco-dynamics of micafungin in a rabbit model of neonatal hematogenous *Candida* meningoencephalitis**
- **Bridging of the results to neonates by use of population pharmacokinetics and Monte Carlo simulation**

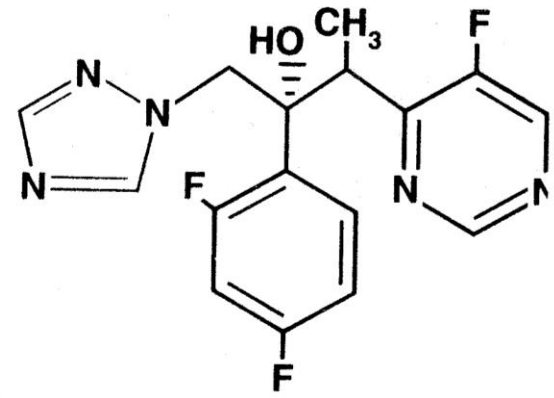
➡ **An experimental dose–microbiological response relationship was apparent in the brain, and near-maximal effect was apparent with doses of 8 mg/kg**

➡ **Monte Carlo simulations revealed that near-maximal antifungal effect was attained at human neonatal doses of 12–15 mg/kg**

***Hope et al. JID 08***

# Voriconazole

# Voriconazole




– ***Non-linear pharmacokinetics***

– ***Complex hepatic metabolization***

- **Substrate/inhibitor of CYP2C9, 3A4, 2C19**
- ***Genetic polymorphisms of CYP2C19***

– ***Number of relevant pharmacokinetic interactions***

– ***Toxicity issues with link to exposure***

# Voriconazole: Pediatric Development

- **Two phase II studies investigating the PK of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg**
- **355 plasma samples in 35 patients**

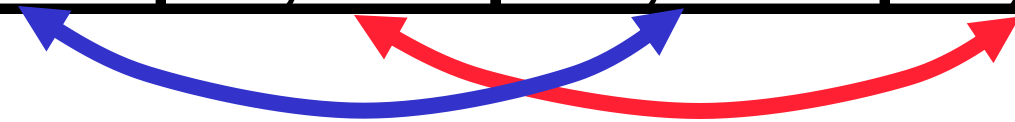
➡ **High interindividual variability**

➡ **faster clearance / linear pharmacokinetics**

***Walsh et al. 02; Walsh et al. 04***

# Voriconazole: Dosage in children 2 to 11 yrs (1)


| Medians | 3mg/kg | | 4mg/kg | |
|---|---|---|---|---|
| | *Paed. | **Adults | *Paed. | **Adults |
| $C_{ave}$ (ng/ml) | 889 | 1155 | 1186 | 3217 |
| AUCτ (ng·h /ml) | 10, 670 | 13, 855 | 14, 227 | 38, 605 |



