

Use of Antifungals in Immunocompromised Patients

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1

Disclosures

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All financial relationships listed for this individual have been mitigated.

2

Objectives

- Recall the prevalence of fungal infections in the immunocompromised population, including oncology patients, and the associated morbidity and mortality rates.
- Describe the current antifungal agents available for the treatment and prevention of fungal infections in immunocompromised patients, including their mechanisms of action, spectrum of activity, and adverse effects.
- Discuss recent changes in antifungal treatment guidelines, including the use of combination therapy, the duration of treatment, and the role of prophylaxis.
- Identify controversies and unanswered therapeutic questions related to antifungal use in immunocompromised patients, such as the optimal management of breakthrough infections and the role of newer antifungal agents in clinical practice.
- Analyze the emerging therapies with unique mechanisms of action for the treatment of invasive fungal infections, such as immunomodulatory agents, biofilm disruptors, and host-directed therapies.

3



Fungal Priority Pathogens:

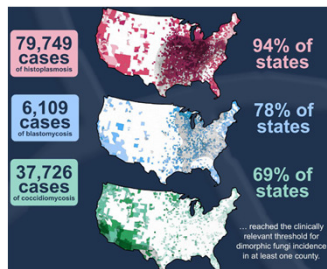
- Guide Research/Public Health
- Systematic Process
 - Incidence, antifungal resistance
 - High associated mortality rates
 - Drug resistance increasing
 - Environmental antifungal use
 - No vaccines available
 - Fortunate to have clinical data this year to aid against these pathogens

Critical group	High group	Medium group
<i>Cryptococcus neoformans</i>	<i>Histoplasma capsulatum</i> (<i>Candida glabrata</i>)	<i>Scedosporium</i> spp.
<i>Candida auris</i>	<i>Histoplasma</i> spp.	<i>Lomentospora prolificans</i>
<i>Aspergillus fumigatus</i>	<i>Eumycetozoa</i> causative agents	<i>Coccidioides</i> spp.
<i>Candida albicans</i>	Mucorales	<i>Pichia kudriavzevii</i> (<i>Candida krusei</i>)
	<i>Fusarium</i> spp.	<i>Cryptococcus gattii</i>
	<i>Candida tropicalis</i>	<i>Talaromyces marneffei</i>
	<i>Candida parapsilosis</i>	<i>Pneumocystis jirovecii</i>
		<i>Pancreaticolides</i> spp.

4

Endemic Mycoses

- Endemic fungi increasingly recognized (climate, host factors, etc.)
- Expansion of endemic regions
 - Histoplasma* (Alberta, MN, WI, MI)
 - Blastomyces* (Westward – *B. helicus*)
 - Coccidioides* (WA, NE, MO?)
- Retrospective analysis >45 million Medicare beneficiaries (2007–2016)
 - Incidence in each U.S. county
 - 100 cases/100,000 person years (*Histo/Cocc*) and 50 cases/100,000 person years (*Blasto*)
- Increased suspicion required
- Diagnosis is frequent outside of traditional regions



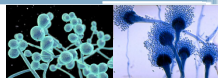
5

Risk Factors and Common Pathogens in Immunocompromised Patients

RISK FACTOR	PATIENT CONDITION	COMMON FUNGAL PATHOGENS
Neutropenia	Acute leukemia Chemotherapy	<i>Candida</i> , <i>Aspergillus</i> , Mucorales (<i>Mucor</i>)
Impaired cell-mediated immunity	Lymphoma, Immunosuppressive therapy (steroids, cyclosporine, chemotherapy, CAR-T)	<i>Cryptococcus neoformans</i> , <i>Candida</i> , <i>Aspergillus</i> , <i>Histoplasma capsulatum</i>
Loss of protective skin barriers	Venipuncture, bone marrow aspiration, urinary catheterization, vascular access devices, radiation, biopsies	<i>Candida</i>
Mucous membranes	Respiratory support equipment, endoscopy, chemotherapy, radiation	
Surgery	Solid organ transplantation	
Blood products, donor organs	Bone marrow transplantation Solid organ transplantation	
Alteration of normal microbial flora	Antimicrobial therapy Chemotherapy Hospital environment	<i>Candida</i> , <i>Aspergillus</i>

