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Isavuconazole activity against moulds in nosocomial and community-acquired infections

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Introduction

- Invasive mould infections remain a major cause of morbidity and mortality in both community-acquired and healthcare-associated settings.
- Isavuconazole, a broad-spectrum triazole antifungal, has demonstrated activity against *Aspergillus* and Mucorales isolates and has emerged as a first-line or alternative therapy for invasive mould infections due to its similar efficacy to other mould-active azoles, favourable safety and tolerability profile, and predictable pharmacokinetics compared to voriconazole and posaconazole.
- To date, data comparing the prevalence and *in vitro* activity against moulds stratified by community-acquired versus nosocomial origin remain limited.

Methods

- 1,947 mould isolates were collected between 2017 and 2024 from medical centres in 22 countries and 52 hospitals.
- Isolates were collected from pneumonia in hospitalized patients (72%), skin/soft tissue infection (11%), and other sites (17%).
- Identification was performed by MALDI-TOF.
- Broth microdilution susceptibility testing was performed by CLSI methodology and breakpoints were interpreted by M38M51S and epidemiological cutoff values (ECV) by M57S current editions.
- Isolates were stratified into community-acquired (culture date within 48 hours of hospital admission) and nosocomial (> 48 hours after admission).

Results

- *Aspergillus* species were the most prevalent clinical isolates recovered for both community-acquired (79%) and nosocomial infections (85%; Figure 1).
- The largest difference in prevalence was an increase in *Aspergillus fumigatus* (60%) among nosocomial infections compared to community-acquired (51%) at the expense of *Scedosporium/Lomentospora* (2%, nosocomial; 6%, community-acquired) and other rare moulds (3%, nosocomial; 7%, community-acquired; Figure 1).
- Isavuconazole was active against *Aspergillus* isolates and displayed identical MIC_{90} values for *Aspergillus* section *Flavi* (MIC_{90}, 1 mg/L), *Aspergillus fumigatus* (MIC_{90}, 1 mg/L), *Aspergillus* section *Nigri* (MIC_{90}, 4 mg/L), and *Aspergillus* section *Terrei* (MIC_{90}, 0.5 mg/L) for both community-acquired and nosocomial subsets (Table 1).
- Greater than 90% of the four major groups of *Aspergillus* spp. displayed wildtype (WT) ECVs or were susceptible (S) by CLSI breakpoints to the mould-active azoles except for voriconazole against *Aspergillus fumigatus* (89.3% S for community-acquired, 89.9% S for nosocomial) and itraconazole against *Aspergillus* section *Nigri* (84.0% WT for community-acquired, 82.1% WT for nosocomial; Table 2).
- MIC_{50} values ≤ 2 mg/L were observed for isavuconazole, itraconazole, and posaconazole against Mucorales group and other rare mould isolates in both community-acquired and nosocomial subsets (Table 1).
- As expected, little to no activity (MIC_{90} >8 mg/L) was observed for all the mould-active azoles against *Fusarium* and *Scedosporium* species, though voriconazole (MIC_{50}, 1 mg/L) and posaconazole (MIC_{50}, 2 mg/L) were active against *Scedosporium apiospermum* (Table 1).

Conclusions

- The prevalence of mould species in community-acquired and nosocomial infections was similar; however, increased incidence of *Aspergillus* species, especially *A. fumigatus*, was observed in nosocomial infections with a corresponding decrease in *Scedosporium* and other rare moulds.
- Isavuconazole shows consistent *in vitro* activity against a broad range of clinically relevant moulds, regardless of infection setting.
- These findings support its role as a treatment option for invasive mould infections while highlighting the need for ongoing surveillance.