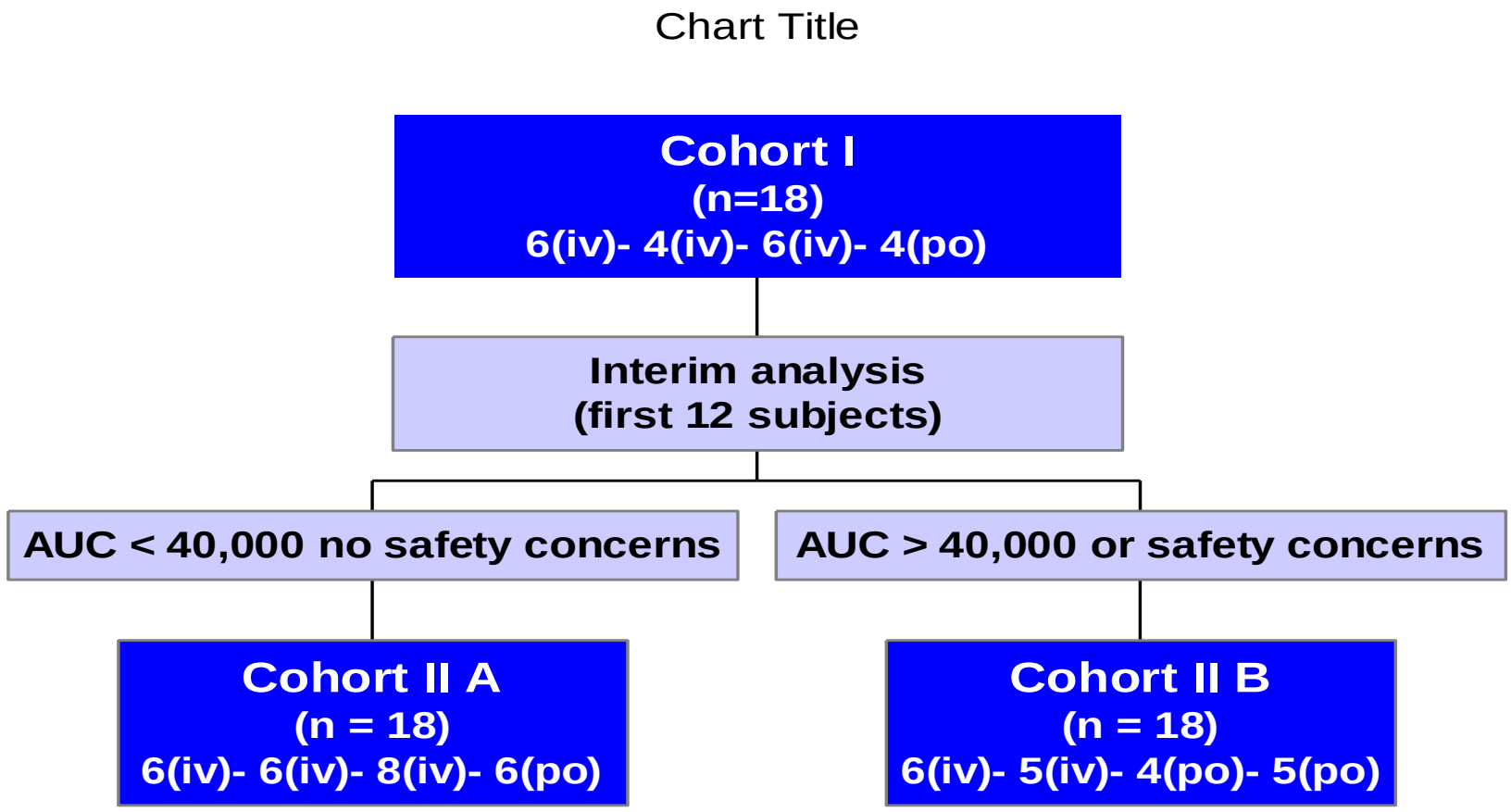
1.3 -fold

2.8 -fold

* 35 subjects from SD and MD PK studies
** 236 healthy volunteers from SD and MD PK studies