6

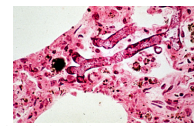
Pathogen-Specific Factors



- *Candida* spp.
 - *Candida albicans* common in neutropenic cancer patients
 - Shifting to increasing numbers of non-*albicans* *Candida* species (*C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*)
 - Decreased rates of azole susceptibility
 - Oral thrush most common; major organs involved in disseminated disease
 - Invasive candidiasis: mortality up to 35%-50%
- *Aspergillus* spp.
 - Typically acquired through inhalation of airborne spores -> lung parenchyma, pulmonary vessels -> pulmonary infarcts, hemorrhage -> disseminated disease
 - Mortality rates 80% -> 30% (prolonged neutropenia)

7

Pathogen-Specific Factors



- *Mucor* spp.
 - Spore inhalation -> rhino-orbital-cerebral & pulmonary infections
 - Hematologic malignancy >> solid tumors
 - Poor prognosis
 - Rhino-orbital-cerebral: 25-60% mortality
 - Pulmonary: 50-70% mortality
 - Disseminated: 90-100% mortality

8

Real-world Use of Mold-Active Triazole Prophylaxis in the Prevention of Invasive Fungal Diseases: Results From a Subgroup Analysis of a Multicenter National Registry

M. Hong Nguyen,^{1,2} Luis G. Sanchez,^{1,2} Peter G. Pappas,¹ Thomas J. Walsh,^{1,2} Joseph Ribala,³ Barbara D. Alexander,⁴ Monica K. Mitsch,⁵ Jennifer Jiang,⁶ Yi Tang,⁷ and George R. Thompson⁸

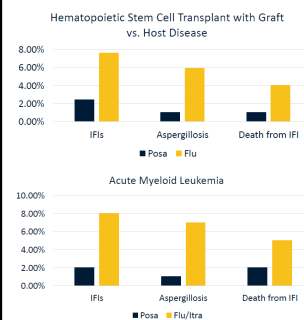
Prophylaxis needed in high-risk patients

- N=2009 patients
- N=1177 prophylaxis
 - Heme malignancy (77%)
- ADR= 14%, discontinuation in 11%
- Breakthrough uncommon- 4-5%
 - Breakthrough: *Aspergillus* (29%), *Candida* (36%)
- Multiple/sequential therapy higher risk (15%)
- Drug discontinuation uncommon
- Azole mold prophylaxis effective

	Isoniazide n=265	Posaconazole n=303	Voriconazole n=272	Multiple/Sequential n=262
Prophylaxis patients with assessment	221	214	226	208
Breakthrough IFI	11 (5.0)	30 (13.9)	9 (4.0)	10 (4.8)
Adverse Drug Reaction	15 (6.8)	48 (22.4)	36 (15.9)	26 (12.5)
Death	4 (1.8)	31 (14.5)	24 (10.6)	48 (22.6)
Less toxicity	4 (1.8)	31 (14.5)	24 (10.6)	48 (22.6)
Median survival increased	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.9)
Aspartate aminotransferase increased	0	0	1 (0.4)	4 (1.9)
Alanine aminotransferase increased	0	0	1 (0.4)	4 (1.9)
Bilirubin increased	2 (0.9)	7 (3.3)	9 (4.0)	11 (5.3)
Liver function test increased	0	9 (4.2)	7 (3.1)	12 (5.8)
Blood alkaline phosphatase increased	1 (0.4)	0	0	3 (1.4)

9

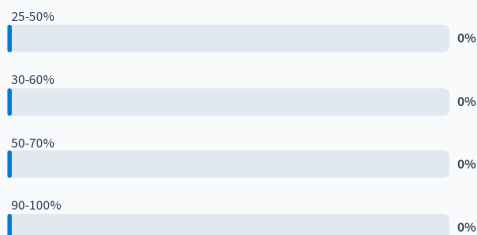
Antifungal Prophylaxis....



- Breakthrough IFIs
 - *Aspergillus*, *Fusarium*, *Mucorales*, *Scedosporium*
- Long-term use ADRs
 - Fluconazole/voriconazole
 - Alopecia
 - Voriconazole
 - Perioritis
 - Phototoxicity
 - Posaconazole
 - Mineralocorticoid excess
- Pharmacokinetic variability
 - TDM not widespread or real-time

10

What is the overall mortality rate for pulmonary mucormycosis?



