

Antifungal Drugs in Neonates and Children

William J. Steinbach, MD

*Assistant Professor of Pediatrics,
Molecular Genetics and Microbiology*

Director, International Pediatric Fungal Network

*Pediatric Infectious Diseases
Duke University Medical Center
Durham, NC USA*

ABLC Population

Pharmacokinetics in Neonates

- Phase II multicenter trial, ABLC for invasive candidiasis (n=28 neonates)
- ABLC at 2.5 mg/kg/d (n=15) or 5 mg/kg/d (n=13) for a median of 21 days
- Terminal half life = 395 hours (approx. 16 days)
- Disposition of ABLC in neonates was similar to other age groups, weight was the only factor that influenced clearance (not gestational age, birthweight, age, etc)
- **Mean blood concentrations did not significantly differ from adult studies**

Pediatric Fluconazole

- Pediatric patients clearance more rapid than adults (Half life 20 hrs vs. 30 hrs)
- > 3 months of age, double doses to 6-12 mg/kg/d
- Neonates – Vd 2-3 fold greater and more variable (Vd falls by 3 months of age)
- Neonates – slow elimination of drug (due to reduced hepatic enzymes and reduced GFR)
 - Half life 88.6 hours at birth
 - Half-life 55 hours 2 weeks of life
 - Consider dosing q72 hrs (wks 1-2), q48hrs (wks 3-4)

Pediatric Voriconazole

- Elimination by *Linear* pharmacokinetics in children following doses of 3 and 4 mg/kg/q12h
- Single dose, Open, two center study in UK
 - 11 Children, ages 2-11 yrs (mean 5.9 yrs)
- Multiple dose, Open, 8 center, two-cohort (ages 2-6, 6-12)
 - 28 children (mean age 6.4 yrs)
- Higher elimination capacity on a weight basis than do adult healthy volunteers

Pediatric Voriconazole

- Extrapolated plasma pharmacokinetics of pediatric doses (5-12 mg/kg/q12h) vs. adult (4 mg/kg/q12h)
 - Pediatric dose of approx. **11 mg/kg/q12h** is equivalent to adult dose of 4 mg/kg/q12h by AUC and plasma concentration
 - This is only valid if linear pharmacokinetics maintained throughout full dosage range

Walsh TJ, et al. *Antimicrob Agents Chemother* 2004;48:2166-72.

- **Correct pediatric dosing was not fully established, but clearly higher than adult dosing – prompted a second PK study**

Extrapolated Voriconazole Plasma Pharmacokinetics

Dose (mg/kg)	AUC (ng x h/ml)	C _{mean}
Pediatric		
5	17,783	1,482
6	21,240	1,778
7	24,897	2,075
8	28,453	2,371
9	32,010	2,668
10	35,567	2,964
11	39,123	3,260
12	42,680	3,557
Adult		
4	38,605	3,217

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2nd Pediatric Voriconazole Pharmacokinetic Study

- Open-label study with two cohorts; 9 patients each
- Ages 2-6 years, 6-12 years
 - 4 mg/kg/dose then 6 mg/kg/dose
 - 6 mg/kg/dose then 8 mg/kg/dose
 - Each child received at least two different doses in escalating order, then switched to PO
- IV doses similar PK parameters within each age cohort, except at 8 mg/kg/dose in **older** age group (34,681 vs. 25,556 ng hr/ml)
- After oral dosing, **older** group also had higher mean AUC values in both doses

2nd Pediatric Voriconazole Pharmacokinetic Study

- Even 8 mg/kg/dose, AUC (34,681) in children was **less than adults at 4 mg/kg/dose** (42,000)
- **High interpatient PK variability**, but no significant differences in the 2-6, 6-12 yrs groups except at 8 mg/kg/dose
- After oral therapy, 2-6 yrs had lower AUC and C_{max} than older children
 - **Oral bioavailability (65%) less than seen in adults (96%)**

2nd Pediatric Voriconazole Pharmacokinetic Study

- EMEA-approved dosing schedule for children
 - Load 7 mg/kg/dose q12h
 - Continue at 7 mg/kg/dose q12h

