IDWEEK 2024 | Poster #P1168

Activity of Isavuconazole and Comparator Agents against Pediatric Fungal Isolates Collected from 2017–2023 in a Global Surveillance Program

Marisa L Winkler, Paul Rhomberg, Kelley Fedler, Abigail L. Klauer, 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 treatment of choice for invasive fungal infections.
- Isavuconazole is also advantageous compared to voriconazole due to its activity against mucormycosis.
- In December 2023, isavuconazole became the first azole antifungal approved by the United States Food and Drug Administration for the treatment of invasive aspergillosis and mucormycosis in patients as young as 1 year old.
- Here, we analyze the *in vitro* activity of isavuconazole against pediatric fungal isolates collected in a global surveillance program.

Methods

- 851 isolates were collected from invasive fungal infections in patients ≤17 years old (1 isolate/patient) from a variety of infection sources.
- 34% of isolates were from Latin America, 29% of isolates were from Europe, 27% of isolates were from North America, and 10% of isolates were from Asia (Figure 1).
- Isolate identification was performed by MALDI-TOF MS and/or molecular methods.
- Susceptibility testing was performed by broth microdilution according to CLSI standards M27 and M38.
- Results were interpreted with CLSI breakpoints or epidemiological cutoff values (ECVs) where applicable (M27M44S, M38M51S, and M57S).

Results

- 61% of isolates were from bloodstream infections, 15% from pneumonia in hospitalized patients, 5% from skin and soft tissue infections, 3% from urinary tract infections, and 16% from other or unnamed infection sources.
- 33.4% (284/851) of isolates were from patients ≤1 year old, 21.9% were from 2- to 5-year-old patients (186/851), 24.0% were from 6- to 12-year-old patients (204/851), and 20.8% of isolates were from patients 13 to 17 years old (177/851).
- A majority of isolates were *Candida* spp. (684/851, 80.4%) but 19 other genera were represented with 14.5% of isolates *Aspergillus* spp. (123/851), 2.9% other molds (25/851), and 19/851 other yeasts (2.2%).
- For *Candida* spp. (off-label for isavuconazole FDA indications) isavuconazole MIC_{50} was ≤0.008 mg/L and MIC_{90} 0.06 mg/L; MICs were lower than those of fluconazole, itraconazole, caspofungin, and amphotericin B but comparable to voriconazole.
- For *Aspergillus* spp. isavuconazole MIC_{50} was 0.5 mg/L and MIC_{90} 2 mg/L; 88.4% of isolates were wildtype to isavuconazole by ECV (includes only species with CLSI-defined ECV, *A.* section *Flavi*, *A.* section *Fumigati*, *A.* section *Nigri*, and *A.* section *Terrei*, 107/121) and values were comparable to itraconazole, voriconazole, and amphotericin B by MIC but a higher percent of isolates were wildtype to amphotericin B by ECV.
- For other molds, isavuconazole MICs ranged from 0.25 mg/L to >8 mg/L.
- For Mucorales (n = 5, *Lichtheimia*, *Mucor*, *Rhizopus*) isavuconazole MICs were 1 mg/L (n = 1), 2 mg/L (n = 2), and 8 mg/L (n = 2).

Table 1. *In vitro* activity of isavuconazole and select comparator agents against pediatric isolates from the SENTRY database in 2017–2023

Organism	Antimicrobial agent	MIC_{50}	MIC_{90}	Range	ECV %WT	ECV %NWT
Candida spp. (684)	Isavuconazole	≤0.008	0.06	≤0.008 to 2		
	Caspofungin	0.03	0.25	≤0.008 to >4		
	Fluconazole	0.25	2	≤0.12 to >128	96.6	3.4
	Itraconazole	0.12	0.5	≤0.06 to 4		
	Voriconazole	≤0.008	0.06	≤0.008 to 8		
	Amphotericin B	0.5	1	0.12 to 2	99.8	0.2
Aspergillus spp. (123)	Isavuconazole	0.5	2	0.12 to 8	89.2[a]	10.8[a]
	Caspofungin	0.03	0.06	≤0.002 to 0.06	100[a]	0[a]
	Itraconazole	1	2	0.25 to >8	88.4[a]	11.6[a]
	Voriconazole	0.5	1	0.12 to 4	89.3[b]	10.7[b]
	Amphotericin B	1	2	≤0.03 to >4	100[a]	0.0[a]
Other molds (25)	Isavuconazole	8	>8	0.25 to >8		
	Caspofungin	>4	>4	≤0.002 to >4		
	Itraconazole	8	>8	0.12 to >8		
	Voriconazole	2	>8	0.12 to >8		
	Amphotericin B	1	>4	0.12 to >4		

