IDWEEK 2025 | Poster #P1193

Activity of isavuconazole against contemporary Mucorales from a worldwide surveillance program

Marisa L. Winkler, Samuel Edeker, Abby L. Klauer, Paul Rhomberg, Mariana Castanheira
Element Iowa City (JMI Laboratories), North Liberty, IA, USA

Introduction

- Isavuconazole is an azole antifungal agent with desirable properties such as lack of QTc prolongation, predictable pharmacokinetics, reduced drug interactions, and excellent tolerability that make it a long-term treatment of choice for invasive fungal infections.
- Isavuconazole is the only US FDA-approved antifungal agent with labeling for the treatment of invasive mucormycosis.
- Liposomal amphotericin B is typically first-line empirical treatment for invasive mucormycosis but has increased toxicity compared to isavuconazole and is only available in an intravenous (IV) formulation while isavuconazole is available for both oral and IV delivery.
- Here, we analyze the *in vitro* activity of isavuconazole against Mucorales isolates collected in a global surveillance program from invasive infections between 2021–2024.

Methods

- 67 isolates were collected from 13 different countries (Figure 1).
- Isolates were from a variety of infection sources (Figure 2).
- Isolate identification was performed by MALDI-TOF MS and/or molecular methods.
- Susceptibility testing was performed by broth microdilution according to CLSI standards M38M51S and M38.
- No epidemiological cutoff values (ECVs) or breakpoints are available for MIC determination; a cutoff of 4 mg/L was used for MIC comparisons across organism groups.

Results

- 36% of isolates were from wounds, 30% of isolates were from the respiratory tract, and 24% of isolates did not have infection source listed.
- There were 6 different genera represented.
  - 3 *Cunninghamella* spp., 7 *Lichtheimia* spp., 17 *Mucor* spp., 2 *Rhizomucor* spp., 37 *Rhizopus* spp., and 1 *Syncephalastrum* spp.
    - The majority of these isolates were not able to be identified to the species level.
- Across all Mucorales, isavuconazole MICs ranged from 0.12 – >8 mg/L with MIC_{50} 2 mg/L (Table 1); 70.1% of isolates had MICs ≤ 4 mg/L (Table 2).
  - This was lower than MIC range and >4-fold lower than the MIC_{50} of voriconazole but comparable to posaconazole (within 2 doubling dilutions).
  - Amphotericin B MICs were at least 2 doubling dilutions lower against all groups.
- In analysis of the different genera (Table 1), lower isavuconazole MICs were observed for *Lichtheimia* (n=7, 100% of isolates ≤ 4 mg/L, MIC_{50} 4 mg/L), *Rhizomucor* (n=2, 100% of isolates ≤ 4 mg/L, MIC_{50} 2 mg/L), and *Rhizopus* (n=37, 89.2% ≤ 4 mg/L, $MIC_{50/90}$ 2/8 mg/L). In contrast, 23.5% of *Mucor* had MICs ≤ 4 mg/L (n=17, $MIC_{50/90}$ >8/>8 mg/L) and 0% of *Cunninghamella* had MICs ≤ 4 mg/L (n=3, MIC_{50} >8 mg/L).
  - For all genera, voriconazole MICs were higher.
  - Posaconazole MICs were lower for *Cunninghamella* (100% isolates inhibited at ≤ 1 mg/L, MIC_{50} 1 mg/L) but similar for *Mucor* (23.5% with MIC ≤ 4 mg/L, $MIC_{50/90}$ >8/>8 mg/L), *Lichtheimia* (100% isolates with MIC ≤ 4 mg/L, MIC_{50} 0.5 mg/L), *Rhizomucor* (100% with MIC ≤ 4 mg/L, MIC_{50} 0.25 mg/L), and *Rhizopus* (92.1% with MIC ≤ 4 mg/L, $MIC_{50/90}$ 0.5/2 mg/L).
  - Amphotericin B MICs were ≤ 2 mg/L for all genera.

Conclusions

- Isavuconazole and posaconazole have low MICs against *Lichtheimia*, *Rhizomucor*, and *Rhizopus* spp. isolates collected from invasive mucormycosis infections worldwide between 2021 and 2024.
  - Higher MICs were observed for *Mucor* spp. and *Cunninghamella* spp. isolates.
  - Results are consistent with previously published isolates from 2017–2020.
- Given its FDA indication, delivery mechanisms, side-effect profile, and drug-drug interactions, isavuconazole is often preferred for long-term treatment of invasive mucormycosis compared to amphotericin B or posaconazole.
- These data support the use of isavuconazole for treatment of invasive mucormycosis if *Lichtheimia*, *Rhizomucor*, or *Rhizopus* spp. are identified as the causative organism but if *Mucor* or *Cunninghamella* spp. are identified, then wait for MIC results.

Funding

This study was supported by Pfizer. Marisa Winkler, Sam Edeker, Paul Rhomberg, Abby Klauer, and Mariana Castanheira are employees of Element Iowa City (JMI Laboratories), which was a paid consultant to Pfizer in connection with the development of this poster.

Acknowledgments

The authors thank all the SENTRY participant centers for their work in providing isolates.

References

CLSI. MM18Ed2E. Interpretive criteria for identification of bacteria and fungi by targeted DNA sequencing. Wayne, PA, Clinical and Laboratory Standards Institute, 2018.