Pediatric Voriconazole Safety/Efficacy

- Retrospective analysis of safety and efficacy within the compassionate release program
 - Open label study; 69 children, 58 with IFI (42 with IA)
 - 23 patients with AE, 3 caused d/c voriconazole
 - Most common AE was elev. transaminases, skin rash
 - Complete / Partial response 45%

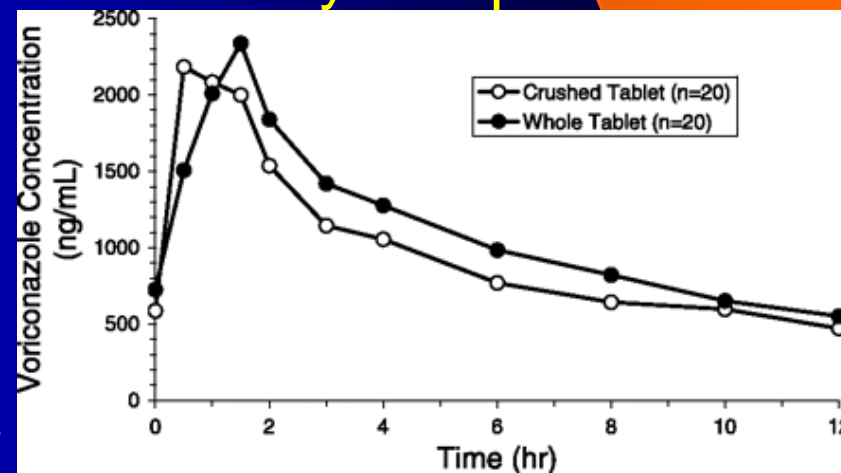
Walsh TJ, et al. *Pediatr Infect Dis J* 2002;21:240-48

- Voriconazole in 7 children with IA (mean age 5 yrs; 2-13 yrs)
 - Hematologic malignancies, prior L-AmB for mean of 6 wks
 - CR (n=2), PR (n=2), Stable (n=1), Failure (n=2)
 - CR/PR coincide with recovery from neutropenia and hem. disease remission
 - Overall response rate 57%; 100-day survival 42%

Cesaro S, et al. *Support Care Cancer* 2003;11:722-7.

Voriconazole: Crushed or Whole Tablets

- IV preparation with cyclodextrin concerns, oral suspension unavailable in some countries
- Open-label, randomized, two-way crossover comparative PK using 20 healthy volunteers
 - Mean AUC for crushed = 9,793 ng h/ml
 - Mean AUC for whole = 11,164 ng h/ml
- Slightly faster time to maximum concentration of drug in serum in crushed tablets (0.5 hrs vs. 1.5 hrs)
- **Conclusion: Crushed tablet bioavailability is equivalent to whole tablet**



Pediatric Posaconazole

- 7 CGD patients, open-label protocol (POS 02095)
 - 2 patients < 18 years old
 - 6 proven, 1 probable IFI
 - 6 complete response, 1 failure

Segal BH, et al. *Clin Infect Dis* 2005;40:1684-1688

- 23 zygomycosis patients, open-label studies
 - 2 patients < 18 years old
 - 70% success (16/23)

Greenberg RN, et al. *Antimicrob Agents Chemother* 2006;50:126-133

Pediatric Posaconazole: Comparison with Adult Levels

- 12 patients (8-17 yrs) from a phase III open-label study
 - Ages: 8, 10, 12, 12, 14, 15, 15, 15, 16, 16, 16, 17
- 800mg/day divided as oral suspension
- Comparison: Adults (18-64 yo) with 800mg/d

Posaconazole plasma concentration (ng/ml)

	<u>Pediatric (n=12)</u>	<u>Adult (n=194)</u>
Mean	776	817
Median	579	626
Range	85.3 – 2,891	0 – 3710

- Suggests posaconazole pharmacokinetics are similar in adults and children
- Dedicated pediatric studies in development

