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Limited Population Pathway for Antifungal Drugs: Meeting the Challenges of Uncommon and Emerging Mycoses

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Investigator of Emerging Infectious Diseases of the Save Our Sick Kids Foundation

Background in Invasive Mycoses

- For past 4 decades
- Caring for pediatric and adult patients with invasive mycoses
- Conducting laboratory and clinical research in invasive mycoses
- Contributed to understanding or approval of 12 licensed systemic antifungal agents currently used in patients
- Studied multiple other investigational agents
- Principal Investigator or Associate Investigator on >100 clinical protocols

- Currently
- Henry Schueler Foundation Scholar in Mucormycosis
- Investigator of Emerging Infectious Diseases of the Save Our Sick Kids Foundation
- Scientific Steering Committee of the Mycosis Study Group
- Executive Committee and Past President of the Medical Mycology Society of the Americas
- Fellow, of the European Confederation of Medical Mycology
- Fellow, Infectious Diseases Society of America
- Founding Director, NYCCaRes (New York City Collaborative Consortium for *Candida auris* Research)

Why are Invasive Fungal Infections Challenging to Treat and What are the Unmet Needs?

- **Major advances in antifungal therapy during the past three decades**
- **High mortality even when treated with current agents**
- **Causes**
  - **Delayed diagnosis**
  - **Immunologically impaired hosts**
  - **Limited therapeutic options**
  - **Antimicrobial resistance (AMR)**

- **Unmet Needs in AMR and resistant/refractory fungal infections (RFIs)**
  - ***Candida* spp (e.g., *Candida auris*)**
  - ***Aspergillus* spp. (e.g., triazole-resistant)**
  - **Mucormycetes**
  - ***Fusarium* spp.**
  - ***Scedosporium/ Lomentospora***
  - **Other hyaline and dematiaceous moulds**

Clin Microbiol and Infect. 25:799–806; 2019
Med Mycol. 57:1–12; 2019
Clin Infect Dis. 67:1621-1630; 2018
J Fungi. 5(3) pii: E57; 2019
Clin Infect Dis. 54 Suppl 1:S67-72; 2012
Semin Respir Crit Care Med.36:706-14; 2015
N Engl J Med. 371:150-60; 2014

Urgent Need for New Antifungal Agents

- **Novel mechanisms of action to overcome fungal pathogens resistant to current antifungal agents**
- **Improved safety profile**
- **Minimal drug-drug interactions**
- **Predictable pharmacokinetics without need for TDM**
- **Especially in critically ill or complex immunocompromised patients receiving multiple medications and suffering from end-organ dysfunction**
- **Patient convenience of parenteral and oral formulations**

- **Note that the emergence of resistance is occurring principally to the antifungal triazole agents, which are the mainstays of oral therapy for most deep mycoses**

J Infect Dis. 216(suppl_3):S474-S483; 2017
Nat Rev Drug Discov. 16:603-616; 2017

What are the Key Resistant Fungal Pathogens?

- ***Candida auris***
- Distinct from other *Candida* spp.
- Simultaneous expansion across several continents
- Survival in inanimate environment
- Persistence of mucocutaneous colonization
- Transmission from both environmental and mucocutaneous sources
- Intrinsic resistance to two or more antifungal agents
- Difficulty in performing randomized trial
- Projections calculate unremitting global expansion warranting an urgently focused effort for development of new antifungal agents to meet this public health challenge

- **Mucormycetes**
- Mucormycosis carries a lethality of 40-80% in various studies
- Current protocol-defined therapy still demonstrates mortality >60%
- Inflects painful, devastating, and debilitating morbidity for many survivors
- Estimated number of cases is 1-3/million
- Rare disease
- No means of a randomized trial
- Important model for prior approval offers critical option for these and other pathogens

What are the Key Resistant Fungal Pathogens?

- ***Fusarium* spp.**
- **Lethality infections varies from 40 to 90%**
- **Strains may be completely resistant to triazoles and amphotericin B**
- **Other strains may only be susceptible to voriconazole or to amphotericin B leaving limited options**
- **No means of a randomized trial**
- **Prior second line approval for *Fusarium* spp. offers potential pathway**

- ***Scedosporium/Pseudallescheria/ Lomentospora***
- **Resistant to amphotericin B, echinocandins**
- ***Lomentospora prolificans* is completely resistant to all three major classes**
- **Prior second line approval for *Scedosporium* spp. offers potential new pathway**

What are Possible Solutions of Study Designs beyond Randomized Trials for RFIs?

- 1. Open label, non-randomized, multicenter phase 2 study of investigational agent for primary treatment of a pathogen-targeted RFI
  - Developed in conjunction with a proof of concept randomized trial for a more common invasive fungal infection; e.g., candidemia
  - Developed with proof of concept open label non-randomized data in more common mycoses
- 2. Open label, non-randomized, multicenter phase 2 study of investigational agent for primary treatment of two or more types of pathogen-targeted RFIs
  - Developed with a proof of concept randomized trial for a more common invasive fungal infection; e.g., aspergillosis
- 3. Adaptive designs are feasible but require relatively larger populations

What are Possible Solutions of Study Designs beyond Randomized Trials for RFIs?

- Open label Non-randomized
  - Controls
  - Historical data/prior publications
  - Meticulously documented contemporaneous controls
- Supportive data for efficacy
  - *In vitro* studies
    - e.g., MICs, timed kill assays, hollow fiber studies
  - *In vivo* studies
    - SPARC: Several, Predictive, Aligned, Robust, Complementary
- Meticulously documented outcomes
- Expert review panels
- Regulatory Precedent in Medical Mycology
  - Voriconazole: second line for infections caused by *Fusarium* spp and *Scedosporium* spp
  - Isavuconazole: first line for mucormycosis

What are Possible Solutions of Study Designs beyond Randomized Trials for RFIs?

- **Consider review model based upon precedent for rare cancers and other orphan diseases**
  - **Single arm, multicenter studies**
  - **Small cohorts (often <100)**
  - **Real-world evidence**
  - **Historical controls**
  - **Pooled safety and efficacy results**
  - **e.g.,**
    - **erdafitinib**
    - **lorlatinib**
    - **acalabrutinib**
    - **larotrectinib**

Conclusions

- **Urgent need for new antifungal agents targeting resistant fungal pathogens**
- **Critical need to meet the public health challenge of RFIs**
- **Infections occur in our most vulnerable patient populations resulting in potentially severe morbidity and high mortality.**
- **Novel regulatory pathways have an important role in meeting the challenges of RFIs**