Antifungal therapy in children

Adilia Warris MD PhD FRCPCH
Clinical Reader
Pediatric Infectious Diseases Specialist

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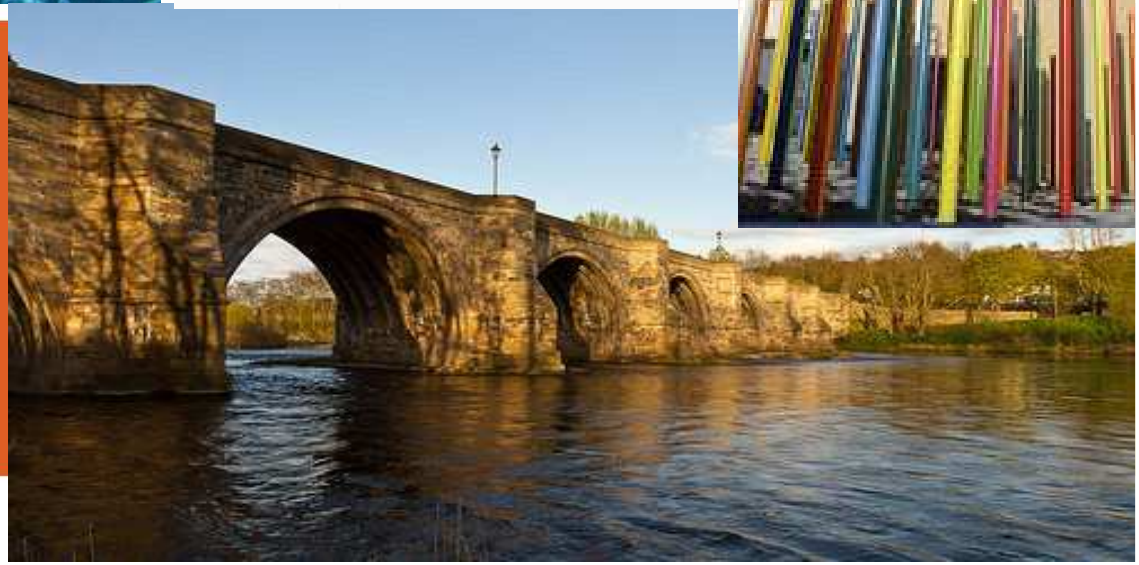

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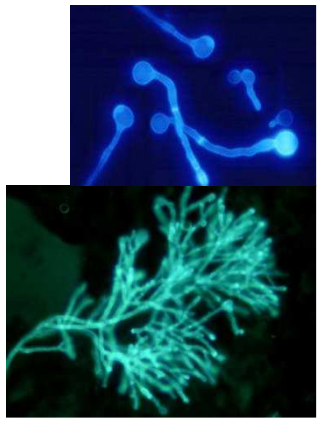
Invasive fungal infections in Pediatrics

- Children and adolescents are similarly vulnerable to IFDs relative to adults, and have similar presentations, distributions and patterns of fungal diseases

- However, differences exist as to
  - underlying conditions and epidemiology
  - usefulness of newer diagnostic tools
  - pharmacology of antifungal agents
  - evidence from interventional phase III studies



Underlying conditions

- Premature neonates
  - Increase <26 wks GA and <750 grams BW
- Primary immunodeficiencies
  - Inborn errors in one component of the immune system
- Paediatric cancer/HSCT patients
  - Treatment, prognosis and comorbidities are different

Fungal epidemiology

- Premature neonates
  - *C. albicans* and *C. parapsilosis*; rarely moulds
- Primary immunodeficiencies (phagocyte disorders)
  - Moulds mainly; *A. fumigatus* and *A. nidulans* in CGD
- Paediatric cancer/HSCT patients
  - *Candida* species, moulds mainly *A. fumigatus*

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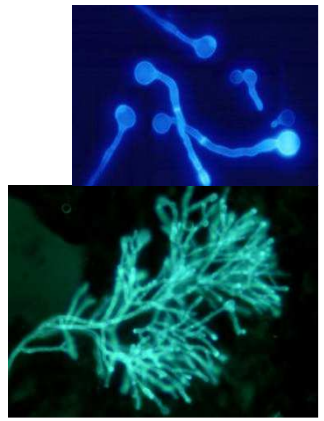
Paediatric Recommendations (as in guidelines) based on:

- Efficacy in phase II and III trials in adults
- Availability / assessment of paediatric
  - quality PK data
  - safety data
  - supportive efficacy data
- regulatory approval needs to be taken in account as well



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Drug Development in Pediatrics - EMA Regulatory Guidance Summary

- Clinical studies on pharmacokinetics, safety and tolerance are a prerequisite
- If underlying conditions, cause of targeted disease and expected response to therapy are similar

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

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). http://www.tga.gov.au/docs/pdf/euguide/ich/271199en.pdf; 2001. Accessed July 26, 2011.

Antifungal	Approved indications	Specific paediatric comments
D-AmB	Treatment IFI	PK not different from adults
L-AmB	Treatment IFI Empirical therapy neutropenia	PK not different from adults
Flucytosine	Treatment (combi) candidiasis	No PK and safety data for children
Fluconazole	Therapy & Prophylaxis *Candida* infections	Optimal dosages uncertain, esp. in neonates
Itraconazole	Therapy superficial *Candida* infections; 2nd line therapy IC/IA; prophylaxis neutropenia	Limited PK data 2 – 17 yrs; no PK data <2 yrs; not licensed < 18yrs in EU
Posaconazole	2nd line therapy IC/IA; therapy OPC, prophylaxis AML/MDS/alloHSCT	Limited PK data, not licensed <18yrs (EU), licensed in US for prophylaxis ≥13 yrs
Voriconazole	Therapy IA and IC in non-neutropenic pts.	High PK variability; not licensed <2 yrs; not licensed for prophylaxis
Caspofungin	Therapy IC; 2nd line therapy IA; empiciral therapy neutropenia	Robust PK and safety data
Micafungin	Therapy OPC, IC; prophylaxis of IC in neutropenia	Robust PK and safety data; optimal dosing neonates to be defined
Anidulafungin	Therapy IC in non-neutropenia	No PK data yet; not licensed <18 yrs

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Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

Neonatal candidiasis

- AmB-d 1 mg/kg/d is recommended
- Fluconazole 12 mg/kg/d is a reasonable alternative
- Echinocandins should be used with caution
- IV catheter removal strongly recommended

CID 2009

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp.

W. W. Hope[1†], E. Castagnola[2†], A. H. Groll[3†], E. Roilides[4†], M. Akova[5], M. C. Arendrup[6], S. Arikan-Akdagli[7], M. Bassetti[8], J. Bille[9], O. A. Cornely[10], M. Cuenca-Estrella[11], J. P. Donnelly[12], J. Garbino[13], R. Herbrecht[14], H. E. Jensen[15], B. J. Kullberg[12], C. Lass-Flörl[16], O. Lortholary[17,18], W. Meersseman[19], G. Petrikkos[20], M. D. Richardson[21], P. E. Verweij[12], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

Aspergillus guideline to follow……..

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly designed randomized controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*Added index:
$_r$: Meta-analysis or systematic review of randomized controlled trials.
$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
$_h$: Comparator group is a historical control.
$_u$: Uncontrolled trial.
$_a$: Published abstract (presented at an international symposium or meeting).

CMI 2012

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Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation

Andreas H Groll, Elio Castagnola, Simone Cesaro, Jean-Hugues Dalle, Dan Engelhard, William Hope, Emmanuel Roilides, Jan Styczynski, Adilia Warris, Thomas Lehrnbecher, on behalf of the Fourth European Conference on Infections in Leukaemia, a joint venture of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS), and the European Leukaemia Net (ELN)

	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
Quality of evidence	
I	Evidence from one or more properly randomised, controlled trial
II	Evidence from one or more well designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from more than one centre); from multiple time series; or from striking results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

According to Kish, for the Infectious Diseases Society of America, 2001.[12]

***Table 1*: Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations**

Lancet Oncology 2014

Fungal epidemiology of candidemia

Species distributions of *Candida* bloodstream isolates stratified by patient age group, SENTRY Antimicrobial Surveillance Program (2008–2009)

Species	% by age (years) (no. of isolates tested)					
	0–19 (256)	20–39 (116)	40–59 (326)	60–79 (436)	80–99 (105)	Total (1239)
C. albicans	50.0	51.7	47.5	52.3	46.7	50.0
C. glabrata	2.0	15.5	21.8	20.9	28.6	17.4
C. parapsilosis	28.5	16.4	15.3	12.6	17.1	17.4
C. tropicalis	12.9	10.4	9.5	9.6	3.8	9.8
C. krusei	0.8	3.5	2.1	1.4	2.9	1.8
Miscellaneous[a]	5.8	2.5	3.8	3.2	0.9	3.6

Pfaller, Diagn Microb Inf Dis 2008

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Epidemiology of Pediatric Candidemia

TABLE 1. Characteristics of candidemia episodes and distribution of the isolated species