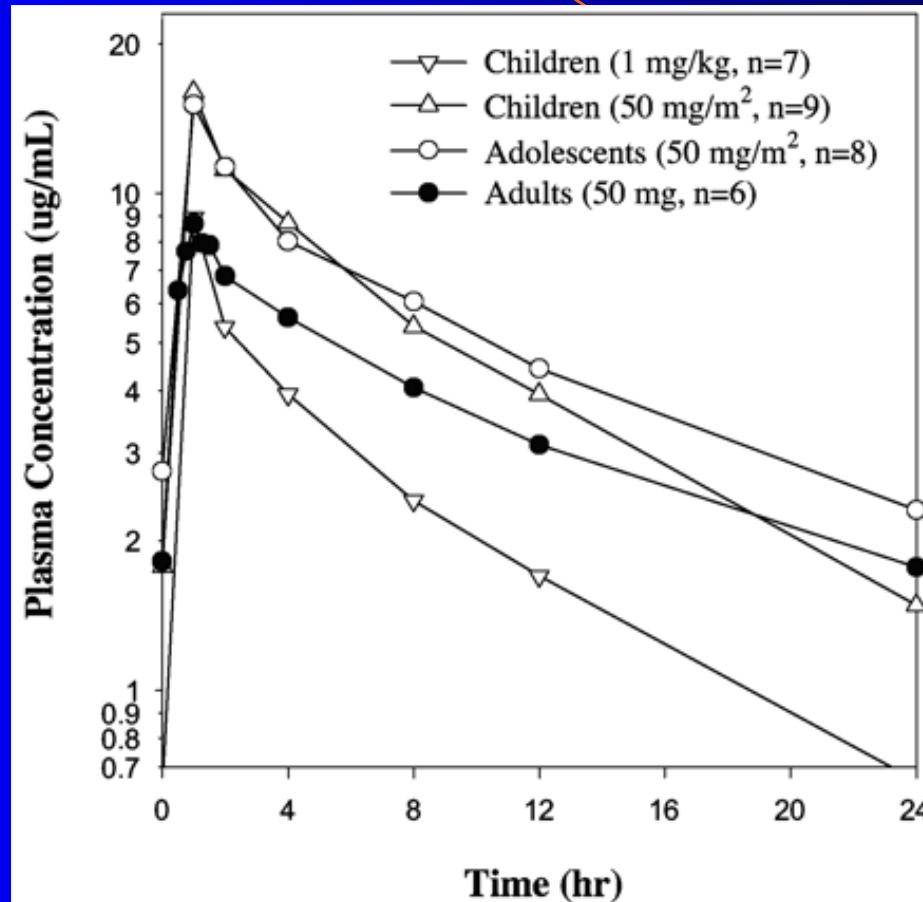
New Dedicated Pediatric Posaconazole Pharmacokinetic Study

- Hematology / Oncology Patients with Febrile Neutropenia
- Dose escalation
- Attempts to determine if PK really is similar to adult patients
- Protocol finalized in Summer 2007

Pediatric Caspofungin

- *Adult dosing: Load 70 mg, then 50 mg once daily*
- Eight US medical centers, enrolled 39 patients
- Patients (ages 2-17) with new-onset febrile neutropenia
 - Children age 2-11 yrs
 - Children age 12-17 yrs
 - Initial plan to use weight-based approach at 1 mg/kg/d and 1.5 mg/kg/d
 - Protocol amended after first nine patients enrolled to study a BSA approach at 50 mg/m²/d and 70 mg/m²/d
 - Max dose for any group was 70 mg/day
- PK compared two historical cohorts of adult patients
- Enrollment:
 - Caspo 50 mg/m²/d (2-11 yrs): Mean 7.3 yrs (3 children from 2-6 yrs)
 - Caspo 50 mg/m²/d (12-17 yrs): Mean 14.0 yrs

Caspofungin Mean Plasma Concentration-Time Profiles



Compared to adult patients with mucosal candidiasis
Pediatric = day 4 of therapy; Adults = day 9 of therapy

Differences in Pediatric Caspofungin Dosing

- Weight-based (1 mg/kg/d) resulted in suboptimal (plasma concentrations in all children relative to adults (50 mg/d):
 - AUC_{0-24} 41-46% less ($p < 0.001$)
 - C_{24} 67-69% less ($p < 0.001$)
 - B-phase half-life 37% less ($p = 0.001$)
- BSA dosing revealed adolescent and pediatric concentrations descend more rapidly than adults
- BSA dosing consistent across pediatric ages, but statistically significant decreases in end-of-infusion concentrations of caspofungin with increasing age
- Critical PK parameter appears to be concentration-dependent, rather than time-dependent

