Development Considerations of Antifungal Drugs to Address Unmet Medical Need

Pediatric Antifungal Drug Development Considerations

Aspasia Katragkou MD, PhD
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
  - 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); Zygomyc.net, FungiScope
Use of Antifungal Agents in Pediatrics

• Data on Antifungal Utilization in Pediatrics are sparse

• Increased Antifungal utilization overtime
  o Retrospective cohort study, Pediatric Health Information System, 25 US pediatric hospitals, from 2000-2006
    o Prescription significantly increased-> 32/1,000 hospitalization (2000) 38/1,000 hospitalizations (2006) (p=0.03)
  o Canadian Univ Hospital (400 pediatric beds)
    o 2.97-fold increase of antifungal agent consumption 2005-2011

• Sub-optimal dosing of antifungal agents in children
  o Point prevalence ARPEC study, 226 centers around the world, 1 mo – 18 yrs, Oct-Dec 2012
  o Most common indication was medical prophylaxis > empirical treatment of febrile neutropenia > treatment of confirmed or suspected IFI (14%)
  o Most frequently prescribed antifungal were fluconazole and amphotericin B deoxycholate
  o 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 ClinicalTrials.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

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

## Dosage Relations in Pediatric Antifungal Pharmacology

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

## Dosage Relations in Pediatric Antifungal Pharmacology

<table>
<thead>
<tr>
<th>Compound</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
<th>Relationship between Adult and Pediatric Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>50 mg IV</td>
<td>50 mg/m²</td>
<td>Non-linear</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg IV</td>
<td>2-10 mg/kg</td>
<td>Non-linear</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>100 mg IV</td>
<td>1.5 mg/kg</td>
<td>Linear</td>
</tr>
</tbody>
</table>

Children are not Little Adults

Specific considerations for Antifungal Agents

- PK Changes from Infants to Adolescents to Adults
  - Allometric scaling:
    - $P_{child} = P_{adults} \cdot [WT/70]^x$, 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

PK variability in children

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

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_{0-24} 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)*
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

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

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

Conclusions & Future Perspectives

• IFI severe complications of the most vulnerable pediatric population (neonates, severely ill, immunocompromised)
• Children=therapeutic orphans
• Historical Challenges in 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
Acknowledgments

Mentors
Emmanuel Roilides, MD, PhD
Thomas J. Walsh, MD, PhD
Thank you