*Walsh et al. AAC 04*

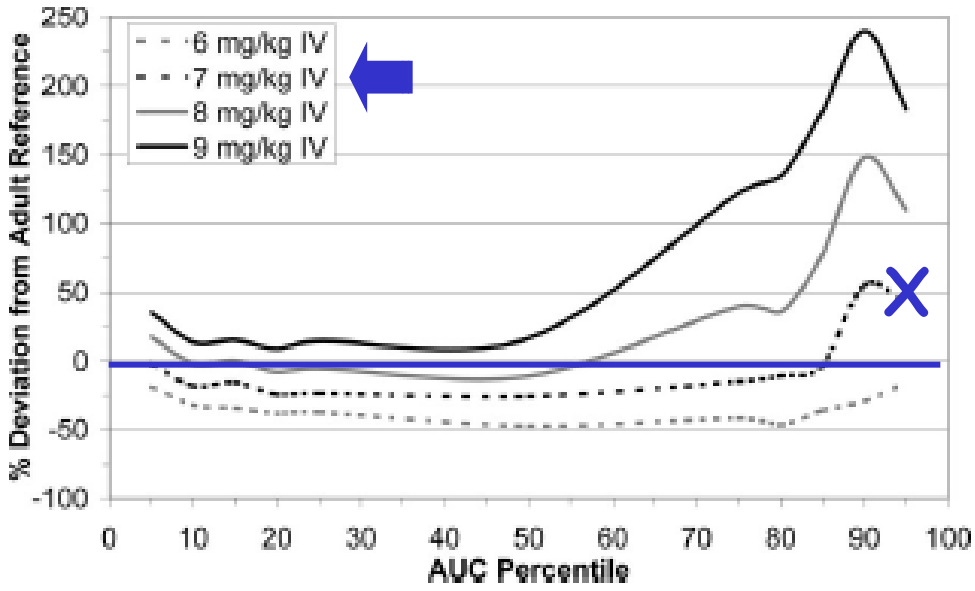
# VCZ in children 2-11 yrs: A 1501037

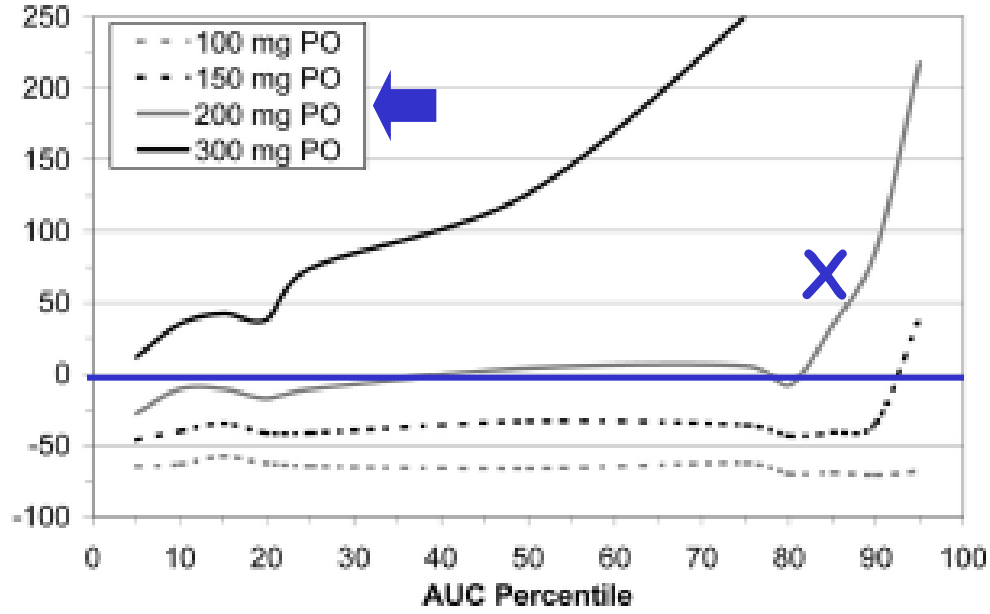



*Walsh et al. AAC 2010*

# VCZ in children 2-11 yrs: A 1501037 Pop-PK Analysis

Percent deviations from the reference adult population AUC distribution (4 mg/kg BID IV; 200 mg BID PO)