Pediatric Caspofungin

- Retrospective analysis of compassionate use
 - 25 patients received at least 1 dose
 - 13 documented, 8 suspected, 4 prophylaxis
 - 13 patients were neutropenic
 - All 21 patients with documented / suspected also received liposomal amphotericin B; others also with itraconazole (n=3), voriconazole (n=3)
 - Possible drug-related AEs in 3 (12%) patients
 - No efficacy data presented

Pediatric Caspofungin

- Multicenter, Retrospective
- 64 patients (48/64 with hematologic malignancies)
 - Proven (n=17), Probable (n=14), Possible (n=17), Empiric therapy (n=16)

<u>Response</u>	<u>Proven</u>	<u>Probable</u>
Complete	5	3
Partial	7	4
Stable	3	3

- Empiric: 11/13 completed empiric therapy without breakthrough
- Overall survival 75% at EOT and 70% at 3 months post-EOT

Prospective, Multicenter Trial of Caspofungin in Pediatric Patients

- Interim analysis of 28 patients (planned 50 patients)
- Esophageal candidiasis (n=1), invasive candidiasis (n=17), invasive aspergillosis (n=10)
- Most candidemia with primary therapy (14/17), most IA with salvage therapy
- Response Rates
 - Invasive Candidiasis 88% (15/17)
 - Esophageal Candidiasis 100% (1/1)
 - Invasive Aspergillosis 50% (5/10) all for salvage

Pediatric Anidulafungin

- Phase I/II dose escalation study
 - 5 centers, Persistent neutropenia at risk for IFI
 - 2 age cohorts (2-11 yrs, 12-17 yrs)
 - 2 Dosage levels (0.75 and 1.5 mg/kg/day) with double loading dose

	<u>0.75 mg/kg/d</u>	<u>1.5 mg/kg/d</u>
	(n=12)	(n=7)
C_{max}	4.10	6.67
Half-life	25.5 hrs	20.3 hrs

- Pediatric patients receiving 0.75 mg/kg/d or 1.5 mg/kg/d have similar PK to adults receiving 50 or 100 mg/d, respectively
- Anidulafungin can be dosed based on body weight, *but not related to age (> 2 yrs)*

Multicenter Phase I Pediatric Febrile Neutropenic Patients

- 7 centers, Patients aged 2-17 yrs
- Micafungin administered within 24 hours of beginning antibacterial agents for F+N
- Six Micafungin dosing levels studied
 - 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 mg/kg/d
- Age 2-12 yrs (n = 58), Age 13-17 yrs* (n = 20)
 - *Highest dose studied in the 13-17 year olds was 1.5 mg/kg/day
- Mean Age: 7.1 yrs (range 2-12 yrs)