Abbreviations: MIC, minimum inhibitory concentration; ECV, epidemiological cutoff value by CLSI guidelines; WT, wildtype; NWT, nonwildtype
[a]Includes only species with CLSI-defined ECV, *A.* section *Flavi*, *A.* section *Fumigati*, *A.* section *Nigri*, and *A.* section *Terrei*
[b]WT for voriconazole is a combination of isolates in *A.* section *Fumigati* susceptible by breakpoint and *A.* section *Flavi*, *A.* section *Nigri*, and *A.* section *Terrei* WT by ECV while NWT includes *A.* section *Fumigati* intermediate and resistant isolates by breakpoint
Organisms include *Candida albicans* (119), *C. dubliniensis* (1), *C. fabianii* (1), *C. glabrata* (17), *C. guilliermondii* (4), *C. intermedia* (1), *C. kefyr* (3), *C. krusei* (2), *C. lipolytica* (1), *C. lusitaniae* (27), *C. nivariensis* (1), *C. orthopsilosis* (3), *C. parapsilosis* (62), *C. paranguosa* (1), *C. pelliculosa* (4), *C. pseudohaemulonii* (1), *C. rugosa* (1), *C. sphaerica* (1), *C. tropicalis* (20), *Aspergillus alabamensis* (1), *A. flavus* (1), *A. flavus* species complex (9), *A. fumigatus* (94), *A. lentulus* (1), *A. niger* (3), *A. niger* species complex (6), *A. ochraceus* species complex (3), *A. tamarii* (1), *A. terreus* (4), *A. terreus* species complex (1), *A. ungus* (1), *Alternaria alternata* (1), *Exophiala dermatitidis* (1), *Fusarium oxysporum* species complex (1), *F. solani* species complex (2), *Gibberella fujikuroi* species complex (2), *Lichtheimia corymbifera* (1), *Lomentospora prolificans* (2), *Paecilomyces lilacinus* (1), *Rasamsonia argillacea* (1), *Rhizopus microsporus* group (1), *Scedosporium apiospermum* (1), *S. apiospermum*/*Scedosporium boydii* (4), *S. boydii* (1), unspeciated Curvularia (3), unspeciated *Mucor* (2), and unspeciated *Rhizopus* (1).

Figure 1. Geographic distribution of collected pediatric fungal isolates

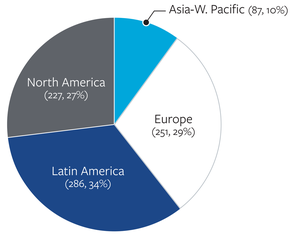


Figure 2. Source of infection of collected isolates

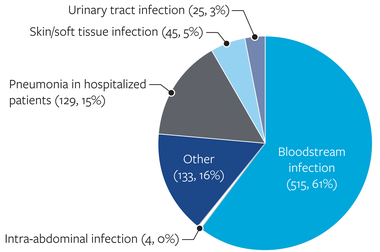


Figure 3. Age distribution of isolates, ≤1 year old (284/851, 33.4%), 2 to 5 years old (186/851, 21.9%), 6 to 12 years old (204/851, 24.0%), and 13 to 17 years old (177/851, 20.8%)

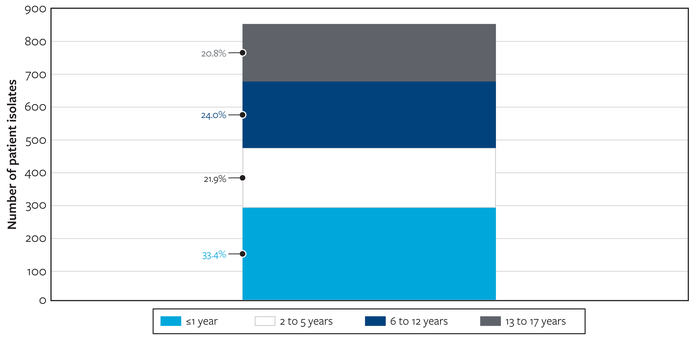
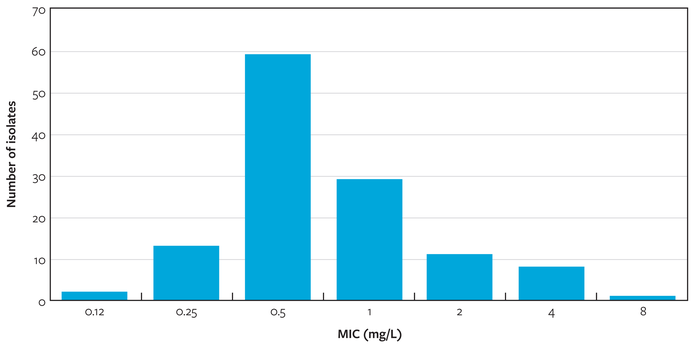


Figure 4. MIC distribution of isavuconazole against *Aspergillus* spp. isolates collected from pediatric patients



Conclusions

- Isavuconazole had good *in vitro* activity against pediatric fungal isolates from a worldwide surveillance program.
- MICs were low for *Candida* and *Aspergillus* spp. and comparable to or lower than other azole antifungal agents.
  - Isavuconazole is approved by the FDA for treatment of *Aspergillus* infections but treatment of *Candida* is off-label.
- Isavuconazole MICs were elevated to non-*Aspergillus* molds, but comparable to other agents, highlighting the need for continued novel antifungal agent development against non-*Aspergillus* molds.

Funding

This study was supported by Pfizer. Marisa Winkler, Paul Rhomberg, Abigail 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. M27Ed4E. Reference method for broth dilution antifungal susceptibility testing of yeasts. Wayne, PA, Clinical and Laboratory Standards Institute, 2017.

CLSI. M27M44SEd3E. Performance Standards for Antifungal Susceptibility Testing of Yeasts. Wayne, PA, Clinical and Laboratory Standards Institute, 2022.

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.

https://newsroom.astellas.us/2023-12-08-FDA-Approves-Expanded-Use-of-CRESEMBA-R-isavuconazonium-sulfate-in-Children-with-Invasive-Aspergillosis-and-Invasive-Mucormycosis

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

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/IDWeek2024_23-PZR-02_A2_isavu_peds.pdf

Charges may apply. No personal information is stored.