*Karlsson et al. AAC 09*

# Voriconazole:
# Initial Pediatric Dose

**Dose recommendation for pediatric patients** ***2 to 11 yrs***

- **2x7 mg/kg IV without loading**
- **2x200 mg PO without loading**

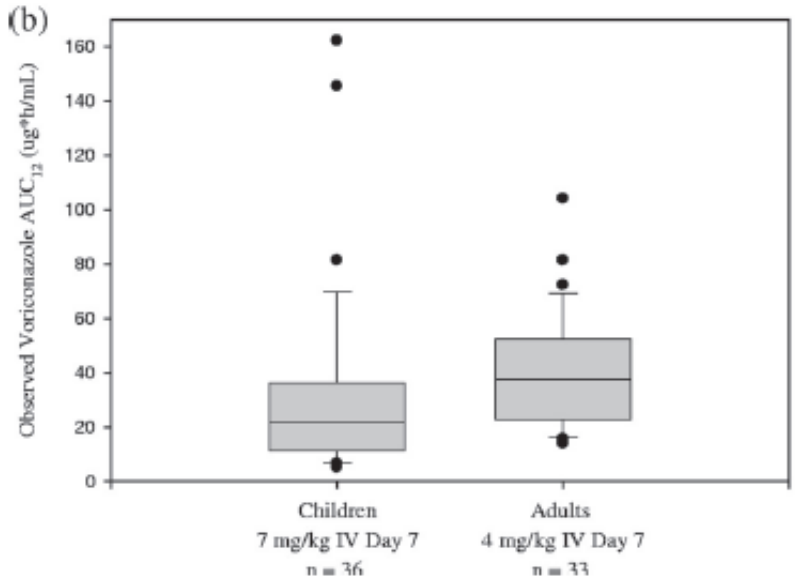
**Dosage for adolescents ≥12 yrs**

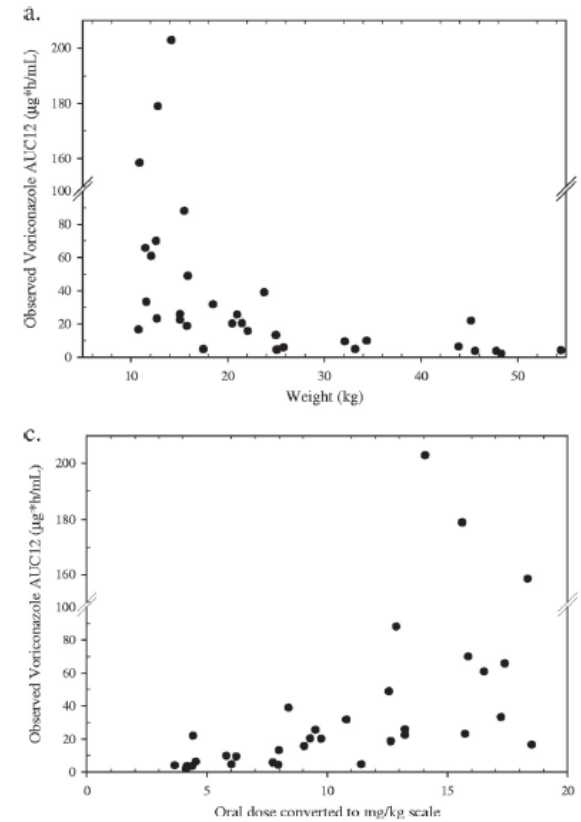
- **2x4 mg/kg IV (2x6 mg day 1)**
- **2x200 mg PO (2x400 mg day 1)**

➡ ***Dosage validation (exposure and safety) in two subsequent pediatric PK trials***

# Voriconazole: Pediatric Dose Finding

40 immunocompromised **children 2 to <12 ,**
7 mg/kg IV BID, switched to 200 mg PO BID