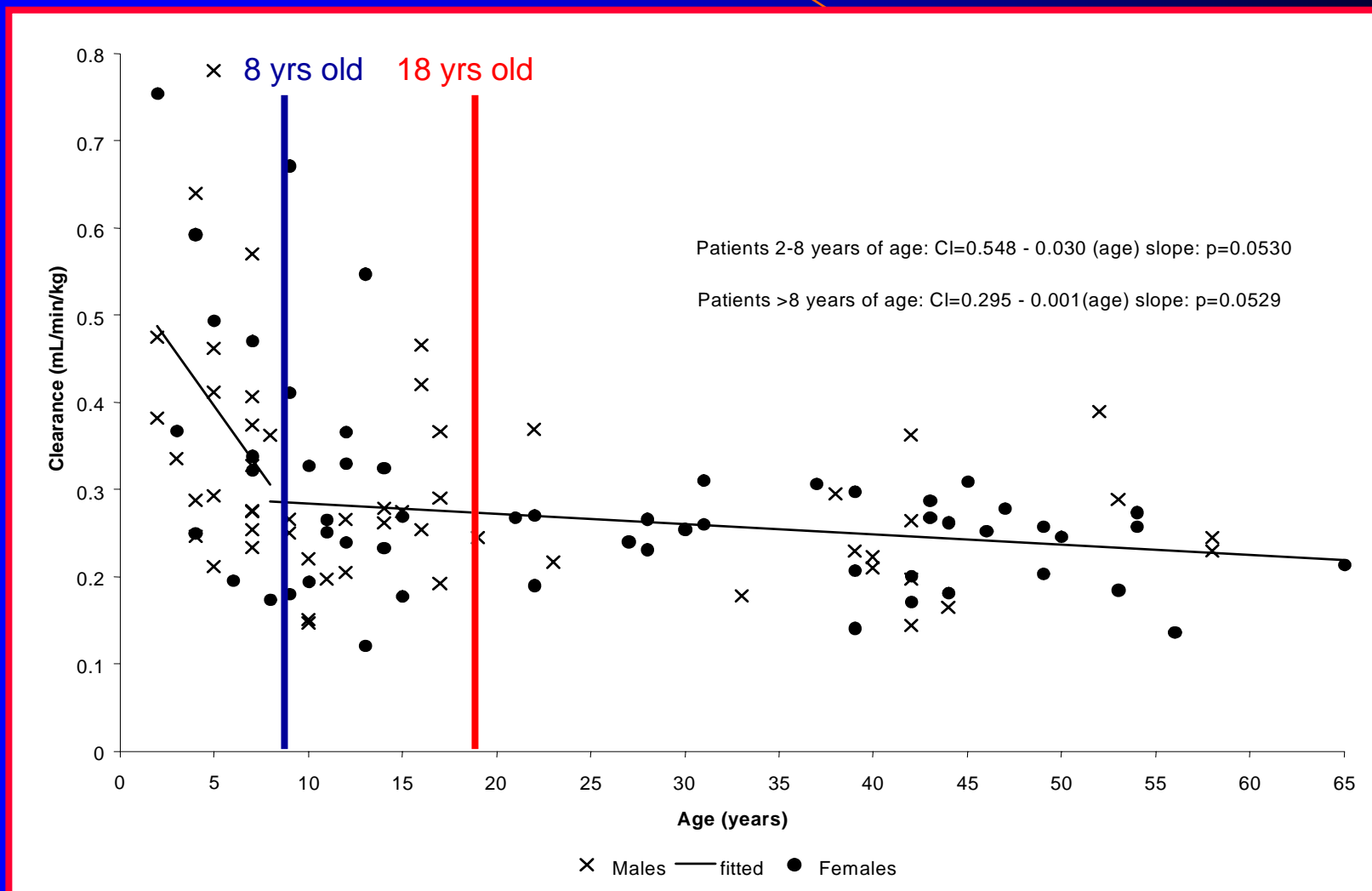
Age is Important for Micafungin

- <8 yo had clearance 1.3 – 1.5 times greater than children > 8yo

	<u>2-8 yo</u>	<u>9-17 yo</u>
Clearance (ml/min/kg)	0.385 ± 0.15	0.285 ± 0.12
V _{ss} (L/kg)	0.35 ± 0.18	0.28 ± 0.09
Half-life (hours)	11.6 ± 2.8	13.3 ± 4.3

- Linear plasma pharmacokinetics over dosage range studied
- Dose 1.5 x adult dose would be appropriate (4.5 mg/kg ?)

Individual Plasma Clearance Values in Pediatric (Protocol 98-0-043) and Adult (Protocol 97-0-041) Patients on Day 1 of Dosing



Population Pharmacokinetics of Micafungin in Pediatric Patients

- Population PK analysis of 72 children (ages 2-17 yrs) dosed at 0.5 – 4.0 mg/kg/day as empirical febrile neutropenia therapy
- Allometric model (relating body function and morphology to body size) with best fit
 - Showed that clearance in smaller children is higher than predicted on the basis of weight alone
- To achieve equivalent AUC to adults receiving 100, 150, and 200 mg/day, pediatric patients required a dose of $3.38 \times \text{weight}^{0.25}$, $5.07 \times \text{weight}^{0.25}$, $6.77 \times \text{weight}^{0.25}$
- Non-linear relationship between weight and clearance
- Therefore, as weight decreases, progressively higher doses of micafungin (mg/kg) are required to achieve equivalent drug exposure
 - These doses are higher than predicted on the basis of weight alone, and especially in children weighing < 10-15 kg