Patient characteristic	No. (%) of episodes										
	Total	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. glabrata*	*C. guilliermondii*	*C. lusitaniae*	*C. krusei*	*C. famata*	*R. glutinis*	*T. asahii*
Age											
<1 month	72 (35.4)	38 (52.8)	24 (33.3)	3 (4.2)	4 (5.5)		1 (1.4)	1 (1.4)	1 (1.4)		
1–12 months	45 (22.2)	14 (31.1)	26 (63.4)	1 (2.2)	2 (4.4)	1 (2.2)	1 (2.2)				
1–15 years	86 (42.4)	22 (25.6)	45 (52.3)	8 (9.3)	2 (2.3)	4 (4.6)	2 (2.3)	1 (1.2)		1 (1.2)	1 (1.2)
Gender											
Male	123 (60.6)	47 (38.2)	58 (47.2)	8 (6.5)	2 (1.6)	2 (1.6)	1 (0.8)	2 (1.6)	1 (0.8)	1 (0.8)	1 (0.8)
Female	80 (39.4)	27 (33.7)	37 (46.2)	4 (5.0)	6 (7.5)	3 (3.8)	3 (3.8)				
Location at time of fungemia											
NICU	27 (13.3)	14 (51.9)	9 (33.3)	1 (3.7)	1 (3.7)	1 (3.7)			1 (3.7)		
Pediatric ICU	38 (18.7)	15 (39.5)	15 (39.5)	1 (2.6)	2 (5.3)	1 (2.6)	2 (5.3)	1 (2.6)			1 (2.6)
General ward	138 (67.9)	45 (32.6)	71 (51.4)	10 (7.2)	5 (3.6)	3 (2.2)	2 (1.4)	1 (0.7)		1 (0.7)	
Total episodes	203	74 (36.5)	95 (46.8)	12 (5.9)	8 (3.9)	5 (2.5)	4 (2.0)	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)

Pemán, J Clin Microb 2011

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Epidemiology of Pediatric Candidemia

Candida species isolated	N=449	N=310	N=139
C. albicans	180 (40%)	133 (43%)	47 (34%)
C. dubliniensis	7 (2%)	3 (1%)	4 (3%)
C. glabrata	40 (9%)	27 (9%)	13 (9%)
C. guilliermondii	**9 (2%)**	**3 (1%)**	**6 (4%)**
C. krusei	16 (4%)	8 (2.5%)	8 (6%)
C. parapsilosis	100 (22%)	73 (23.5%)	27 (19%)
C. lusitaniae	24 (5%)	18 (5.5%)	6 (4%)
Other *Candida* species	62 (14%)	43 (14%)	19 (14%)
Unknown *Candida* species	**11 (2%)**	**2 (0.5%)**	**9 (6%)**

Children 3 months – 18 years of age
Study period 5 years
20 US and 10 EU sites

Palazzi et al, PIDJ 2014

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ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

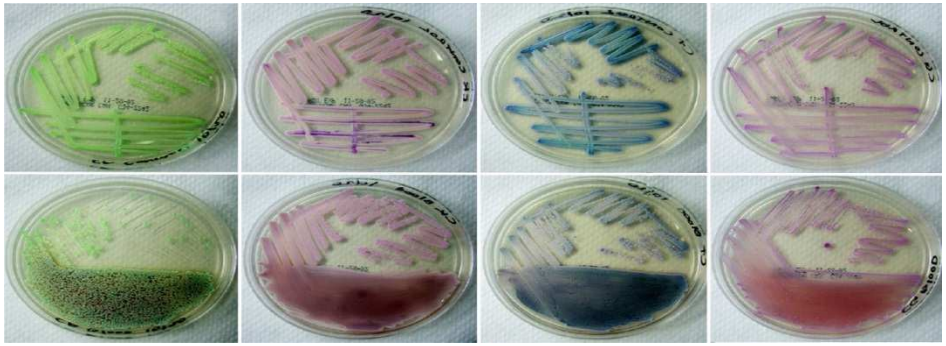
Response rates per species:

C. albicans	ANF > FCZ (p<0.01)
C. glabrata	ANF > FCZ
C. tropicalis	ANF > FCZ
C. parapsilosis	FCZ (83.3%) > ANF (63.6%)

Reboli, NEJM 2007

Antifungal activity in the lab

Species	AmB	FLU	ITRA	VORI	POSA	Echinocandins
C. albicans	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	- ?
C. glabrata	+	±	+	+	+	+
C. krusei	+	±	+	+	+	+



Silva, JCM 2009

Ikeda, Med Mycol 2009

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Epidemiology of Pediatric Candidemia

- Echinocandin resistance among pediatric *Candida* species isolates: 4 out of 200 > 2%
  - 1/95 *C. parapsilosis*
  - 1/74 *C. albicans*
  - 2/12 *C. tropicalis*

Species (no. of isolates tested)	Drug	MIC (mg/liter)			No. (%) of resistant isolates	
		Range	50%	90%	CLSI	Species-specific clinical breakpoint[c]
C. parapsilosis (95)	AND	0.016–4	1	2	2	0
	CAS	0.008–2	0.5	0.5	0	0
	MCF	0.016–8	1	2	1 (1.1)	1 (1.1)
	FZ	0.12–8	1	2	0	0
	ITZ	0.016–0.25	0.06	0.12	0	ND
	VOR	0.008–0.12	0.008	0.03	0	0
	POS	0.008–1	0.03	0.12	0	ND
	AMB	0.12–1	0.25	0.5	0	ND
	FLC	0.06–1	0.06	0.25	0	ND

Pemán, J Clin Microb 2011

NEONATES

Relevance of Neonatal Candidiasis

- Incidences;
  - > 1500 g < 1%
  - < 1500 g 10% in the USA and Italy
    2.1% in the UK
    2.2% in Australia/New Zealand
  - < 1000 g 5.1-26% in the USA
    1% in the UK
    5.4% in Australia/New Zealand
- Mortality; 20-40%
- Attributable mortality; around 10%

Stoll, Ped 2002; Lopez Sastre, Am J Perinatol 2003;
Fridkin, Pediatr 2006; Zaoutis, Clin Infect Dis 2007

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ESCMID guideline: Invasive Candidemia (2012)

Recommendation and grading	Comments	References
Oral nystatin, 1 mL 100 000 IU Q8 h (B-II)	Reduction in fungal infection, but no change in mortality, potential gut damage & NEC	[18–20]
Miconazole oral gel 15 mg Q8 h (D-II)	Concerns regarding generation of triazole resistance	[21]
Lactoferrin 100 mg/day alone or in combination with *Lactobacillus* 10^6 colony-forming units per day from the third day of life until either the end of the sixth week of life or until discharge from the NICU (B-II)	Reduction in fungal infection by *Lactobacillus* and lactoferrin	[22–24]
Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in ALL neonates <1000 g in NICUs with high frequency of IC (A-I)	Reduction in *Candida* colonization, fungal infection, but no change in overall mortality. Concerns for neurodevelopmental toxicity, emergence of resistant species	[19,25–37,39]
*Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in NICUs with a lower incidence of IC (i.e. <2%) for neonates: (a) with birth weight <1000 g, (b) who have risk factors (i.e. central venous catheters, third-generation cephalosporins and carbapenems) for the development of IC (B-II)	Decision for prophylaxis is on an individual basis	References as immediately above

*High incidence of IC defined as at least >5%, although the studies performed have been done in NICU settings with incidences > 12%

*five RCTs, 8 historical control studies, and 1 meta-analysis suggesting 91% decrease in IC in neonates < 1000 g

Hope, EJCMID 2012

10.1111/1469-0691.12040

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp.

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 1 mg/kg/day (B-II)	PK in neonates relatively poorly defined, leading to some uncertainty regarding optimal dosage for HCME	Clinical trials in adults [123,124] Pharmacokinetics in neonates [44] Evidence for efficacy and toxicity [43,135]
Liposomal amphotericin B 2.5–7 mg/kg/day (B-II)	PK in neonates remains undefined, leading to some uncertainty regarding optimal dosage for neonates The optimal dosage for HCME is not known	Pharmacokinetics in neonates: nil Evidence for efficacy in neonates [46–48]
Fluconazole 12 mg/kg/day, with consideration given to a loading dose of 25 mg/kg (B-II)	Relatively limited data for the treatment of IC	Evidence for efficacy [51–53] Pharmacokinetics in neonates: [54,55]
Micafungin 4–10 mg/kg/day i.v. (B-II)	The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts. These studies have not been performed for other echinocandins The currently licensed dosage is 2–4 mg/kg/day. If HCME is present, preclinical models and PK-PD bridging studies suggest a higher dosage is required for effective therapy	Evidence for efficacy derived from preclinical models [57] Pharmacokinetics in neonates: [56,58]
Caspofungin 25 mg/m^2/day (C-II)	Relatively limited PK and dosing designed to approximate drug exposure in adults, rather than HCME	Evidence for efficacy [62–64] Pharmacokinetics in neonates: [61]
ABLC 2.5–5 mg/kg/day (C-II)	The Expert Group rated ABLC 'C' because of the relative paucity of clinical data The optimal regimen for the treatment of HCME is not known	Pharmacokinetics in neonates [50] Preclinical data suggests that ABLC is an effective agent for the treatment of HCME [45]