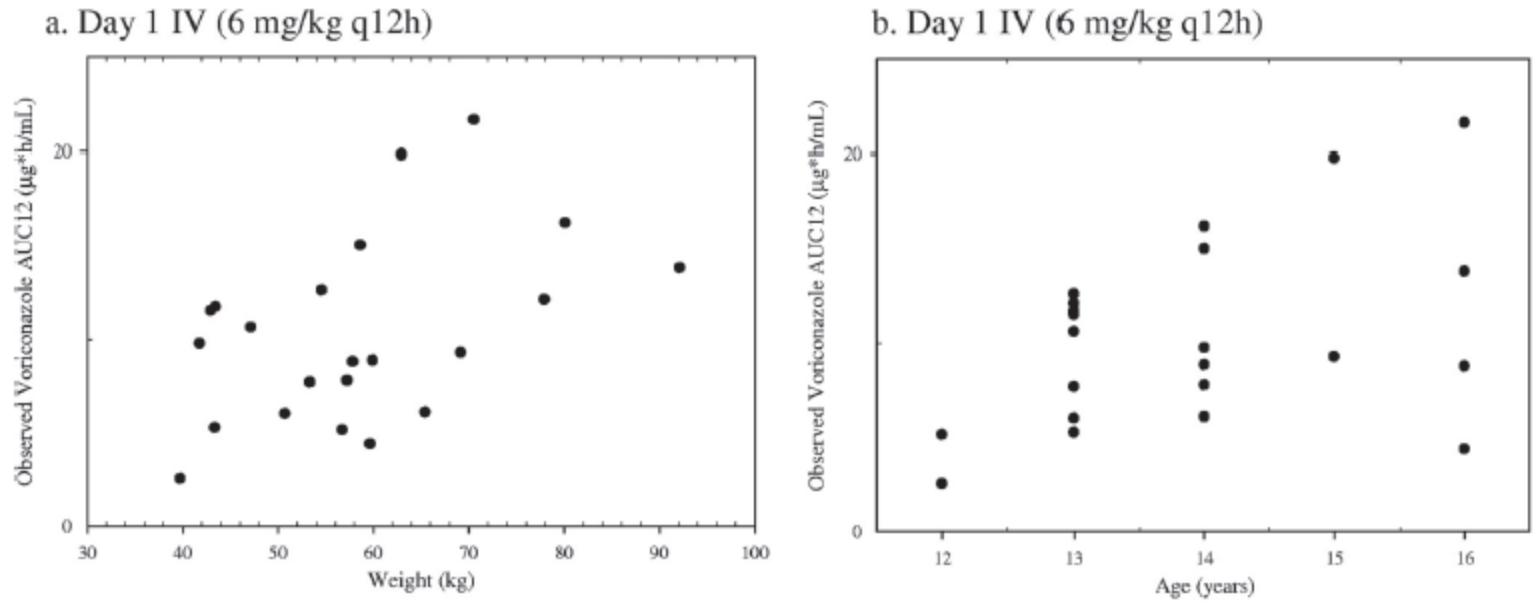




IV doses higher than 7 mg/kg are needed to closely match adult exposures, and a weight-based oral dose may be more appropriate

*Driscoll et al. AAC 2011*

# Voriconazole: Pediatric Dose Finding

26 immunocompromised **adolescents 12 to <17 years**, IV to PO switch, 6 mg/kg IV BID (d1), then 4 mg/kg IV BID, then 300 mg PO




Exposures in adolescents overall comparable to those in adults. ***Young adolescents 12-14 with low body weight may need higher doses***

*Driscoll et al. AAC 2011*

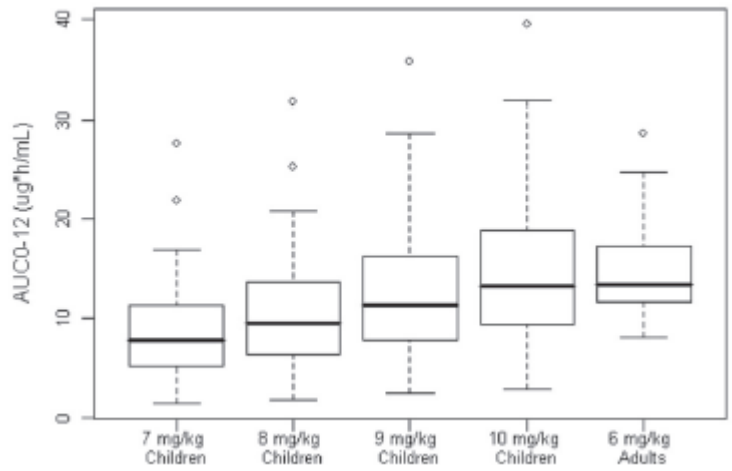
# VCZ in pediatric patients 2-17 years: Population PK Analysis

- **Pooled data from 112 immunocompr. children (2 to <12 yrs),26 immunocompr. adolescents (12 to <17 yrs), and 35 healthy adults**
  - **Different maintenance doses (i.e., 3, 4, 6, 7, and 8 mg/kg BID IV ; 4 mg/kg, 6 mg/kg, and 200 mg BID PO) evaluated in the *children***
  - **The adult dosing regimens (6 mg/kg i.v. BID on day 1, followed by 4 mg/kg BID, and 300 mg orally BID) evaluated in the *adolescents***
- **Two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten) elimination developped**
- **Deterministic simulations based on individual parameter estimates from the final model to derive dosage**