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12

ANTIFUNGAL RESISTANCE & other concerns

- Fluconazole
 - *C. glabrata*
 - Majority of isolates at MIC 16-32 (if using EUCAST breakpoint)
 - 10% resistance at MIC ≥ 64 (CLSI breakpoint)
 - Typically, cross-resistant amongst azoles
 - *C. albicans*, *C. parapsilosis*, *C. auris*
 - Elevated MICs to fluconazole/voriconazole
 - Isavuconazole, posaconazole maintain some activity
- Overutilization
- Significant adverse effects with long-term use
 - Alopecia (fluconazole, voriconazole)
 - Perioritis, phototoxicity (voriconazole)
 - Posaconazole (mineralocorticoid excess)
- Drug-drug interactions
- Inter-patient pharmacokinetic variability, therapeutic drug monitoring

13

ANTIFUNGAL ACTIVITY: *CANDIDA* SPECIES

Species	AmB	Flu	Itra	Vori	Posa	Isavu	Echino
<i>C. albicans</i>	✓	✓	✓	✓	✓	✓	✓
<i>C. glabrata</i>	✓	✓/R	✓/R	✓/R	✓/R	✓/R	✓
<i>C. krusei</i>	✓	X	✓	✓	✓	✓	✓
<i>C. parapsilosis</i>	✓	✓	✓	✓	✓	✓	↑ MICs
<i>C. tropicalis</i>	✓	✓	✓	✓	✓	✓	✓
<i>C. auris</i>	✓/R	✓/R	✓/R	✓/R	✓/R	✓/R	✓

X = no in vitro activity; ✓ = in vitro activity; ✓/R = resistance is common

AmB = Amphotericin B formulations; Flu = Fluconazole; Itra = itraconazole; Vori = voriconazole; Posa = posaconazole; Isavu = isavuconazole; Echino = echinocandins (caspofungin, micafungin, anidulafungin)

14

ANTIFUNGAL ACTIVITY: other SPECIES

Species	AmB	Flu	Itra	Vori	Posa	Isavu	Echino
<i>Aspergillus</i> spp.	✓ (not A. terreus)	X	✓	✓	✓	✓	On combination
Mucorales	✓	X	X	X	✓	✓	X
Cryptococcus and Dimorphic fungi	✓	✓	✓	✓	✓	✓	X
<i>Fusarium</i>	✓/R	X	X	✓/R	✓/R	✓/R	X
<i>Scedosporium</i>	X	X	X	✓/R	✓/R	✓/R	X

X = no in vitro activity; ✓ = in vitro activity; ✓/R = resistance is common

AmB = Amphotericin B formulations; Flu = Fluconazole; Itra = itraconazole; Vori = voriconazole; Posa = posaconazole; Isavu = isavuconazole; Echino = echinocandins (caspofungin, micafungin, anidulafungin)

15

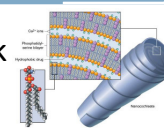
Which of the following is a known limitation of voriconazole for use in treating invasive mold infections?

- Not readily available in multiple formulations 0%
- Pharmacokinetic (drug level) challenges 0%
- Not effective against most species of *Aspergillus* 0%
- Cyclodextrin component of drug causes unnecessary toxicity when given orally 0%

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17

New kids on the same block



- Oral enochleated amphotericin B (MAT 2203, phase II)
 - Spiral lipid bilayer fuses to target fungal cell membranes, minimal exposure to healthy cells
- Oteseconazole (FDA approved for RVVC, Phase I for invasive infections)
 - No clinically significant CYP3A4 or P-GP interactions
 - Active against some fluconazole-resistant *C. albicans*
 - 138-day half-life...drug exposure window of almost 2 years! – May cause fetal harm based on animal studies
- Opelconazole (phase III)
 - Inhaled formulation using off-the-shelf nebulizers. Prophylaxis and treatment of aspergillosis
- Rezafungin (phase III)...

18

Rezafungin



- Novel, once-weekly IV echinocandin
- Analogue of anidulafungin, designed for increased stability and improved PK (half-life = 133h)
- Enables once-weekly dosing and front-loaded plasma exposure
- Ongoing studies: prophylaxis (fungal + PJP), azole-resistant candidiasis, prolonged duration therapy

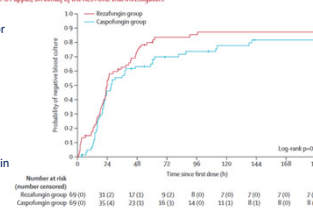
	PHASE 3 TREATMENT TRIAL ReSTORE	PHASE 3 PROPHYLAXIS TRIAL ReSPECT
Potential Indication	Treatment of candidaemia & invasive candidiasis	Prophylaxis against IFD caused by <i>Aspergillus</i> , <i>Candida</i> & <i>Pneumocystis</i> in allogeneic blood and marrow transplant patients
Trial Size	187 patients in primary evaluable population (mITT)	462 patients
Trial Status	Complete	Ongoing

