Development Considerations of
Antifungal Drugs to Address Unmet
Medical Need

Pediatric Antifungal Drug Development Considerations

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Disclaimer

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Objectives

Outline

- Epidemiology of invasive fungal infections (IFI) in children
- Use of Antifungal Agents in Pediatrics
- Antifungal Agent Clinical Trials in Pediatrics
- Pipeline of Antifungal Agents in Pediatrics
- Challenges in pediatric trial and what can be done

Epidemiology of Invasive Fungal Infections (IFI) in pediatrics

- *Candida* spp the leading cause of IFI in children
  - Predominance of non-albicans Candida spp. in pediatrics (56%), neonates (52%)
  - *Candida auris* in children
    - Pediatric patients have only been reported in Asia and S. America (case series)
    - Common risk factors: premature neonates, ICU patients, post-surgery, hematologic malignancies
    - Mortality 30% (lower than adults 30-60%)
  - RF: prematurity, surgery in infants, malignancy in children
  - Mortality ≈ 10%-30%
  - The incidence of candidemia neonates and infants declining after 2009, remains stable 2012-2015
- Aspergillosis most common mould infection
  - *Aspergillus fumigatus* and *Aspergillus flavus*
  - RF: hematological malignancies, solid organ transplantation, primary immunodeficiencies
  - Mortality ≈ 18%
- Mucorales family
  - *Rhizopus* spp, *Lichthemia* spp, *Mucor* spp
  - RF: hematological malignancies, other malignancies, HSCT, SOT, trauma/surgery, diabetes mellitus
  - Mortality ≈ 33%

Benedict K et al J Pediatr Infect Dis Soc 7: e78; Warris A. Arch Dis Child 103: 891; Steinbach WJ. Clin Microbiol Infect 16: 1321; Pana ZD et al JPIDS 6 (Suppl 1): S3; International Pediatric Fungal Network (IPFN); Zygomyco.net, FungiScope

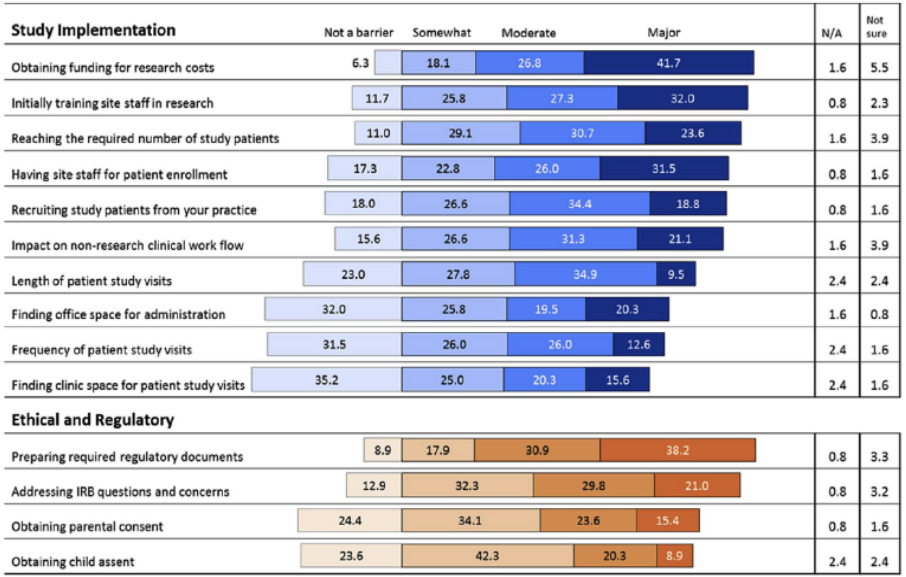
Use of Antifungal Agents in Pediatrics

- Data on Antifungal Utilization in Pediatrics are sparse
- Increased Antifungal utilization overtime
  - Retrospective cohort study, Pediatric Health Information System, 25 US pediatric hospitals, from 2000-2006
    - Prescription significantly increased-> 32/1,000 hospitalization (2000) 38/1,000 hospitalizations (2006) (p=0.03)
  - Canadian Univ Hospital (400 pediatric beds)
    - 2.97-fold increase of antifungal agent consumption 2005-2011
- Sub-optimal dosing of antifungal agents in children
  - Point prevalence ARPEC study, 226 centers around the world, 1 mo – 18 yrs, Oct-Dec 2012
  - Most common indication was medical prophylaxis > empirical treatment of febrile neutropenia > treatment of confirmed or suspected IFI (14%)
  - Most frequently prescribed antifungal were fluconazole and amphotericin B deoxycholate
  - **Sub therapeutic doses were prescribed in 47% of cases**
- Inadequacy of well designed clinical trials and PK-PD data for neonates and children