CLSI. M38Ed3E. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, third edition. Wayne, PA, Clinical and Laboratory Standards Institute, 2018.

CLSI. M57SEd4E Epidemiological Cutoff Values for Antifungal Susceptibility Testing, 4th Edition. Wayne, PA, Clinical and Laboratory Standards Institute, 2022.

CLSI. M38M51SEd3E Performance Standards for Antifungal Susceptibility Testing of Filamentous Fungi, 3rd Edition. Wayne, PA, Clinical and Laboratory Standards Institute, 2022.

Carvalhaes, C.G., Rhomberg, P.R., Huband, M.D., Pfaller, M.A. and Castanheira, M. *J. Fungi*. 2023, 9(2), 241.

Lewis, J.S., et al. *Antimicrob Agents and Chemother*. 2022, 66(9), PMID: 35969068

Maertens, J.A., et al. *Lancet*, 2016, 387(*100200*), 760–769. PMID: 26684607

Table 1. Antifungal activity including MIC range (mg/L), $MIC_{50/90}$ (mg/L), for isavuconazole and comparator agents for all tested Mucorales

Organism (n)	isavuconazole		voriconazole		posaconazole		amphotericin B	
	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$
All Mucorales (67)	0.12 – >8	2/>8	0.5 – >8	>8/>8	0.06 – >8	0.5/>8	≤0.03 – 2	0.25/1
Cunninghamella spp. (3)	>8	>8/*	>8	>8/*	0.25 – 1	1/*	1 – 2	2/*
Lichtheimia spp. (7)	0.12 – 4	4/*	2 – >8	>8/*	0.06 – 4	0.5/*	0.06 – 0.25	0.06/*
Mucor spp. (17)	1 – >8	>8/>8	>8	>8/>8	0.5 – >8	>8/>8	≤0.03 – 0.25	0.12/0.25
Mucor circinelloides (11)	4 – >8	>8/>8	>8	>8/>8	0.5 – >8	>8/>8	0.06 – 0.25	0.12/0.25
Unspeciated *Mucor* (6)	1 – >8	2/*	>8	>8/*	0.5 – >8	>8/*	≤0.03 – 0.25	0.06/*
Rhizomucor spp. (2)	2 – 4	2/*	>8	>8/*	0.25 – 1	0.25/*	0.06 – 0.25	0.06/*
Rhizopus spp. (37)	0.12 – 8	2/8	0.5 – >8	8/>8	0.12 – >8	0.5/2	0.06 – 2	0.25/1
Rhizopus microsporus (18)	1 – 8	2/4	8 – >8	>8/>8	0.25 – >8	1/>8	0.06 – 1	0.25/0.5
Rhizopus oryzae species complex (15)	0.5 – 8	1/8	0.5 – >8	8/>8	0.12 – 1	0.25/0.5	0.06 – 2	0.25/1
Syncephalastrum (1)	4	NA	4	NA	1	NA	≤0.03	NA

*MIC_{50} only as < 10 organisms represented
NA, not applicable

Table 2. Cumulative percent of Mucorales at each MIC (mg/L) for isavuconazole and comparator agents

Antimicrobial Agent		Dilution (mg/L)														Total isolates	MIC_{50}	MIC_{90}
		0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>			
Amphotericin B	Cumulative percent of isolates				4.5	20.9	46.3	74.6	89.6	95.5	100					67	0.25	1
	Number of isolates				3	11	17	19	10	4	3							
Isavuconazole	Cumulative percent of isolates					0	3	3	10.4	31.3	52.2	70.1	80.6		100	67	2	>8
	Number of isolates					0	2	0	5	14	14	12	7		13			
Posaconazole	Cumulative percent of isolates				0	1.5	4.5	28.4	50.7	73.1	74.6	76.1	76.1		100	67	0.5	>8
	Number of isolates				0	1	2	16	15	15	1	1	0		16			
Voriconazole	Cumulative percent of isolates							0	3	3	6	14.9	34.3		100	67	>8	>8
	Number of isolates							0	2	0	2	6	13		44			

Figure 1. Geographic distribution of collected fungal isolates

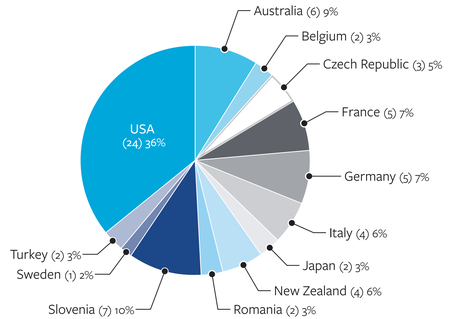
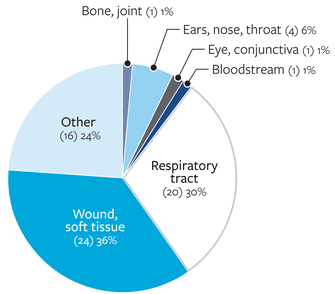


Figure 2. Source of infection of collected isolates



Contact

element

Marisa Winkler, MD, Ph.D.
Element Iowa City (JMI Laboratories)
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: marisa.winkler@element.com

SCAN ME

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/IDWeek2025_25-PZR-03_P1_Zygomycetes_Isavu.pdf

Charges may apply. No personal information is stored.