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Real life treatment of neonatal candidemia

	N=77 (UK)	N=25 (IPFN)
fluconazole	42 (55%)	8 (32%)
L-AmB	26 (34%)	4 (16%)
AmB-d	12 (9%)	-
caspofungin	-	9 (34%)
micafungin	-	2 (8%)

IPFN; international paediatric fungal network, 15 US & 9 EU sites

Oeser et al, CMI 2014; Steinbach et al, PIDJ 2012

10.1111/1469-0691.12040

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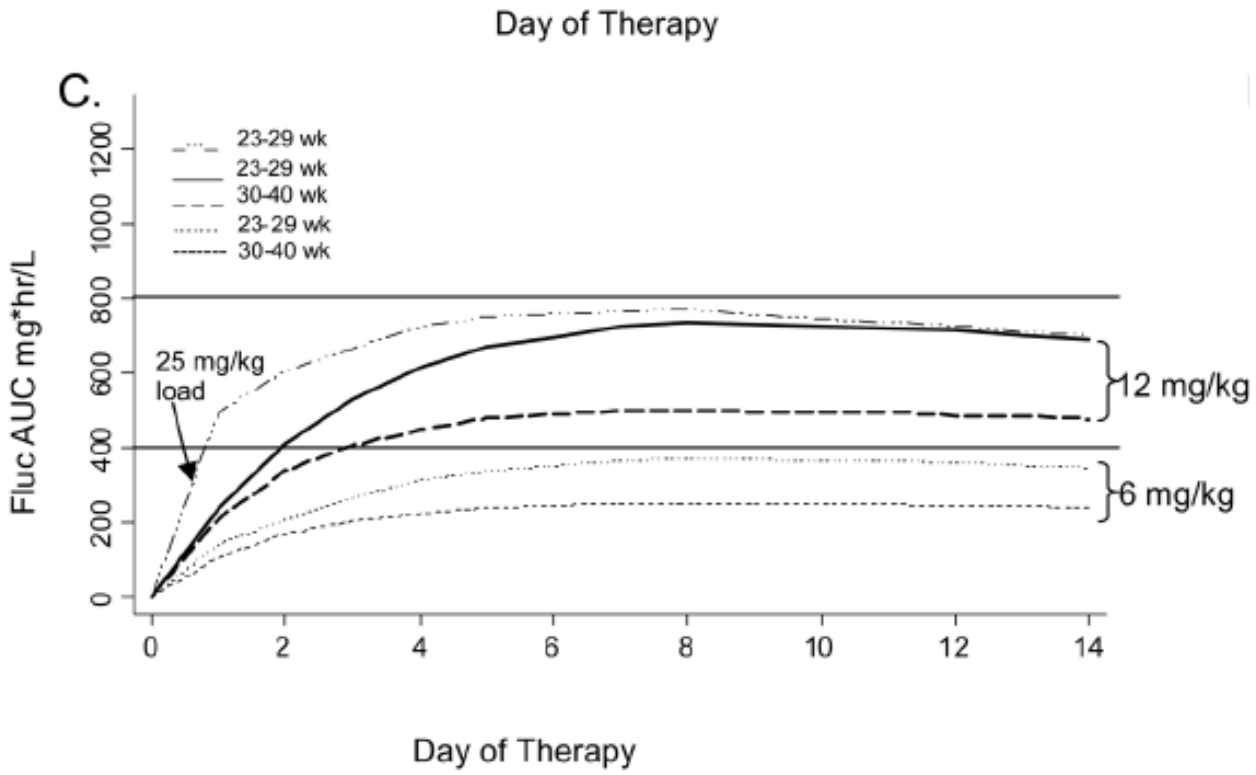
Fluconazole dosing issues in neonates



357 samples from 55 neonates (23-40 wks)

Wade *AAC* 2008, Wade PIDJ 2009

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Fluconazole Loading Dose Pharmacokinetics and Safety in Infants

Lauren Piper, MD, P. Brian Smith, MD, MPH, MHS,* Christoph P. Hornik, MD,* Ira M. Cheifetz, MD,* Jeffrey S. Barrett, PhD,† Ganesh Moorthy, PhD,† William W. Hope, MD, PhD,‡ Kelly C. Wade, MD, PhD,† Michael Cohen-Wolkowiez, MD,* and Daniel K. Benjamin, Jr., MD, MPH, PhD**

PIDJ 2011

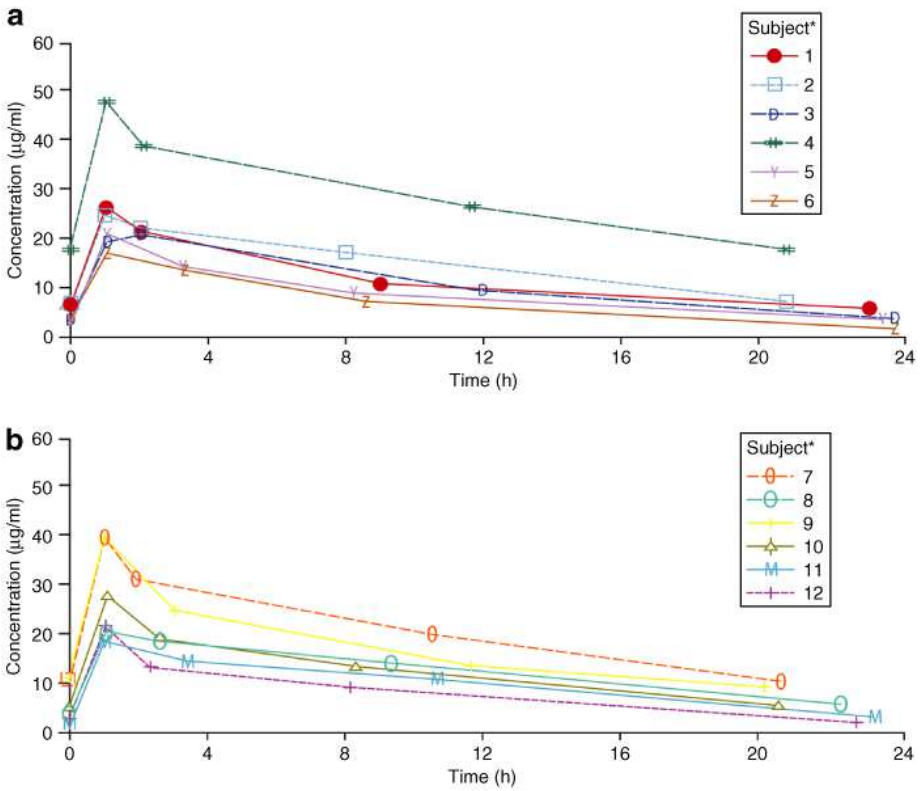
- Median age 17 d (14-41 d)
- Median GA 37 wks (35-39 wks)
- Median BW 2.8 kg (2.0-3.1 kg)

Outcome: SAFE

TABLE 1. Pharmacokinetic Parameters

Subject	Age (d)	Serum Creatinine	Clearance (mL/kg/h)	Vd (mL/kg)	Half Life (h)	Kel (h^{-1})	AUC_{0-24} (mg*h/L)
1	6	1.0	27	785	19.9	0.050	493
2	13	1.3	14	1441	73.4	0.013	350
3	14	0.8	12	1522	91.4	0.010	338*
4	14	0.5	18	1021	39.1	0.025	466
5	19	1.2	9	1061	79.4	0.012	493
6	36	0.5	21	711	23.8	0.042	598
7	55	0.3	23	882	27.2	0.036	506
8	59	0.2	14	1635	81.2	0.012	271
Median (IQR)	17 (14–41)	0.7 (0.4–1.1)	16 (13–21)	1051 (858–1461)	56 (26–80)	0.02 (0.01–0.03)	479 (347–496)

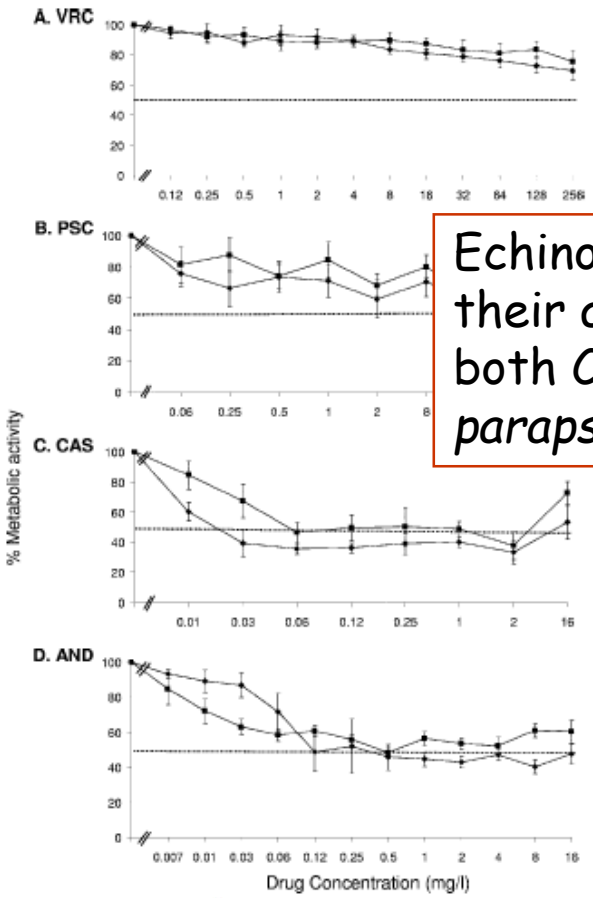
Micafungin: Clinical neonatal data



- Open-label study MICA
- 13 premature neonates (suspected of proven candidiasis)
- 7 mg/kg (< 1000g)
  10 mg/kg (> 1000g)
- Well tolerated
- Exposure levels adequate for CNS coverage

Benjamin, Clin Pharmacol Ther 2010

Role for echinocandins against *Candida* bioflims?