Prasad PA et al Ped Infect Dis J 27: 1083; Guillot J et al J Ped Pharmacol Ther 19; 196;
Lestner JM et al Antimicrob Agents Chemother 59; 782; Menson EN et al BMJ 332; 1183

Antifungal Agent Clinical Trials in Pediatrics

- US Data: number of Registered Clinical Trials in Adults x10 compared to children
- *ClinicalTrials.gov* data: Clinical Trials in fungal infections in adults x3 compared to children (977 vs 351)
- 17,495 pediatric Trials registered on Clinical Trials.gov, Oct 2007-Sept 2017
  - 122 systemic antibacterial or antifungal drug trials industry or US federal funding
  - 80% involved antibacterials, 19% antifungals, 1% both
  - <1% (122/17,495) pediatric clinical trials
  - 30% antibacterial trials and 10% antifungal trials included neonates



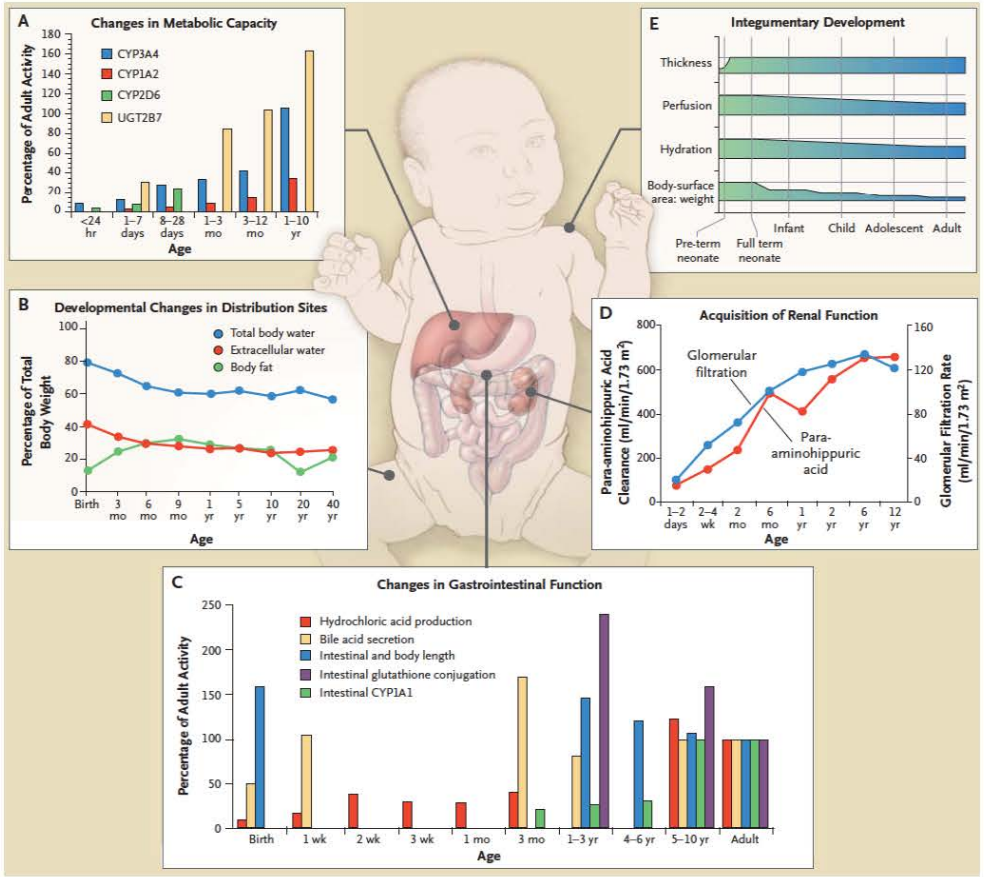
Study Implementation	Not a barrier	Somewhat	Moderate	Major	N/A	Not sure
Obtaining funding for research costs	6.3	18.1	26.8	41.7	1.6	5.5
Initially training site staff in research	11.7	25.8	27.3	32.0	0.8	2.3
Reaching the required number of study patients	11.0	29.1	30.7	23.6	1.6	3.9
Having site staff for patient enrollment	17.3	22.8	26.0	31.5	0.8	1.6
Recruiting study patients from your practice	18.0	26.6	34.4	18.8	0.8	1.6
Impact on non-research clinical work flow	15.6	26.6	31.3	21.1	1.6	3.9
Length of patient study visits	23.0	27.8	34.9	9.5	2.4	2.4
Finding office space for administration	32.0	25.8	19.5	20.3	1.6	0.8
Frequency of patient study visits	31.5	26.0	26.0	12.6	2.4	1.6
Finding clinic space for patient study visits	35.2	25.0	20.3	15.6	2.4	1.6
Ethical and Regulatory						
Preparing required regulatory documents	8.9	17.9	30.9	38.2	0.8	3.3
Addressing IRB questions and concerns	12.9	32.3	29.8	21.0	0.8	3.2
Obtaining parental consent	24.4	34.1	23.6	15.4	0.8	1.6
Obtaining child assent	23.6	42.3	20.3	8.9	2.4	2.4

