

Isavuconazole activity against moulds in ICU and non-ICU infections

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Introduction

- Invasive mould infections cause high morbidity and mortality, particularly among critically ill patients.
- Optimal antifungal selection in the Intensive Care Unit (ICU) is complicated by altered pharmacokinetics, organ dysfunction, and polypharmacy.
- Patients with non-hematologic malignancies are increasingly recognized as being at risk for invasive mould disease, particularly in the setting of critical illness, corticosteroid exposure, cytotoxic chemotherapy, prolonged hospitalization, and mechanical ventilation.
- Isavuconazole, a broad-spectrum triazole with activity against both *Aspergillus* and Mucorales, has emerged as a preferred treatment for invasive mould disease in critically ill populations.
- This study evaluated the *in vitro* activity of isavuconazole in comparison with other mould-active azoles among isolates from infections originating from ICU and non-ICU populations.

Methods

- 1,988 mould isolates were collected between 2017 and 2024 from medical centres in 23 countries and 54 hospitals.
- Identification was performed by MALDI-TOF; broth microdilution was performed by CLSI methodology.
- Breakpoints were interpreted by M38M51S and epidemiological cutoff values (ECV) by M57S current edition.
- Isolates were stratified into ICU and non-ICU subsets.

Results

- Aspergillus* species were the most prevalent clinical isolates recovered for both ICU (87%) and non-ICU (79%; Figure 1).
- The largest difference in prevalence was an increase in *Aspergillus fumigatus* (64%) among ICU infections compared to non-ICU (50%) at the expense of *Scedosporium/Lomentospora* species (1%, ICU; 6% non-ICU) and other rare moulds (2%, ICU; 6% non-ICU-acquired; Figure 1).
- Isavuconazole was active against *Aspergillus* isolates and displayed similar MIC₉₀ values for *Aspergillus* section *Flavi* (MIC₉₀, 1 mg/L), *Aspergillus* section *Fumigati* (MIC₉₀, 1 mg/L), *Aspergillus* section *Nigri* (MIC₉₀, 4–8 mg/L), *Aspergillus* section *Terrei* (MIC₉₀, 0.5 mg/L) for ICU and non-ICU subsets (Table 1).
- Greater than 90% of the four major groups of *Aspergillus* displayed wildtype (WT) ECVs or were susceptible (S) by CLSI breakpoints to the mould-active azoles except for voriconazole against *Aspergillus fumigatus* (88.9% S for ICU, 89.8% S for non-ICU) and the ICU subsets against *Aspergillus* section *Nigri* for voriconazole (89.4% WT) and itraconazole (76.6% WT) (Table 2).
- MIC₅₀ values ≤ 2 mg/L were observed for isavuconazole, itraconazole, and posaconazole against Mucorales group isolates in both ICU and non-ICU subsets (Table 1).
- As expected, little to no activity (MIC₉₀ >8 mg/L) was observed for all the mould-active azoles against *Fusarium* and *Scedosporium/Lomentospora* species (Table 1).

Conclusions

- The prevalence of mould species in ICU and non-ICU infections was similar; however, increased incidence of *Aspergillus* species, especially *A. fumigatus*, was observed in ICU infections with a corresponding decrease in *Scedosporium* and other rare moulds.
- Isavuconazole demonstrated consistent *in vitro* potency against *Aspergillus* species and Mucorales and maintained similar MIC distributions in ICU and non-ICU isolates, supporting its broad applicability across clinical settings.
- Given its favorable pharmacologic profile, including reliable exposure, absence of cyclodextrin, and balanced safety in patients with organ dysfunction, isavuconazole remains well-suited for use in critically ill patients with suspected or confirmed mould infections.

References

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Figure 1. Prevalence of mould species found in ICU (n=612) and non-ICU (n=1,376)