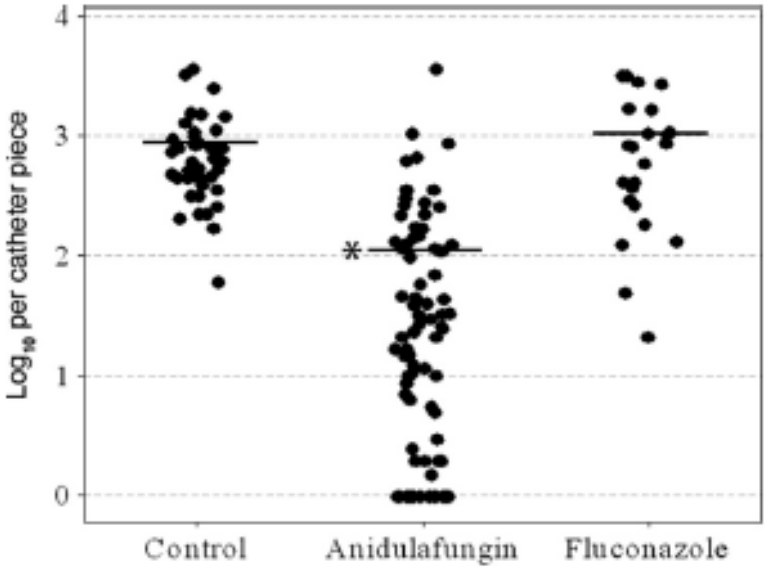


Echinocandins retain their activity against both *C. albicans* and *C. parapsilosis* biofilms

Katragkou *AAC* 2008

In Vivo Efficacy of Anidulafungin against Mature *Candida albicans* Biofilms in a Novel Rat Model of Catheter-Associated Candidiasis▽

Soňa Kucharíková,[1,2,3] Hélène Tournu,[1,2] Michelle Holtappels,[1,2] Patrick Van Dijck,[1,2]* and Katrien Lagrou[4]



AAC 2010

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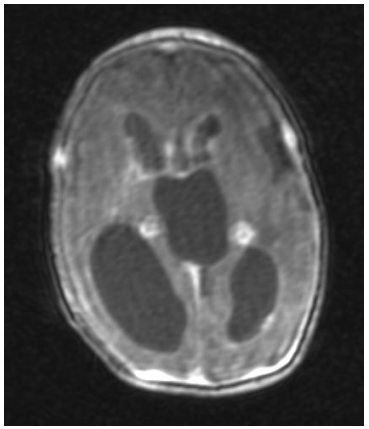
AAC Journals.ASM.org

Favorable Outcome of Neonatal Cerebrospinal Fluid Shunt-Associated *Candida* Meningitis with Caspofungin

Jop Jans,[a] Roger J. M. Brüggemann,[b,e] V. Christmann,[c] Paul E. Verweij,[d,e] Adilia Warris[a,e]

Departments of Pediatric Infectious Diseases,[a] Pharmacy,[b] Neonatology,[c] and Medical Microbiology,[d] Radboud University Medical Centre, Nijmegen, Netherlands; Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Medical Centre, Nijmegen, Netherlands[e]



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PEDIATRIC CANCER/HSCT PATIENTS

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Stratification of Risk of IFIs in Paediatric Cancer / HSCT Patients

Risk stratum	Patient population
High risk (≥ 10 %)	-acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HSCT -high risk ALL**
Low risk (≤5 %) *	-acute lymphoblastic leukemia ** -non-*Hodgkin* lymphoma's -autologous HSCT
Sporadic occurrence *	-pediatric solid tumors (NB: Tx-liver) -brain tumors -*Hodgkin's* lymphoma

* consider that low and sporadic risk is not equal to no risk

** depending on the protocol and additional risk factors, risk for IFD may exceed 10 %

Groll '99; Hovi 2000; Lin 2001; Benjamin 2002; Zaoutis 2004; Zaoutis 2005; Zaoutis '06; Rosen 2005; Crassard 2007; Sung 2007; Kobayashi 2008; Kaya 2009; Castagnola 2010; Hale 2010; Mor 2011; Kaya 2011; Watanabe 2011; Srinivasan 2013; Maron 2013; Hol 2014

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Management strategies

	Recommendation and grading	Comments	References
Empirical antifungal therapy	If chosen as a strategy, it should be initiated in high-risk granulocytopenic paediatric patients after 96 h of fever of unclear cause that is unresponsive to broad-spectrum antibacterial agents (B-II), and be continued until resolution of neutropenia in the absence of suspected or documented invasive fungal disease (B-II). Both caspofungin (50 mg/m² per day; day 1, 70 mg/m²; maximum 70 mg per day) and liposomal amphotericin B (1–3 mg/kg per day) can be recommended (A-I). A similar approach can be chosen in granulocytopenic patients who develop recurrent fever after defervescence on initiation of broad-spectrum antibacterial agents (no grading). In patients already receiving mould-active antifungal prophylaxis, switching to a different class of mould-active antifungal agents seems reasonable (no grading)	Randomised clinical trials with both caspofungin and liposomal amphotericin B done in paediatric patients show similar safety and efficacy relative to much larger trials in adults with similar study design. Both compounds are approved for empirical antifungal therapy in both children and adults. Empirical antifungal therapy might also be considered in individual persistently febrile patients with low-risk disorders and profound and persistent granulocytopenia and severe mucosal damage (no grading)	Clinical trials in paediatric patients: 57–60; pharmacokinetic studies in paediatric patients: appendix, pp 1–3; clinical trials in adults: 7,8, appendix p 5
Pre-emptive (diagnostic-driven) antifungal therapy	Pre-emptive (diagnostic-driven) therapy might be an alternative to the empirical antifungal approach (no grading)	No data in children; feasibility shown in adults and accepted as an alternative to the empirical approach in high-risk adult granulocytopenic patients. Rapid availability of pulmonary CT and galactomannan results are a prerequisite; capability of undertaking bronchoscopies with bronchoalveolar lavage is desirable.	Clinical trials in adults: 61–63; recommendations in adults: 8,64

Table 4: **Recommendations for empirical and pre-emptive antifungal therapy in paediatric patients with cancer or haemopoietic stem-cell transplantation**

ECIL-guideline

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Role of Management Strategies in Reducing Mortality From Invasive Fungal Disease in Children With Cancer or Receiving Hemopoietic Stem Cell Transplant

A Single Center 30-year Experience

TABLE 2. Multivariable Analysis of Risk Factors for 90-days Mortality From Invasive Fungal Disease

	HR	95% CI	LRT, P-value
Type of treatment for underlying disease			
Chemotherapy	*ref.*	—	0.0005
Autologous HSCT	0.94	0.37–2.39	
MRD HSCT	1.49	0.54–4.11	
AD-HSCT	3.96	1.99–7.85	
Type of identified pathogen (by means of histology, cultures, antigen detection)			
Not identified (possible IFD)	*ref.*	—	0.0014
Yeast	0.38	0.16–0.91	
Mold	1.34	0.68–2.63	
Year of diagnosis of IFD			
1983–1990	*ref.*	—	0.0242
1991–1999	0.36	0.15–0.85	
2000–2005	0.33	0.13–0.83	
2006–2012	0.24	0.09–0.60	

From empiric.....