19

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

George H Thompson III, Alex Sotgiu, Oliver A Cornely, Bart Jan Kullberg, Martin Kollef, Josep Vazquez, Patrick M Hoxon, Matteo Bazzoli, John Pullman, Matthew Chagalukiewicz, Ivan Poromanskii, Cecilia Diagne, Anita F Das, Taylor Sandison, Peter C Pappas, on behalf of the ReSTORE trial investigators

- 199 pts with invasive candidiasis (rezafungin (100) or caspofungin followed by fluconazole (100))
 - REZA 400mg IV on day 1, 200mg day 8
 - CAS 70mg IV x 3 days min; FLU following improvement
- Primary endpoint global response at day 14 (EMA):
 - Cure – REZ 55 (59%) vs CAS 57 (61%)
- Primary endpoint all cause 30-day mortality (FDA):
 - REZ 22 pts (24%) vs CAS 20 (21%)
- More rapid clearance of BCx in REZ group (P=0.18)
- AEs similar between groups; drug-related AEs (<3% in both)
- → FDA approval



20

Olorofim (phase iii)

- Inhibitor of fungal dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis
- Highly protein bound, excellent tissue distribution (kidney, liver, lung, brain)
- 45-82% bioavailable
- Substrate of CYP3A4
- Unique spectrum: *Aspergillus* (including azole-resistant), *Scedosporium*, *Lomentospora*, endemics, *Fusarium* but NOT *Mucorales* or yeasts (*Candida*, *Cryptococcus*)
- Role: multi-resistant mold infections, including azole-resistant aspergillosis

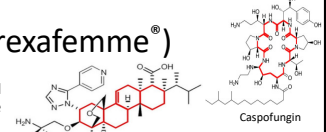
- Phase II trial for refractory, resistant, or intolerance:
 - First 100 patients:
 - d42 overall complete/partial response – 43%; stable 26%
 - d84 overall complete/partial response – 37%; stable 22%
 - AEs gastrointestinal (mild) and hepatic (9.9% rate of ALT/AST elevations judged at least possibly due to olorofim; managed with dose reduction or pause; discontinued in 2.5%)



21

Ibrexafungerp (brexafemme®)

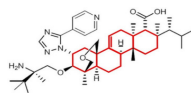
- Enfumafungin-derived triterpenoid class of (1→3)- β -D-glucan synthase inhibitor
- Spectrum: similar to echinocandins, enhanced activity against *C. auris*
- Lower rate of resistance
- Oral formulation
 - VVC (300mg BID x 1 day), ~\$500
 - RVVC (VVC regimen monthly x 6 mos)
- Phase 3 studies: oral/IV for invasive candidiasis, esophageal candidiasis
- Phase 2/3 studies: invasive aspergillosis



- Substrate of CYP3A4, mild inhibitor of other enzymes
 - Ketoconazole increases AUC 6x
 - Avoid with moderate-strong inducers of CYP3A4
- CANDLE study (RVVC)
 - 65.4% patients without recurrence at 24 weeks vs. 53.1% on placebo
 - Common adverse effects: HA, nausea, abd pain, diarrhea

22

Ibrexafungerp (brexafemme®)



	PHASE 3 Open-label Single-Arm	PHASE 3 Open-label Single-Arm	PHASE 3 Open-label Single-Arm
	FURI	CARES (<i>Candida auris</i>)	MARIO
Potential Indication	Intolerance, refractory fungal infections including <i>Candida</i> spp, <i>Aspergillus</i> spp, Endemics	Treatment of <i>Candida auris</i> infections	Treatment of invasive candidiasis and candidemia
Trial Size	>200 patients in primary evaluable population (mITT)	~30	~220
Trial Status	Complete	Complete	Ongoing

23

Choose the fungal organism not within the spectrum of activity of olorofim

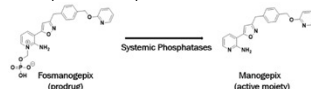
Aspergillus spp.	0%
Fusarium spp.	0%
Candida spp.	0%
Lomentospora spp.	0%

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25

Fosmanogepix (phase iii)

- Targets protein maturation through inhibition of the fungal enzyme Gwt1, an inositol acyltransferase essential for trafficking and anchoring mannoproteins to the fungal cell membrane and wall
- Spectrum: *Candida*, including *C. auris* (not *C. krusei*), *Cryptococcus*, endemics, *Aspergillus*, *Fusarium**, *Scedosporium*, *Lomentospora*, variable activity vs *Mucorales*
- > 90% oral bioavailability
- Well tolerated in phase II studies, mild transient HA as most common AE
- No known dose limiting toxicity
- Role: invasive candidiasis, aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis... (*mucorales*?)