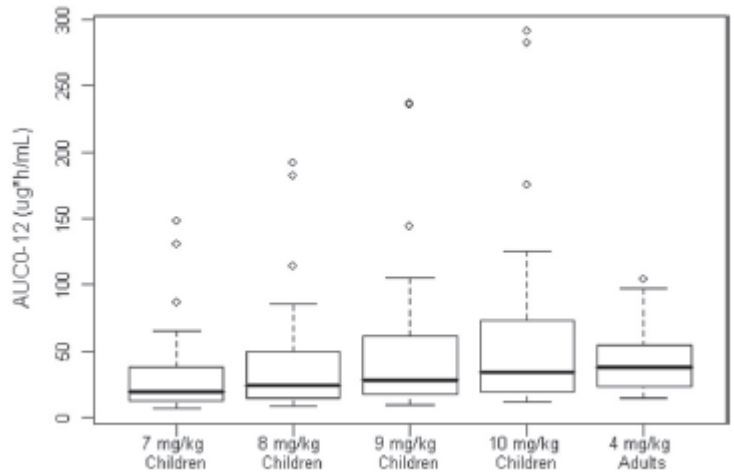
*Friberg et al. AAC 2012*

# VCZ in children 2-11 yrs: Predicted comparative exposures

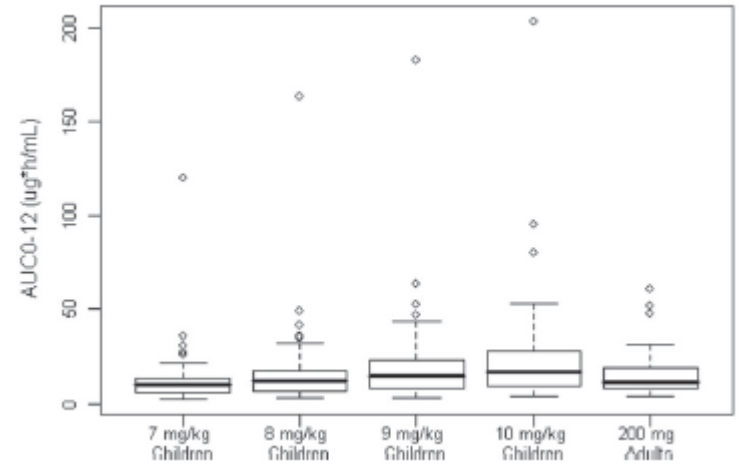
a) Day 1 IV




b) Day 7 IV (Steady State)



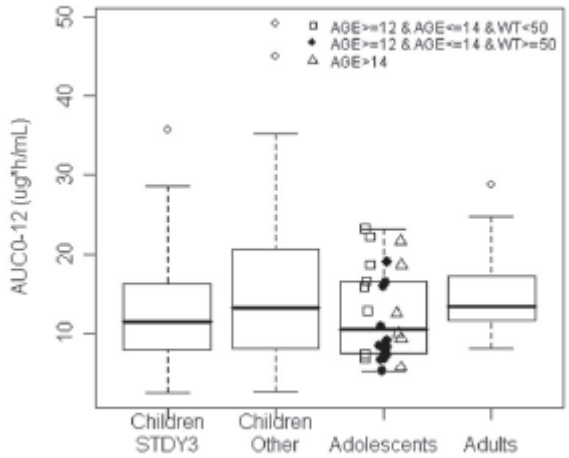

c) Day 7 Oral (Steady State)



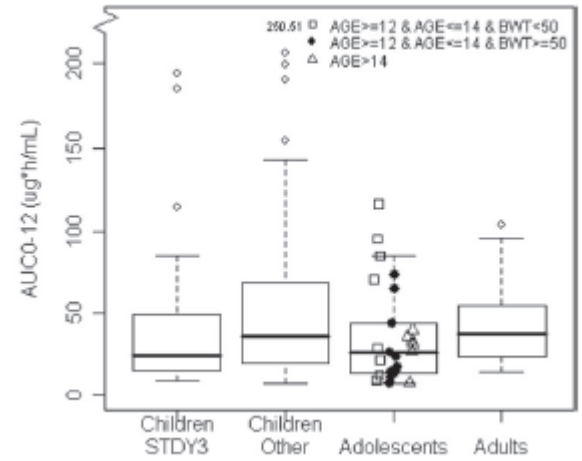

*Friberg et al. AAC 12*

# VCZ in adolescents: Predicted comparative exposures

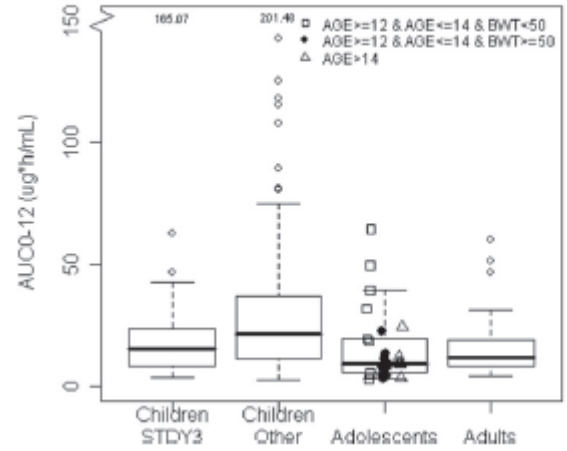
a) Day 1 IV – 9 or 6 mg/kg




b) Day 7 IV (Steady State) – 8 or 4 mg/kg




c) Day 7 Oral (Steady State) – 200 mg or 9 mg/kg (max of 350 mg)