Improved diagnostic tools
Increased availability of antifungals

Higher number of IFI's diagnosed
Lower mortality

...to pre-emptive treatment

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Invasive candidiasis in infants and children

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 0.6–1 mg/kg/day (C-I)	Lipid preparations of amphotericin B have a more favourable toxicity profile Issues related to supply in some European countries	Clinical trials in adults [123,124] PK studies in children [132] Evidence for safety and efficacy in children with invasive candidiasis: Nil
Liposomal amphotericin B 3 mg/kg/day (A-I)		Clinical trials in adults and children [48,127] PK studies in children [105] Safety in children [48]
Fluconazole 8–12 mg/kg/day (B-I)	Fungistatic antifungal activity	Evidence for efficacy in adults [123,139] PK studies in children [73] Evidence for safety and efficacy in children [75]
Voriconazole (day 1: 9 mg/kg Q12h, then 8 mg/kg BID i.v.); and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12–14 year olds weighing >50 kg; after last dose of chemotherapy until neutrophil recovery (B-I)	Fungistatic antifungal activity Spectrum extends to *Candida glabrata* and *Candida krusei* TDM should be considered	Evidence for efficacy in adults [134] PK studies in children: [84–88] TDM dosing target: [89–91]
Micafungin <40 kg 2–4 mg/kg (A-I)	Well conducted PK trials to define dosages that lead to comparable drug exposures in children The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts.	Efficacy established in clinical trials in children and adults [48,127] PK studies in children: [96,97] Safety/efficacy in children [98]
Anidulafungin 3 mg/kg as a single loading dose followed by 1.5 mg/kg/day (B-II)	Some uncertainty about optimal paediatric regimen because of relatively limited PK data No data for efficacy and safety in children	Evidence for efficacy in adults [128] PK studies in children [129]
Caspofungin Loading dose 70 mg/m^2/day, followed by 50 mg/m^2/day. Option to increase to 70 mg/m^2/day if clinically indicated, maximum absolute dose of 70 mg/day (A-I)		Evidence for efficacy in adults [124] PK studies in children [125] Evidence for safety in children [126]
Amphotericin B Lipid Complex (B-II)	Relatively limited clinical data for efficacy and safety No PK data for children	Evidence for efficacy and safety [131,140] PK in children: nil

A=strongly recommended; I=evidence 1 randomized trial

Hope, CMI 2012

UMC St Radboud
University Children's Hospital

Invasive candidiasis in children with cancer and HSCT

	Recommendation and grading	Comments	Key references
Invasive candidosis			
Caspofungin	50 mg/m² per day (day 1, 70 mg/m²) intravenously in one dose (B-II)	Fungicidal activity, consider for granulocytopaenic and cardiovascularly unstable patients; echinocandins have higher MICs against *Candida parapsilosis* group; however, no diminished efficacy against these species has been noted in randomised clinical trials	Clinical trials in adults: 5,8, appendix pp 5,6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix p 3
Fluconazole	8–12 mg/kg per day intravenously in one dose (maximum 800 mg per day; B-II)	Fungistatic activity; not recommended for infections by *Candida krusei* and *Candida glabrata*	Clinical trials in adults: 5,8, appendix pp 5,6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix p 2
Liposomal amphotericin B	3 mg/kg per day intravenously in one dose (B-II)	Fungicidal activity, consider for granulocytopenic and cardiovascularly unstable patients	Clinical trials in adults: 8, appendix, pp 5,6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Micafungin	2–4 mg/kg per day intravenously (in children weighing ≥50 kg, 100–200 mg) in one dose (B-II)	Fungicidal activity, consider for granulocytopenic and cardiovascularly unstable patients; echinocandins have higher MICs against *C parapsilosis* group; however, no diminished efficacy against these species has been noted in randomised clinical trials	Clinical trials in adults: 5,8, appendix pp 5,6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix p 3
Voriconazole	Children aged 2–<12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally; children aged ≥15 years or 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally plus TDM (B-II)	Fungistatic activity; relative to fluconazole, spectrum extends to *C glabrata* and *C krusei*; not approved in patients aged <2 years; TDM is suggested; dosing target: trough concentration 1·0–5·0 mg/L	Clinical trials in adults: 5,8, appendix pp 5,6; TDM dosing target: 51,52; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 2,3
Amphotericin B lipid complex	5 mg/kg per day intravenously in one dose (C-II)	Fungicidal activity; lower grading because of absence of completely published first-line phase 3 data and only a few paediatric pharmacokinetic studies	Clinical trials in adults: 5,8, appendix pp 5,6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2

Moderate evidence to support recommendation for use

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Real life treatment of Pediatric Candidemia

	All Episodes n (%)	US Study Sites Episodes n (%)	Non-US Study Sites Episodes n (%)
Antifungal Agent Used ≥2 consecutive days	**N=1072**	**N=586**	**N=486**
Amphotericin B	35 (3%)	24 (4%)	11 (2%)
Amphotericin B Lipid Complex	**25 (2%)**	**19 (3%)**	**6 (1%)**
Liposomal Amphotericin B	156 (15%)	93 (16%)	63 (13%)
Echinocandins	**224 (21%)**	**171 (29%)**	**53 (11%)**
Fluconazole	**548 (51%)**	**225 (38%)**	**323 (66%)**
Flucytosine (5-FC)	**6 (1%)**	**6 (1%)**	**0 (0%)**
Itraconazole	1 (~0%)	0 (0%)	1 (1%)
Voriconazole	65 (6%)	36 (6%)	29 (6%)
Terbinafine	2 (~0%)	2 (1%)	0 (0%)
Other	**10 (1%)**	**10 (2%)**	**0 (0%)**

Palazzi et al, PIDJ 2014

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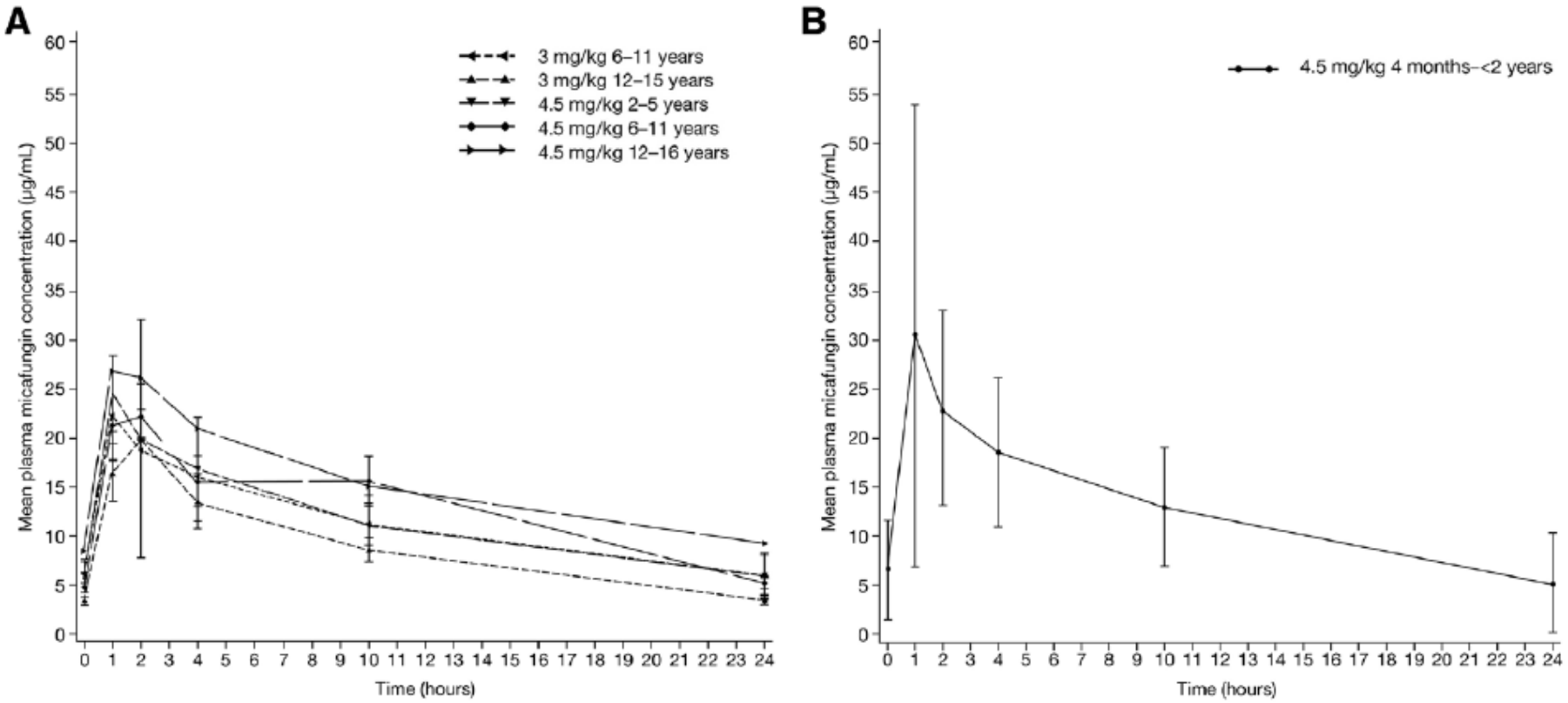
mmfi MEDICAL MYCOLOGY & FUNGAL IMMUNOLOGY

Safety and Pharmacokinetic Profiles of Repeated-dose Micafungin in Children and Adolescents Treated for Invasive Candidiasis