Provider perceptions of potential study implementation and ethics regulatory barriers to pediatric clinical trial implementation

ClinicalTrials.gov; Greenberg RG et al Contemp Clin Trials Commun 9: 7; Thaden J et al Pediatrics 142; e20171849

Children are not Little Adults

Developmental changes that influence Drug Disposition in Infants, Children and Adolescents



Differences in Infections and Hosts: Pediatrics vs Adults

- **Differences in Mycoses**
- Increased incidence of hematogenous *Candida* meningoencephalitis (HCME) in pediatric vs adult patients
- Lower attributable mortality of candidemia in children vs adults
- Different imaging features children with invasive aspergillosis
- Tinea capitis in children, not adults

- **Differences in hosts**
- Neonates
- Primary immunodeficiencies
- Decreased frequency of co-morbidities

McCarthy MW et al: J Pediatric Infect Dis Soc. 6(3): e123-e133; Walsh TJ et al J Fungi 5:11; Katragkou A et al: J Pediatric Infect Dis Soc 6 (suppl_1):S22-S31; Antachopoulos C et al Eur J Paediatr. 166:1099-117

Dosage Relations in Pediatric Antifungal Pharmacology

Compound	Adult Dosage	Pediatric Dosage	Relationship between Adult and Pediatric Dosages
DAmB	0.5-1.0 mg/kg IV	0.5-1.0mg/kg IV	Linear
LAmB	3.0-7.5 mg/kg IV	3.0-7.5 mg/kg IV	Linear
ABLC	3.0-7.5 mg/kg IV	3.0-7.5 mg/kg IV	Linear
Fluconazole	400 mg (6 mg/kg) IV/PO	12 mg/kg IV/PO	Non-linear
Itraconazole CD	200 mg PO BID	2.5 mg/kg PO BID	Linear
Voriconazole	3-4 mg/kg IV	4-8 mg/kg IV	Non-linear
Posaconazole suspension	400-800 mg PO	Target not achieved	Non-linear
Isavuconazole	200 mg IV, PO	10 mg/kg IV, PO	Non-linear

Walsh TJ et al, AAC 41: 1944; Walsh TJ et al, AAC 61:e01477; Lee JW, et al. J. Pediatr. 120: 987; Groll AH, et al. AAC. 46: 2254; Walsh TJ et al AAC 54: 4116; Walsh TJ et al AAC 48: 2166; Walsh TJ et al Pediatr Infect Dis J 21: 240 ; Arrieta AC, et al. PLOS ONE; 14:e0212837