Comparing Pediatric and Neonatal Micafungin Pharmacokinetics

Children

500 – 1000 grams

> 1000 grams

Children 2-8 yrs

Half life

5.5 hrs

8 hrs

12hr

Clearance

97.3 ml/hr/kg

55.9 ml/hr/kg

32.2 ml/hr/kg

- Shorter half-life and more rapid clearance per kg in neonates versus children

Open-label, Non-Comparative Study of New or Refractory Candidemia

Micafungin 50 mg/d (1 mg/kg if < 40 kg) for *C. albicans*

Micafungin 100 mg/d (2 mg/kg if < 40 kg) for *non-albicans Candida*

- Dose escalation allowed for incomplete response
 - Adult patients n=106 (84.1%)
 - **Pediatric (<16 yo) patients** n=20 (15.9%)
- Overall Complete/Partial response 83.3% (105/126)
 - 87.5% (63/72) in patients with a new infection
 - 76.0% (19/25) in patients with a refractory infection
 - 84.9% (90/106) in adult patients
 - **75.0% (15/20) in pediatric patients**
 - **11 neonates (including 5 premature) – 8/11 with complete response**

Micafungin vs. Fluconazole for HSCT Prophylaxis

- Randomized, Double-blind, Phase III Non-inferiority study (n=882)
 - 72 centers in the US and Canada
 - HSCT candidates \geq 6 months old

	<u>Micafungin (n=425)</u>	<u>Fluconazole (n=457)</u>
Pediatric (< 16 yrs)	9.2% (39/425)	9.8% (45/457)
Adult (16 – 64 yrs)	83.0% (353/425)	85.1% (389/457)
Adults (> 64 yrs)	7.8% (33/425)	5.0% (23/457)

Treatment Success

	<u>Micafungin</u>	<u>Fluconazole</u>
Pediatric <16 yrs	69.2% (27/39)	53.3% (24/45)
Adult 16-64 yrs	81.1% (313/386)	75.7% (312/412)
Adult > 64 yrs	97.0% (32/33)	69.6% (16/23)

Collaborative Pediatric Groups

There has never been a large scale, prospective, dedicated pediatric invasive fungal infection study for diagnosis or treatment

International Pediatric Fungal Network

- Currently 55 world-wide sites
 - United States (n=35); International (n=20)
- Electronic CRF capture
 - Web-based entry, SQL database
- Future laboratory storage
 - Collaboration with CDC
- Sponsored by various Companies / Foundations

DUKE UNIVERSITY SCHOOL OF MEDICINE International Pediatric Fungal Network

pfn.pediatrics.duke.edu



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International Pediatric Fungal Network

About the International PFN

Dedicated to Understanding Pediatric Fungal Invasive Infections and Antifungals Through Global Collaboration

PFN Pediatric Fungal Network
The incidence of pediatric invasive fungal disease is increasing. Coordinated clinical and laboratory investigative efforts have enhanced our understanding of fungal disease and improved the treatment of adult patients. However, most of these efforts have not incorporated children and neonates. Pediatric exclusion has limited our knowledge of the epidemiology and pathophysiology of pediatric fungal disease and has resulted in a paucity of data regarding the safety and efficacy of pediatric antifungal therapy. Previous pediatric cooperative models in other disciplines, including the Children's Oncology Group and the Pediatric AIDS Clinical Trials Group, have successfully advanced our understanding and treatments of other childhood diseases.

The multi-center International Pediatric Fungal Network (PFN) was created to gain a complete understanding of the scope and character of pediatric fungal infections in order to improve the care of our patients. The primary mission of the PFN is to increase the knowledge of pediatric invasive fungal infections and discern any undescribed characteristics or outcomes unique to pediatric patients through a coordinated network of scientific investigation. In addition to advancing our understanding of the fundamental epidemiology of pediatric invasive fungal infections, the PFN will serve as an effective vehicle of cohesive investigators and centers to conduct ground-breaking diagnostic and therapeutic clinical trials focused on pediatric fungal infections, diagnostic surrogates, and antifungals. Clinical information on patients is captured through a secure electronic portal to maximize efficiency of data collection and analysis. Investigators are linked through conference calls and meetings to both plan future studies and analyze results.