Daniel K. Benjamin, Jr., MD, PhD, MPH, Jaime G. Deville, MD,† Nkechi Azie, MD,‡ Laura Kovanda, BA,§ Mike Roy, PhD,§ Chunzhang Wu, PhD,§ and Antonio Arrieta, MD¶*

PIDJ 2013



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Treatment of invasive aspergillosis

Invasive aspergillosis, first line			
Voriconazole	Children aged 2–<12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally; children aged ≥15 years or 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally plus TDM (A-I)	A-I recommendation based on the pivotal phase 3 trial in adults; not approved in patients aged <2 years; TDM is suggested; dosing target: trough concentration 1·0–5·0 mg/L; current treatment of choice for infections involving the CNS; a switch in class is to be considered in patients with breakthrough aspergillosis on mould-active azole prophylaxis	Clinical trials in adults: 5,8, appendix p 6 TDM dosing target: 51,52; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 2,3
Liposomal amphotericin B	3 mg/kg per day intravenously in one dose (B-I)	Pivotal phase 3 trial was comparison between two different dose strategies but no head-to-head comparison with the reference agent at the time of its conduct (ie, voriconazole)	Clinical trials in adults: 5,8, appendix p 6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Amphotericin B lipid complex	5 mg/kg per day intravenously in one dose (B-II)	No controlled first-line data but solid second-line experience in treatment-naive patients receiving the compound on the basis of its improved safety profile relative to amphotericin B deoxycholate	Clinical trials in adults: 5,8, appendix p 6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Antifungal combination therapy	Echinocandin plus polyene or triazole (C-III)	Pivotal randomised clinical trial not fully published; preliminary data suggest no differences in the primary endpoint	Clinical trials in adults: 65–68; safety and efficacy data in paediatric patients: 69

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Azole dosing issues: voriconazole in children

IMPACT OF THERAPEUTIC DRUG MONITORING OF VORICONAZOLE IN A PEDIATRIC POPULATION

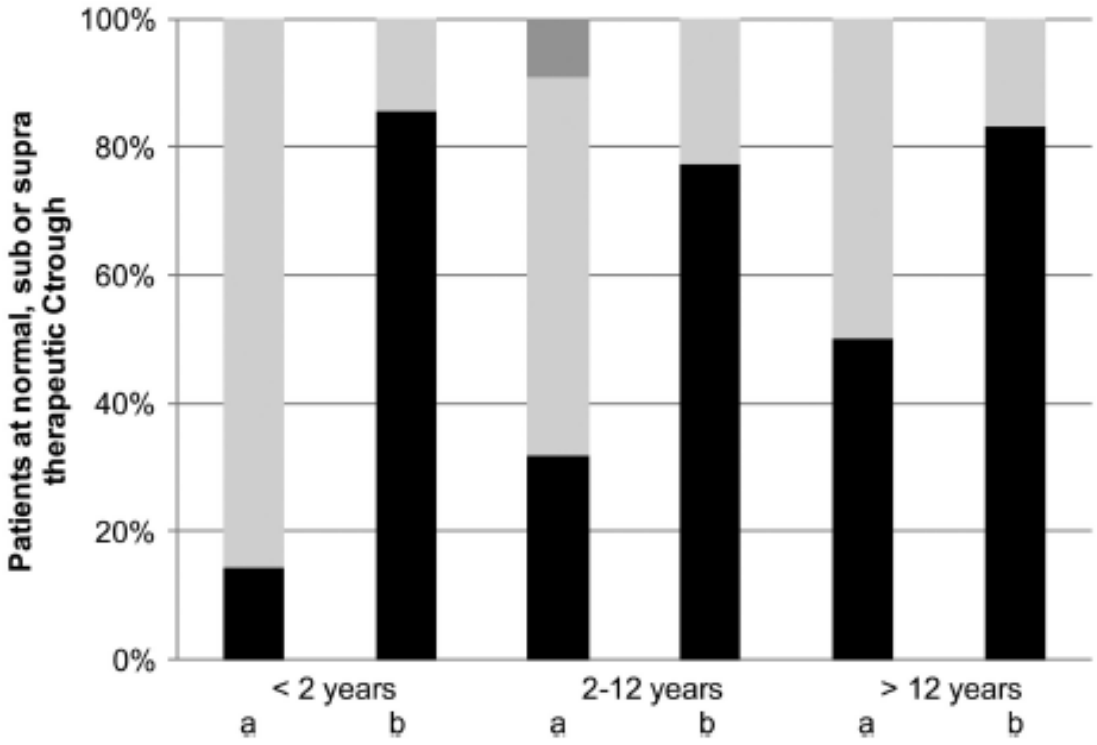
Roger J. M. Brüggemann, PharmD,†*
Jan W. M. van der Linden, MD,†‡§
Paul E. Verweij, MD, PhD,†‡ David M. Burger, PharmD, PhD,†*
and Adilia Warris, MD, PhD†§

PIDJ 2011

- Recommended dosing schedule at that time: 2 dd 7 mg/kg iv or 2 dd 200 mg po (<12 yrs)
- 44% initial trough levels < 1 mg/L

Highly Variable Plasma Concentrations of Voriconazole in Pediatric Hematopoietic Stem Cell Transplantation Patients

Imke H. Bartelink,[a,b] Tom Wolfs,[a] Martine Jonker,[b] Marjolein de Waal,[a] Toine C. G. Egberts,[b,c] Tessa T. Ververs,[b] Jaap J. Boelens,[a] Marc Bierings[a]



380 trough levels in 60 kids

35% initial levels adequate
After adjustment 80%

AAC 2012

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Azole dosing issues: relationship with outcome?

Mean plasma concn (μg/ml)	No. of patients (% success)[a]		
	Total, n = 825 (69)	Yeast infected, n = 432 (77)	Mold infected, n = 388 (60)
<0.5	87 (57)	52 (63)	34 (47)
0.5–<1.0	75 (71)	34 (82)	40 (60)
1.0–<1.5	94 (71)	38 (84)	56 (63)
1.5–<2.0	100 (74)	47 (87)	53 (62)
2.0–<3.0	151 (75)	70 (80)	80 (70)
3.0–<4.0	100 (78)	53 (81)	47 (74)
4.0–<5.0	71 (70)	46 (85)	25 (44)
5.0–<6.0	47 (60)	24 (71)	23 (48)
6.0–<8.0	55 (51)	37 (54)	17 (47)
8.0–<10.0	26 (62)	18 (78)	8 (25)
≥10.0	19 (58)	13 (85)	5 (0)

- Trough levels < 1 mg/L associated with a 2.6-fold increased odds of death (95% CI 1.6-4.8, p=0.002)

Neely, CID 2010
Troke, AAC 2011

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Pediatr Blood Cancer 2013;60:82–87

Importance of Voriconazole Therapeutic Drug Monitoring in Pediatric Cancer Patients With Invasive Aspergillosis

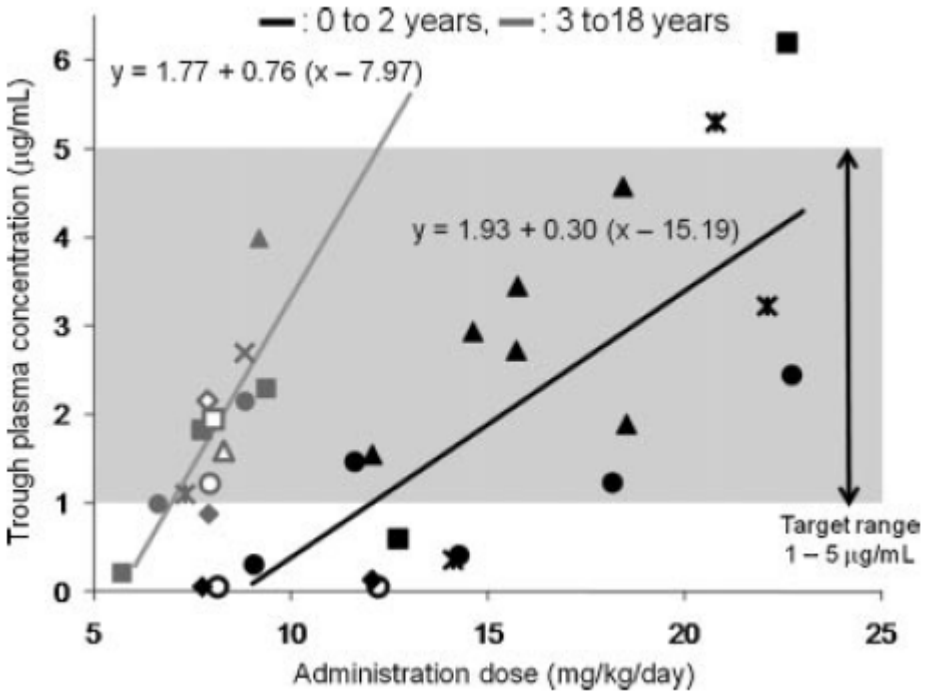
Soo-Han Choi, MD,[1] Soo-Youn Lee, MD,[2] Ji-Young Hwang, PhD,[3,4] Soo Hyun Lee, MD,[1] Keon Hee Yoo, MD,[1] Ki Woong Sung, MD,[1] Hong Hoe Koo, MD,[1] and Yae-Jean Kim, MD[1]*