Dosage Relations in Pediatric Antifungal Pharmacology

Compound	Adult Dosage	Pediatric Dosage	Relationship between Adult and Pediatric Dosages
Caspofungin	50 mg IV	50 mg/m^2	Non-linear
Micafungin	100 mg IV	2-10 mg/kg	Non-linear
Anidulafungin	100 mg IV	1.5 mg/kg	Linear

Walsh TJ, et al. AAC. 49:4536-4545; Benjamin DK, Jr et al. AAC. 50: 632; Benjamin DK Jr et al Clin Pharmacol Ther 87: 93; Smith PB, et al. PIDJ 28:412; Hope WW, et al. AAC. 54:2633; Kovanda LL, et al. PIDJ. 37:580

Children are not Little Adults

Specific considerations for Antifungal Agents

- PK Changes from Infants to Adolescents to Adults
  - Allometric scaling:
  - $P_{child} = P_{adults} \bullet [WT/70]^{x}$, where x may be vary widely
- PK variability in children
- Therapeutic targets for antifungal agents differ in young infants

Watt KM et al Pediatr Infect Dis J. 31 (6): 635

PK Changes from Infants to Adolescents

- Pediatric dosing extrapolated from adults (linear modeling)
- Changes in renal function, drug-metabolism enzymes, body composition -> not always successful
- Risk of under- or over- dose -> greater risk of death, morbidity and resistance development
- Phase 1, open label, sequential group dose, **Micafungin PK** assessed in febrile neutropenic children
  - Micafungin PK is linear, clearance independent of dose
  - Drug clearance higher in children 2-8 years old
  - **Younger children x 1.5 higher dose than those for adults**
- Sub study Phase 3, analyzed **Micafungin PK** parameters children < 5 years vs > 5 years old
  - Children < 5 years old lower peak concentration and lower overall exposure
  - Children < 5 year old higher M-5 concentration and increased clearance
- Phase 1, multicenter, open label sequential dose trial of **Micafungin in premature neonates**
  - Infants even higher Micafungin clearance and volumes of distribution
  - Doses 5-7 mg/kg to achieve adult exposures

Seibel NL et al Antimicrob Agents Chemother 49: 3317; Heresi GP et al Pediatr Infect Dis J 25: 1110; Undre NA et al Pediatr Infect Dis J; 31: 630

PK variability in children

- Inter-individual PK variability is influenced by age
- Micafungin increased variability in younger patients
  - Neonates have increased inter-individual variability in micafungin clearance
- Voriconazole was wide variability in all ages
  - In adults variability is due to non-linear PK
  - In children variability is due to linear PK
  - Over the range 4-8 mg/kg q12h the elimination of voriconazole is non linear (2-11 years)
  - Young children < 3 years increased variability in trough concentrations which do not correlate with the dose (3.4-15 mg/kg)
- TDM should be routine in young children

Doby EH et al Pediatr Infect Dis J; 31: 632; Purkish L et al Br J Clin Pharmacol; 56 (S1): 10; Walsh TJ et al Antimicrob Agents Chemother 54: 4116; Walsh TJ et al Antimicrob Agents Chemother 48: 2166; Walsh TJ et al Pediatr Infect Dis J 21: 240

Therapeutic targets for antifungal agents differ in young infants

- Animal models & case series show that *Candida* spp. frequently invade CNS in young infants
- All infants < 3 months with systemic candidiasis assumed to have *Candida* meningoencephalitis (HCME)
- CNS compartments are difficult to access for PK sampling in humans
- Bridging studies combining animal and human data with computer simulation has been successful
  - PK/PD studies of Micafungin in rabbit model of HCME
  - Micafungin penetrates most compartments of CNS
  - High plasma concentrations required to achieve therapeutic tissue levels
  - A neonatal dose of ≈9 mg/kg results in a similar mean $AUC_{0\text{-}24}$ at a steady state to an adult dose of 150 mg and children aged 2-17 receiving 2 mg/kg
  - Near maximal effect with neonatal doses 12-15 mg/kg (stimulation findings)
- Open label study of micafungin in neonates with invasive candidiasis Micafungin doses 7 and 10 mg/kg/day provides exposure levels adequate for CNS coverage

Hope WW et al J Infect Dis; 197: 163; Benjamin DK Jr et al Clin Pharmacol Ther 87; 93