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Pediatric Fungal Network

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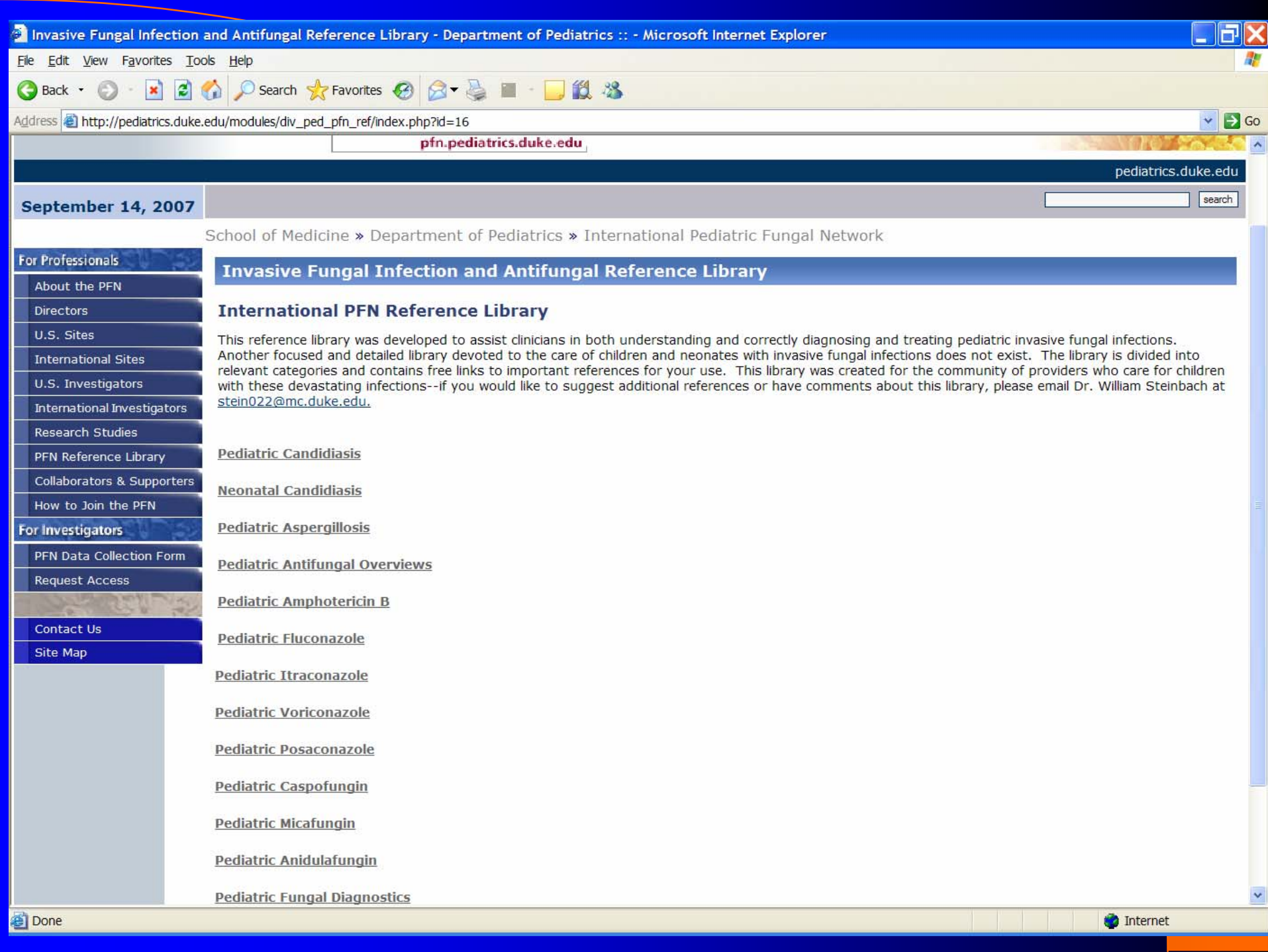
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Invasive Fungal Infection and Antifungal Reference Library

International PFN Reference Library

This reference library was developed to assist clinicians in both understanding and correctly diagnosing and treating pediatric invasive fungal infections. Another focused and detailed library devoted to the care of children and neonates with invasive fungal infections does not exist. The library is divided into relevant categories and contains free links to important references for your use. This library was created for the community of providers who care for children with these devastating infections--if you would like to suggest additional references or have comments about this library, please email Dr. William Steinbach at stein022@mc.duke.edu.

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