TABLE III. Relationship Between Outcomes at Week 6 of Voriconazole Therapy and Voriconazole Trough Levels

	No. of proven/probable IA patients (<12yrs vs.≥12 yrs)	No. of samples[a]	Trough levels		*P*-value
			<1 μg/ml	≥1 μg/ml	
Outcome					0.0121
Success	11 (5 vs. 6)	66	13 (19.7%)	53 (80.3%)	
Failure	9 (5 vs. 4)	38	16 (42.1%)	22 (57.9%)	

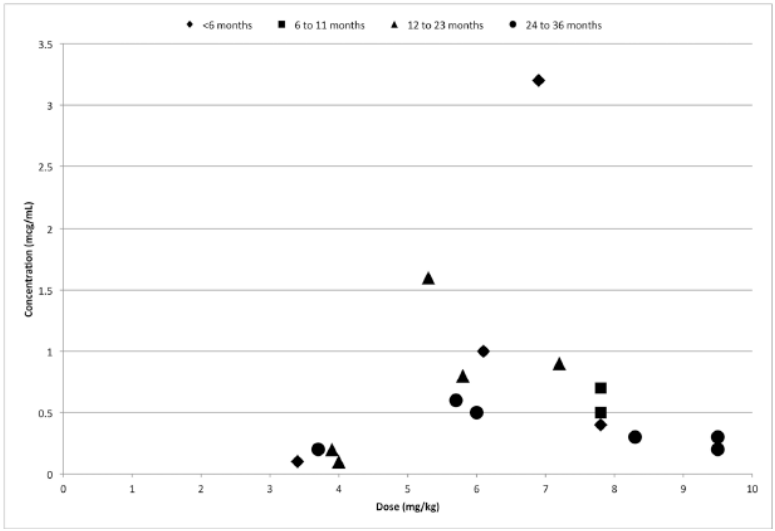
Azole dosing issues: voriconazole in children

16 kids, median 9 yrs (0-18 yrs)
< 3 yrs 6 (37.5%)
≥ 3 yrs 10 (62.5%)



Shima, PBC 2010

10 kids < 3 yrs of age



Doby, PIDJ 2011

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Azole dosing issues: posaconazole in children

Posaconazole Therapeutic Drug Monitoring in Pediatric Patients and Young Adults with Cancer

Valeria A Bernardo, Shane J Cross, Kristine R Crews, Patricia M Flynn, James M Hoffman, Katherine M Knapp, Jennifer L Pauley, Alejandro R Molinelli, William L Greene

cancer. At St. Jude Children's Research Hospital, the recommended posaconazole dose in patients weighing less than 34 kg is 18-24 mg/kg daily, given in 4 divided doses. For patients aged 13 years or older or those weighing 34 kg or more, the recommended dose is 800 mg daily, given orally in 4 divided doses.

< 34 kg: 18-24 mg/kg daily in 4 doses

Table 1. Patient Characteristics

Sex, n (%)	
female	15 (45)
male	18 (55)
Age, years	
median	11.5
range	0.5-23.2
Race, n (%)	
white	24 (73)
black	6 (18)
other	3 (9)
Underlying condition, n (%)	
ALL	10 (30.3)
AML	11 (33.3)
relapsed ALL	3 (9)
relapsed AML	1 (3)
relapsed Hodgkin lymphoma	1 (3)
CML	1 (3)
aplastic anemia/glioblastoma multiforme	1 (3)
chronic granulomatous disease	2 (6)
chronic mucocutaneous candidiasis	1 (3)
severe combined immunodeficiency	1 (3)
astrocytoma	1 (3)
Indication, n (%)	
empiric treatment	19 (57.5)
treatment of documented infection	14 (42.5)

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia.

Bernardo, Ann Pharm 2013

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Table 3. Relationship Between Patient Age, Dosage, Patient Weight, and Posaconazole Concentrations

Parameter	Cp <0.7 µg/mL	Cp ≥0.7 µg/mL	p Value[a]
Pts., n	12	21	
Pts. receiving high-risk medications, n (%)	4 (33)	8 (38)	1.0[b]
Pt. age, years			
mean (SD)	12.3 (7.2)	8.4 (6.0)	
median	13.7	8.5	0.08 (173.0)
Cp, µg/mL			
median	0.4	1.4	
range	0.025-0.69	0.70-3.26	
Days from start of therapy to first Cp, n			
median	10	10	
range	3-77	2-269	0.4 (146.5)
Pts. with Cp measured at SS, n (%)	9 (75)	14 (67)	
Dosage, mg/kg/day			
median	12.9	20.0	0.02 (186.5)
range	6.5-26.8	9-32.8	
Pt. weight, kg			
median	57.2	30.0	0.14 (166.0)
range	11-123	7-88	

Cp = plasma concentration; SS = steady-state.
[a]p Values calculated using Mann-Whitney *U* test unless otherwise noted.
[b]p Value calculated using Fisher exact test.

Table 4. Comparison of Patient Age and Posaconazole Plasma Concentration

Parameter	Age <13 years	Age ≥13 years	p Value[a]
Pts., n	21	12	
Pts. with Cp ≥0.7 µg/mL, n	16	5	(0.06)[b]
Cp, µg/mL			
median	0.8	0.6	0.3 (152.0)
range	0.22-2.04	<0.125-2.98	
Dosage, mg/kg/day			
median	22.0	11.9	<0.001 (223.0)
range	9-32.8	6.5-20	

Bernardo, Ann Pharm 2013

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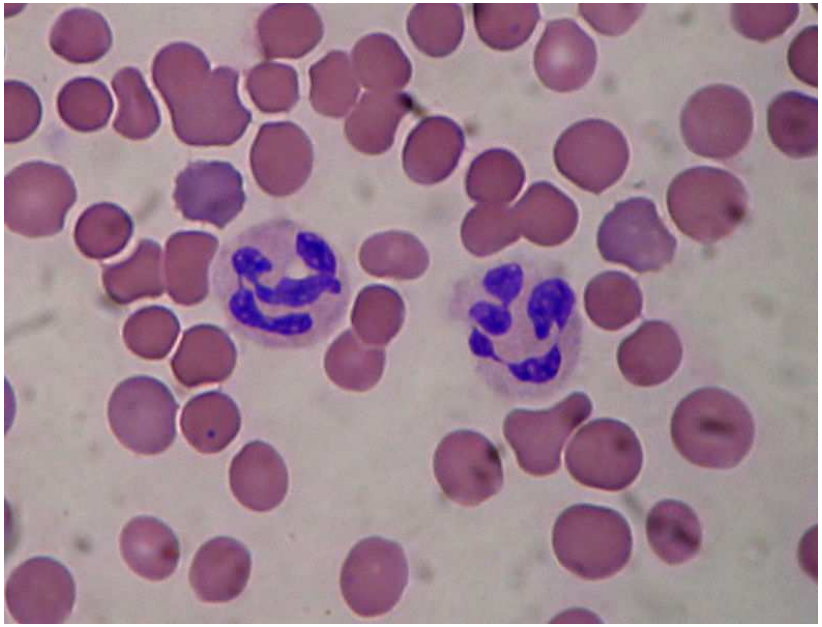
PRIMARY IMMUNODEFICIENCIES



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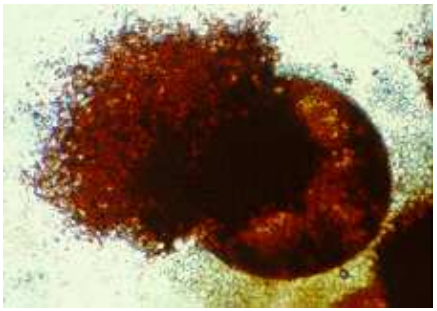
Stratification of risk of IFIs in children with primary immunodeficiencies

Immune deficit	Clinical disorders	Fungal infections
Humoral	XLA, AR-agammaglobulinemia, CVID, IgA-deficiency	very unlikely
Cellular	SCID, diGeorge, hyper-IgM, Wiskott-Aldrich	sporadic, variable
Phagocytic	CGD, MPO, LAD, congenital neutropenia	*Aspergillus* frequent in CGD (25-40%), *Candida* less common
Complement	deficiencies specific factors or MBL	very unlikely
Others	hyper-IgE syndrome, CMC, defects IFNy/IL12	*Aspergillus* in HIES, superficial mycoses in HIES & CMC

A. nidulans and CGD

- *Emericella nidulans* (teleomorph)
- other species cause rarely human infections
- not encountered in other patient groups
- increased virulence and mortality when compared to *A. fumigatus* (50% vs. 5-10%)



Cleisthothecium showing numerous ascospores

Asci with Ascospores

Thick-walled Hülle cells (25um) surrounding the cleisthothecium

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Susceptibilities of *Emericella* spp.