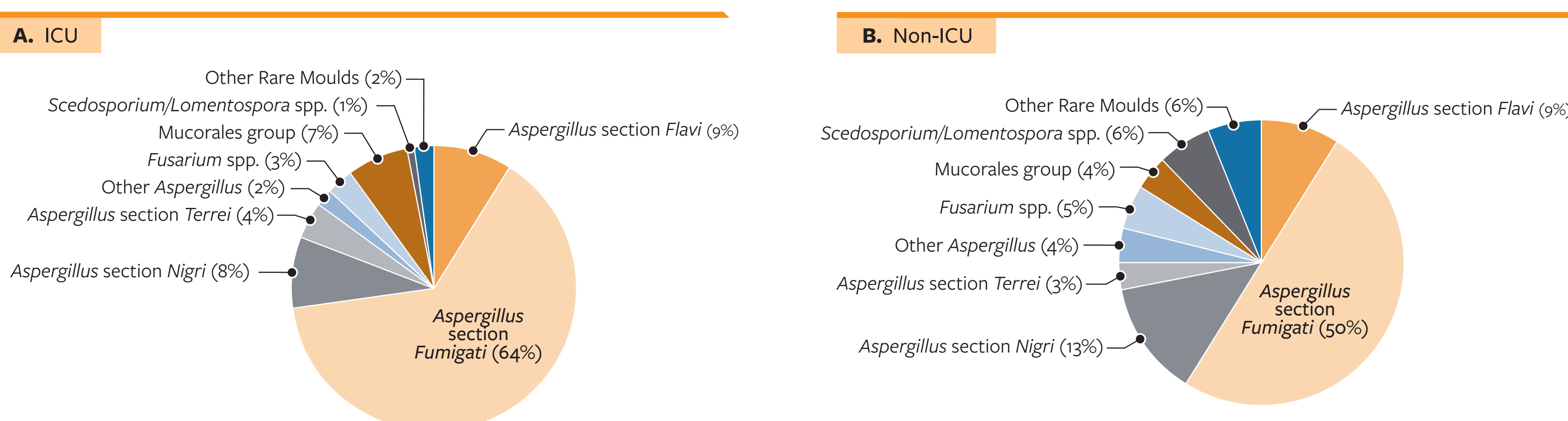


Table 1. Antifungal activity of mould-active azoles (mg/L) against moulds from community-acquired and nosocomial infections

Organism group (no. isolates)	Isavuconazole				Itraconazole				Posaconazole				Voriconazole			
	ICU		Non-ICU		ICU		Non-ICU		ICU		Non-ICU		ICU		Non-ICU	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Aspergillus</i> section <i>Flavi</i> (181)	0.5	1	0.5	1	0.5	1	0.5	1	0.25	0.5	0.25	0.5	0.5	1	0.5	1
<i>Aspergillus</i> section <i>Fumigati</i> (1,078)	0.5	1	0.5	1	1	1	1	1	0.25	0.5	0.25	0.5	0.5	1	0.5	1
<i>Aspergillus</i> section <i>Nigri</i> (221)	2	8	2	4	2	>8	2	8	0.5	1	0.5	1	1	4	1	2
<i>Aspergillus</i> section <i>Terrei</i> (67)	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0.25	0.5	0.25	0.25	0.5	0.5	0.25	0.5
Other <i>Aspergillus</i> spp. (71) ^a	0.12	4	0.25	2	1	>8	0.5	8	0.5	>8	0.25	>8	0.25	8	0.25	4
<i>Fusarium</i> spp. (87)	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	8	>8	8	>8
Mucorales group (96)	2	>8	2	>8	1	>8	2	8	0.5	>8	0.5	>8	>8	>8	>8	>8
<i>Scedosporium/Lomentospora</i> spp. (87)	8	ND	8	>8	>8	ND	>8	>8	>8	ND	>8	>8	1	ND	1	>8
Other Moulds (100) ^b	4	>8	1	>8	>8	>8	0.5	>8	0.5	8	0.25	>8	4	>8	0.5	>8

ICU, intensive care unit; ND, not determined
^aSpecies include: *A. caelatus* (1), *A. mellensis* (1), *A. nidulans* (20), *A. nidulans* species complex (14), *A. ochraceus* species complex (1), *A. sclerotiorum* (4), *A. sydowii* (3), *A. unguis* (4), *A. ustus* (5), *A. ustus* species complex (9), *A. versicolor* (7), Unspecified *Aspergillus* (2)
^bSpecies include: *A. alternata* (1), *A. pullulans* (1), *E. attenuata* (2), *E. dermatitidis* (13), *M. romeroi* (1), *M. cirrosus* (2), *M. ruber* (1), *P. variotii* (11), *P. chrysogenum* (2), *P. citrinum* (2), *P. georgiense* (1), *P. richardsiae* (1), *P. ilacinum* (18), *R. argillacea* (6), *R. argillacea* species complex (5), *S. brevicaulis* (1), *S. brevicaulis*/*S. brumptii* (3), *T. longibrachiatum* (1), Unspecified *Bipolaris* (1), Unspecified *Chaetomium* (1), Unspecified *Cunninghamella* (3), Unspecified *Curvularia* (8), Unspecified *Exophiala* (1), Unspecified *Paecilomyces* (7), Unspecified *Penicillium* (1), Unspecified *Phialemoniopsis* (1), Unspecified *Sarocladium* (1), Unspecified *Scopulariopsis* (1), Unspecified *Trichoderma* (1), *V. gallopava* (2)

Table 2. Percentage of wildtype by ECV or susceptible by breakpoint for *Aspergillus* isolates tested against mould-active azoles

Organism group (no. isolates)	Isavuconazole		Itraconazole		Posaconazole		Voriconazole	
	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU
<i>Aspergillus flavus</i> complex (176)	100.0	98.3	100.0	100.0	98.2	100.0	100.0	100.0
<i>Aspergillus fumigatus</i> (1,067)	95.1 ^a	92.8 ^a	93.0	91.3	—	—	88.9 ^a	89.8 ^a
<i>Aspergillus niger</i> complex (209)	91.5	96.9	76.6	90.7	97.9	99.4	89.4	97.5
<i>Aspergillus terreus</i> complex (66)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

ICU, intensive care unit
^aSusceptibility based on CLSI M38M51S, wildtype based on CLSI M57S