26

Fosmanogepix (phase iii)

Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by *Candida auris*: Results from a Phase 2 Trial

Antifungal Agents and Chemotherapy

James A. Vazirani¹, Peter G. Pappas², Kenneth Boller³, Patricia Pank⁴, Paul A. Blau⁵, Margaret Davidson⁶, Eric Oprea⁷, Pamela Kline⁸, James Gorman⁹, Michael R. Hodge¹⁰

Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidemia: results from a Phase 2 trial

Peter G. Pappas¹, James A. Vazirani², Kenneth Boller³, Patricia Pank⁴, Paul A. Blau⁵, Margaret Davidson⁶, Eric Oprea⁷, Pamela Kline⁸, James Gorman⁹, Michael R. Hodge¹⁰

- Phase 2
- > 18 years, invasive candidiasis or candidemia *C. auris*
- FMGX (loading dose 1000mg IV twice daily followed by 600mg IV daily – switch to oral allowed on day 4)
- 1° endpoint – treatment at EOST: 89% success
 - No treatment discontinuations or study drug related AEs
- MIC_{range}: CLSI, 0.008–0.015 μ g/mL

- Phase 2
- > 18 years, first-line treatment for candidemia
- FMGX (loading dose 1000mg IV twice daily followed by 600mg IV daily – switch to oral allowed on day 4)
- 1° endpoint – treatment at EOST: (16/20) 80% success
 - No treatment discontinuations or study drug related AEs
- MIC_{range}: CLSI, 0.002–0.03 μ g/mL

Available through a compassionate use program


Journal of Antimicrobial Chemotherapy

27

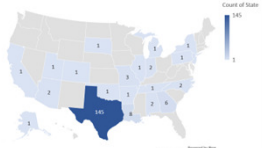
Clinical Infectious Diseases
MAJOR ARTICLE

Update on Outbreak of Fungal Meningitis among U.S. Residents who Received Epidural Anesthesia at Two Clinics in Matamoros, Mexico

Dallas J. Smith¹, Jeremy A.W. Gold², Tom Chiller³, Nirupa D. Bivansingh⁴, Maria Julia Martinsson⁵, Gabriel Garcia Rodriguez⁶, Vladimir Brian Gonzalez Coyote⁵, Cédric Dauger Molins⁷, Samantha Williams⁸, Axel A. Vazquez Dada^{7,8}, Kathryn Byrd^{9,10}, Peter G. Pappas⁸, Thomas F. Patterson¹⁰, Nathan P. Wiederhold¹¹, George R. Thompson III^{12,13}, Luis Ostrosky-Zichner¹⁴, Fungal Meningitis Response Team



- Several patients identified with *Fusarium solani*
 - Highly drug resistant
 - 50% mortality rate as of Sept 7, 2023
 - Cases all linked to one anesthesiologist
- 14% (1/7) case-mortality rate with fosmanogepix
- 65% (11/17) case-mortality without fosmanogepix (PENDING)



28

Choose the correct pipeline antifungal matched with its mechanism of action

Rezafungin: inhibition of lanosterol 14 α -demethylase	0%
Fosmanogepix: inhibition of Gwt1, GPI-anchor protein synthesis	0%
Ibrexafungerp: ergosterol binding, pore formation in fungal membrane	0%
Olorofim: glucan synthesis inhibition	0%

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30

Conclusions

- Morbidity/mortality remains high; diagnosis remains difficult
- Major gaps in current antifungal options
- Multiple novel antifungals
- Unmet needs
 - Mucorales*
 - Multi-resistant non-*Aspergillus* spp. including *Fusarium* spp., *Scedosporium* spp may need alternatives given limited options
 - Disseminated infection from *Coccidioides* spp. – still requires lifelong treatment

31

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32

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33