***Emericella quadrilineata* as Cause of Invasive Aspergillosis**

Paul E. Verweij,* János Varga,†‡ Jos Houbraken,† Antonius J.M.M. Rijs,* Frans M. VerduynLunel,* Nicole M.A. Blijlevens,* Yvonne R. Shea,§ Steven M. Holland,§ Adilia Warris,* Willem J. G. Melchers,* and Robert A. Samson†

drug	*E.nidulans*	*E.quadrilineata*	significance
AmB	2.5	0.5	P < 0.05
ITRA	0.07	0.13	NS
VORI	0.26	0.39	P < 0.05
POSA	0.25	0.22	P < 0.05
CASPO*	0.01	1.83	P < 0.05

Verweij, EID 2008

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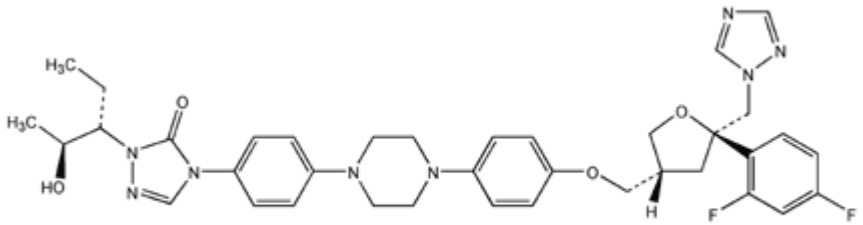
Posaconazole prophylaxis in children

iPOD study

Investigation of
POsaconazole prophylaxis in children with chronic granulomatous
Disease: pharmacokinetics and tolerability



posaconazole

A TWICE DAILY POSACONAZOLE DOSING ALGORITHM FOR CHILDREN WITH CHRONIC GRANULOMATOUS DISEASE

*Marieke E. B. Welzen, PharmD,**
Roger J. M. Brüggemann, PharmD,†*
J. Merlijn Van Den Berg, MD, PhD,‡ Heleen W. Voogt,‡
Jos H. Gilissen,§ Dasja Pajkrt, MD, PhD,‡
Nigel Klein, MD, PhD,¶ David M. Burger, PharmD, PhD,†*
and Adilia Warris, MD, PhD†§

Abstract: Posaconazole (PSZ) may be an attractive alternative for antifungal prophylaxis in children with chronic granulomatous disease. Experience with PSZ in pediatric patients is limited, and no specific dose recommendations exist. A twice daily dosing algorithm based on allometric scaling (body-weight based) for PSZ results in adequate exposure and appears to be safe in children with chronic granulomatous disease.

PIDJ 2011

Posaconazole dosing in children (prophylaxis)

- allometric dosing algoritm

  Dosis (child) = Dosis (adult) x [BW (child) / BW (adult)] $^{0.75}$

Bodyweight (kg)	**Dosing mg 2dd**	**PSZ suspension 2dd**
10 – 14	120	3 ml
15 – 19	160	4 ml
20 – 24	200	5 ml
25 – 29	220	5,5 ml
30 – 34	260	6,5 ml
35 – 39	280	7 ml
≥ 40	300	7,5 ml
adults	3 dd 200 mg	

Van Welzen, PIDJ 2011

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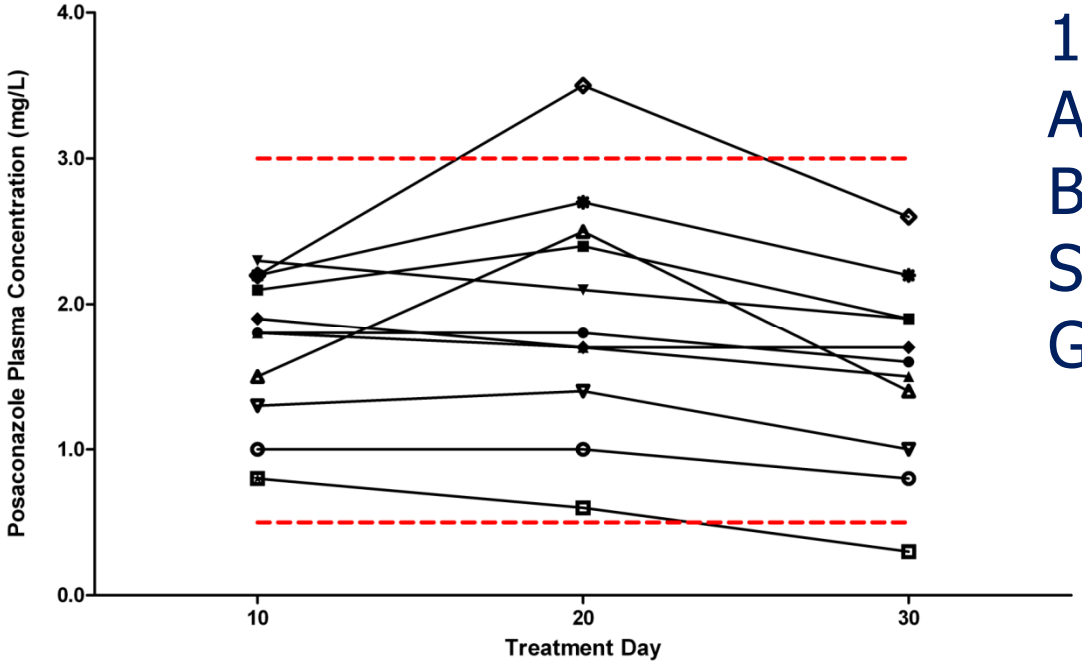
Azole dosing issues: posaconazole in children



12 children
Age range 3 – 15 yrs
BW 15 – 72 kgs
Safe
Good tolerability

Van Welzen, PIDJ 2011

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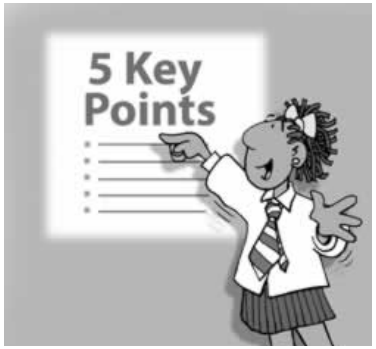
Summary

- Higher fluconazole & micafungine dosages needed in neonates
- Perform TDM when using azoles in pediatrics
- Posaconazole dosing in children needs further investigation
- Diagnostic driven approach feasible and safe
- Echinocandins attractive as 1st line agent for invasive candidiasis, but
  - Dosing issues in neonates (and to lesser extent in children)
  - Expensive and only iv



UMC St Radboud
University Children's Hospital

Mucormycosis, first line			
Amphotericin B lipid complex	5–7·5 mg/kg per day intravenously in one dose (B-II)	Recommendations similar to those for adults	Clinical trials in adults: 9, appendix pp 6,7; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Liposomal amphotericin B	5–10 mg/kg per day intravenously in one dose (B-II)	Recommendations similar to those for adults; preferred for infections involving the CNS or in patients with renal failure	Clinical trials in adults: 9, appendix pp 6,7; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Antifungal combination therapy	Lipid amphotericin B plus caspofungin or plus posaconazole (C-III)	Recommendations similar to those for adults	Clinical data in adults and preclinical data: 9, appendix pp 6,7
Posaconazole	800 mg per day orally in two or four divided doses plus TDM in children aged ≥13 years (no grading)	Recommendations similar to those for adults; non-approved indication; scarce pharmacokinetic data in children aged ≥13 years; TDM is suggested; dosing target inferred from invasive aspergillosis: trough concentration of ≥0·7–1·5 mg/L	Clinical trials in adults: 9, appendix pp 6,7; suggested TDM dosing target: 53,70; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 2,3
Scedosporiosis and fusariosis			
Voriconazole	Children aged 2–<12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally; children aged ≥15 years or 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally plus TDM (B-II)	Approved indication in adults; approved in paediatric patients aged >2 years; TDM is suggested; dosing target: trough concentration 1·0–5·0 mg/L	Clinical trials in adults: 71–73; TDM dosing target: 51,52; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 2,3
Amphotericin B lipid complex	5 mg/kg per day intravenously in one dose (no grading)	Inference made from in-vitro data, animal models, case series, and case reports	Clinical trials in adults: appendix p 6; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Liposomal amphotericin B	3–5 mg/kg per day intravenously in one dose (no grading)	Inference made from in-vitro data, animal models, case series, and case reports	Clinical trials in adults: none; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 1,2
Posaconazole	800 mg per day orally in two or four divided doses plus TDM in children aged ≥13 years (no grading)	Treatment of fusariosis approved in adults; scarce pharmacokinetic data in patients aged ≥13 years, but not approved in the EU in patients aged <18 years; TDM is suggested; dosing target inferred from invasive aspergillosis: trough concentration ≥0·7–1·5 mg/L	Clinical trials in adults: 74,75; suggested TDM dosing target: 53,70; pharmacokinetic, safety, and efficacy data in paediatric patients: appendix pp 2,3