



**Weill Cornell
Medicine**

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

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Henry Schueler Foundation Scholar in Mucormycosis

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%
 - Inflicts 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 RFIIs?

- **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**