

Susceptibility Profile of Mucoralean Fungi Isolated from the United States to Current Antifungal Drugs

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BACKGROUND & OBJECTIVE

- Mucormycosis is an aggressive infection associated with significant morbidity and mortality, especially in immunocompromised individuals and those with poorly controlled diabetes.
- Reported cases per 1,000,000 individuals in the U.S. and Canada were approximately 3 and 1.2, respectively.
- Amphotericin B, posaconazole, and isavuconazole are generally active against members of the order Mucorales, but some isolates may have reduced susceptibility to these antifungals.
- The purpose was to evaluate the species distribution of Mucorales isolates in the U.S. over a 3.5-year period and antifungal susceptibility profiles against these fungi.

MATERIALS & METHODS

- Mucorales isolates received by the Fungus Testing Laboratory for molecular identification and antifungal susceptibility testing between September 2015 and March 2019 were included.
- Species identification was performed by combined phenotypic characteristics and DNA sequence analysis of the ITS and D1/D2 rDNA regions.
- Minimum inhibitory concentrations (MICs) for amphotericin B, itraconazole, posaconazole, and isavuconazole were determined by broth microdilution susceptibility testing according to the methods in the CLSI M38 reference standard.
- MIC ranges, MIC₅₀/MIC₉₀ values, and geometric mean (GM) MICs were determined.

RESULTS

- 942 Mucorales isolates were received and tested. The predominant genera were *Rhizopus* (56.6%) followed by *Mucor* (23.8%).
- Lichtheimia*, *Rhizomucor*, *Syncephalastrum*, and *Cunninghamella* comprised less than 10% of isolates.
- The most predominant species was *Rhizopus arrhizus* (39%), of which 64.8% were *R. arrhizus* var. *arrhizus* and 30.1% *R. arrhizus* var. *delemar*.
- Amphotericin B demonstrated the most potent *in vitro* activity with GM MICs of <0.25 mg/L against all genera, with the exception of *Cunninghamella* sp. (GM MIC 1.21 mg/L; Table 1).
- For the azoles, the most potent agent was posaconazole, followed by itraconazole and isavuconazole.
- Interestingly, *R. arrhizus* var. *arrhizus* and *Rhizopus microsporus* were more susceptible to isavuconazole compared to other genera, and the GM MIC for this azole against *R. arrhizus* var. *delemar* (3.70 mg/L) was markedly higher compared to that against *R. arrhizus* var. *arrhizus* (0.87 mg/L).
- Similar differences in isavuconazole GM MICs were observed between *M. circinelloides* f. *circinelloides* and *M. circinelloides* f. *janssenii* (7.62 mg/L vs. 3.44 mg/L, respectively).

CONCLUSIONS

The majority of Mucorales isolates included in this surveillance study were *Rhizopus* species, followed by *Mucor* and *Lichtheimia* species. Differences in azole and amphotericin B susceptibility patterns were observed between the genera with the greatest variability observed with isavuconazole. Clinical microbiology laboratories should be aware of these species distributions and differences in antifungal susceptibility patterns. Further studies are warranted to determine the clinical implications of these findings.

Table 1. MIC ranges, MIC₅₀/MIC₉₀ values, GM MICs of amphotericin B, isavuconazole, itraconazole and posaconazole against genera within the order Mucorales. Values are expressed in mg/L.

Genus	Antifungal	MIC Range	MIC ₅₀	MIC ₉₀	GM MIC
<i>Rhizopus</i>	Amphotericin B	≤0.03-2	0.25	1	0.19
	Isavuconazole	≤0.125->16	1	4	1.24
	Itraconazole	≤0.125->16	1	4	0.66
	Posaconazole	≤0.125->16	0.25	1	0.28
<i>Mucor</i>	Amphotericin B	≤0.03-8	0.125	0.5	0.12
	Isavuconazole	2->16	8	>16	7.14
	Itraconazole	0.5->16	4	>16	4.33
	Posaconazole	0.125-8	1	2	1.02
<i>Lichtheimia</i>	Amphotericin B	≤0.03-0.5	0.125	0.5	0.15
	Isavuconazole	0.25-8	2	4	1.83
	Itraconazole	0.06-1	---	---	---
	Posaconazole	0.06-1	0.25	0.5	0.27
<i>Syncephalastrum</i>	Amphotericin B	≤0.03-1	0.06	0.5	0.11
	Isavuconazole	0.5->16	16	>16	8.79
	Itraconazole	0.125-8	---	---	---
	Posaconazole	0.06-4	0.5	2	0.68
<i>Cunninghamella</i>	Amphotericin B	0.5-1	1	2	3.32
	Isavuconazole	4->16	16	>16	18.32
	Itraconazole	0.5-2	---	---	---
	Posaconazole	0.25-1	0.5	1	2.35
<i>Apophysomyces</i>	Amphotericin B	≤0.03-0.125	---	---	---
	Isavuconazole	0.5-4	---	---	---
	Itraconazole	0.25-1	---	---	---
	Posaconazole	0.125-0.25	---	---	---
<i>Saksenaee</i>	Amphotericin B	≤0.03	---	---	---
	Isavuconazole	0.25-2	---	---	---
	Itraconazole	0.125-0.25	---	---	---
	Posaconazole	0.06-0.125	---	---	---