Novel antifungal agents under clinical development

Pipeline: 10 pipeline antifungal agents

- **Prophylaxis**
  - ✓ First-time for ALL patients without drug interactions (MAT2203)
- **Invasive candidiasis**
  - ✓ Switch to oral without switching mechanism of action (Ibrexafungerp)
  - ✓ Outpatient once weekly iv treatment (Rezafungin)
- **Aspergillosis**
  - ✓ Additional treatment options (Olorofim, Ibrexafungerp, APX001, VL-2397)
- **Scedosporium / Lomentospora prolificans**
  - ✓ First reliable treatment ever (Olorofim)

Strategies to Optimize Pediatric Clinical Research

Clinical Trial Optimization

- **Optimized data collection and use**
  - Bio analytical optimization (early phase)
    - ultralow-volume assays, dried matrices (blood, plasma, urine spots), micro needle sampling
  - Pragmatic Trial Designs (late phase)
    - real world effectiveness in broader population (minimized inclusion/exclusion criteria, study visits, procedures, central management)
  - Electronic health records (late phase)
    - For outcome data (focus on meaningful, well defined outcomes)

Strategies to Optimize Pediatric Clinical Research

Clinical Trial Optimization

- **Reducing participant Risk**
  - Opportunistic designs (early phase)
  - ➢ reduces extra or unnecessary procedures, higher patient acceptance and enrollment, fluconazole as a proof-of-concept
  - Sparse/scavenged sampling (early phase)
  - ➢ samples from unused or excess specimens obtained for clinical purposes
  - Microdosing
  - ➢ single sub-therapeutic dose (1/100 dose for pharmacologic effect)
  - Efficacy extrapolation (late phase)
  - ➢ Data from adults to children, algorithms to guide extrapolation

Balevic SJ et al J Clin Pharmacol 58: S58; Laughon MM et al Exp Rev Clin Pharmacol 4: 643

Strategies to Optimize Pediatric Clinical Research

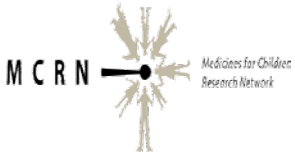
Clinical Trial Optimization

- **Increased efficiency and reduced costs**
  - Master protocols (early and late phase)
  - ➢ evaluate several different agents or diseases in parallel “sub-studies” using a common design, increases operational efficiency, reduces time and cost
- Increased enrolment and collaboration
  - Research Networks
  - ➢ overcoming enrollment barriers, studies more patient-centric

Balevic SJ et al J Clin Pharmacol 58: S58; Laughon MM et al Exp Rev Clin Pharmacol 4: 643

Clinical Data Networks in Children

- Pediatric Trials Network
- Global Research in Pediatrics
- Pediatric Trials Consortium
- Pediatric Trials Network Australia
- Medicines for Children Research Network (MCRN)
- Canadian KidsCAN trial network
- International Pediatric Fungal Network (IPFN)



Strategies to Optimize Pediatric Clinical Research

Stimulation and Modeling

- Optimized study design
  - Clinical Trial Simulations (early and late phase)
    - combine disease modeling with PK/PD modeling to simulate trial design features (effects of disease progression, placebo response and drop out)
    - Increases trial success, operational efficiency and precision
- Predict Effects of Organ Dysfunction
  - Physiologically Based Pharmacokinetics (PBPK)
    - technique mathematically incorporates organ-specific physiologic compartments to describe drug PK, response to therapy, and safety
- Individualized dosing
  - Population PK
  - Bayesian analyses
  - Concentration guided trials

Balevic SJ et al J Clin Pharmacol 58: S58; Laughon MM et al Exp Rev Clin Pharmacol 4: 643

Conclusions & Future Perspectives

- IFI severe complications of the most vulnerable pediatric population (neonates, severely ill, immunocompromised)
- Children=therapeutic orphans
- Historical Challenges is pediatric trial development: low enrollment, poor dose escalation, different disease mechanisms, inadequate study design
- National Research Networks in USA and EU use novel clinical trial designs
- Sparse/scavenged sampling, population PK, “opportunistic” studies address some of the challenges
- **Precision medicine**: precision guided trials, PK/PD modeling, pharmacogenetic testing

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