*Friberg et al. AAC 12*

# Voriconazole:
# Current dosage recommendation

***Children 2 to 11 years and***
***adolescents 12-14 years and <50 kg***

- **2x8 mg/kg IV (day 1: 2x9 mg/kg)**
- **2x9 mg/kg PO (max: 2x350mg)**

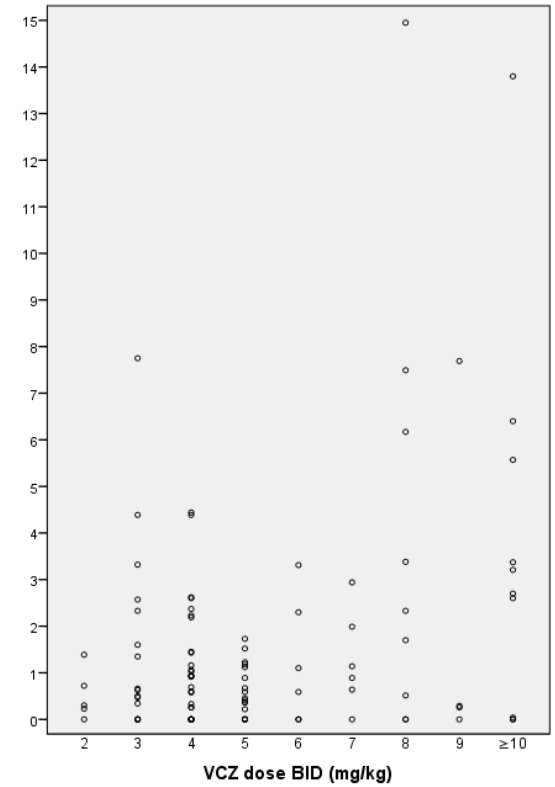
***Adolescents*** **≥12 to 14 years and > 50 kg**
**and those 15 years and beyond:**

- **2x4 mg/kg IV (2x6 mg day 1)**
- **2x200 mg PO (2x400 mg day 1) (adult dose)**

# VCZ TDM in Immunocompromised Pediatric Patients

**74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)**

| Voriconazole trough [mg/L] | No. (%) of samples |
|---|---|
| *< 0.2* | *56 (22.3)* |
| *0.2 – 0.5* | *50 (19.9)* |
| > 0.5 – 1.0 | 39 (15.5) |
| > 1.0 – 2.0 | 36 (14.3) |
| > 2.0 – 5.0 | 50 (19.9) |
| > 5.0 | 20 ( 8.0) |

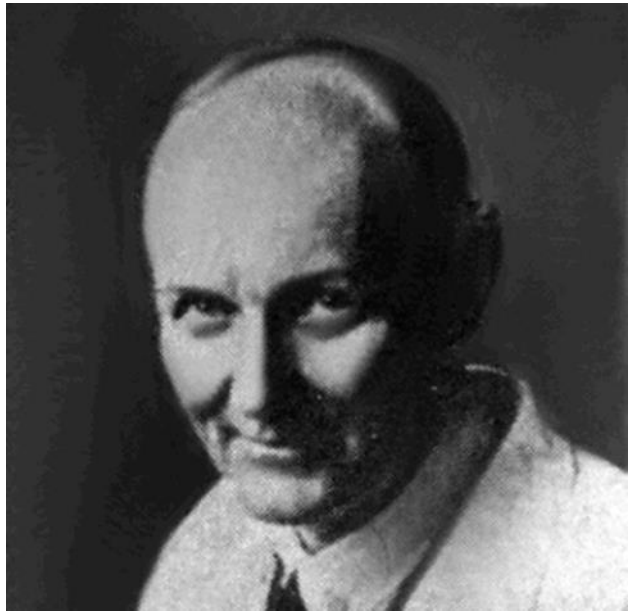



- *no predictable dose-concentration relationships*
- *TDM recommended in guidelines (not in SPC)*

*Pieper et al. AAC 2012*

# Conclusions

# Pharmacological Challenges



- Much has been achieved in the field of pediatric antifungal pharmacology
  - Drug- and age-dependent differences in plasma pharmacokinetics and dosing
  - No apparent differences in safety and tolerance relative to adults
- Increasing number of population PK studies to guide dose finding
  - work well for drugs with robust PK, less well for more complex drugs
- Still very limited number of phase II and IV pediatric validation studies