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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			
	CA		Nosocomial		CA		Nosocomial		CA		Nosocomial		CA		Nosocomial	
	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}
Aspergillus section *Flavi* (166)	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
Aspergillus fumigatus (1,052)	0.5	1	0.5	1	1	1	1	1	0.25	0.5	0.25	0.5	0.5	1	0.5	1
Aspergillus section *Nigri* (220)	2	4	2	4	2	>8	2	>8	0.5	1	0.5	1	1	2	1	2
Aspergillus section *Terrei* (70)	0.25	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.25	0.5	0.25	0.25	0.25	0.5	0.5	0.5
Other *Aspergillus* spp. (70) [a]	0.12	2	0.25	2	0.5	8	1	>8	0.25	>8	0.5	>8	0.25	4	0.25	4
Fusarium spp. (84)	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	8	>8	8	>8
Mucorales group (98)	2	>8	2	8	2	>8	1	8	0.5	>8	0.5	4	>8	>8	>8	>8
Scedosporium/Lomentospora spp. (86)	8	>8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	1	>8	1	>8
Lomentospora prolificans (22)	>8	>8	>8	ND	>8	>8	>8	ND	>8	>8	>8	ND	>8	>8	>8	ND
Scedosporium apiospermum (40)	8	>8	8	ND	>8	>8	>8	ND	2	>8	2	ND	1	1	1	ND
Other Rare Moulds [b] (101)	1	>8	4	>8	0.5	>8	>8	>8	0.25	2	0.5	>8	1	>8	2	>8

CA, community-acquired; ND, not determined

[a] Species include: *Aspergillus nidulans* species complex (37), *A. ustus* species complex (14), *A. versicolor* (8), *A. sclerotiorum* (4), *A. unguis* (3), *A. sydowii* (2), *A. melleus* (1), and *A. ochraceus* species complex (1).

[b] Species include: *Alternaria alternata* (2), *Aureobasidium pullulans* (1), *Exophiala attenuata* (2), *E. dermatitidis* (13), *Medicopsis romeroi* (1), *Microascus cirrosus* (2), *Monascus ruber* (1), *Paecilomyces variotii* (12), *Penicillium chrysogenum* (2), *P. citrinum* (2), *P. georgiense* (1), *Pleurostomophora richardsiae* (1), *Purpureocillium lilacinum* (18), *Rasamsonia argillacea* species complex (11), *Sarocladium kiliense* (1), *Scopulariopsis brevicaulis* / *S. brumptii* (4), *Trichoderma longibrachiatum* (1), Unspeciated *Bipolaris* (1), Unspeciated *Chaetomium* (1), Unspeciated *Cunninghamella* (3), Unspeciated *Curvularia* (6), Unspeciated *Exophiala* (1), Unspeciated *Paecilomyces* (7), Unspeciated *Penicillium* (1), Unspeciated *Phialemoniopsis* (1), Unspeciated *Saroclad*ium (1), Unspeciated *Scopulariopsis* (1), Unspeciated *Trichoderma* (1), and *Verruconis gallopava* (2).

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

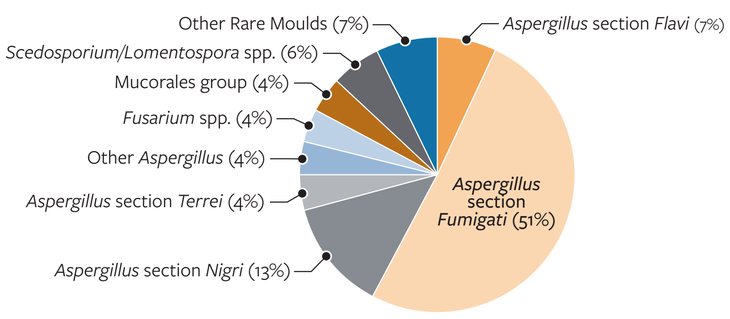
Organism group (no. isolates)	Isavuconazole		Itraconazole		Posaconazole		Voriconazole	
	CA	Nosocomial	CA	Nosocomial	CA	Nosocomial	CA	Nosocomial
Aspergillus section *Flavi* (166)	97.8%	100%	100%	100%	100%	98.6%	100%	100%
Aspergillus fumigatus (1,052)	91.5% [a]	94.0% [a]	91.8%	91.8%	—	—	89.3% [a]	89.9% [a]
Aspergillus section *Nigri* (220)	93.9%	98.2%	84.0%	82.1%	98.8%	100%	95.1%	92.9%
Aspergillus section *Terrei* (70)	97.7%	100%	100%	100%	100%	100%	100%	100.0%

CA, community-acquired

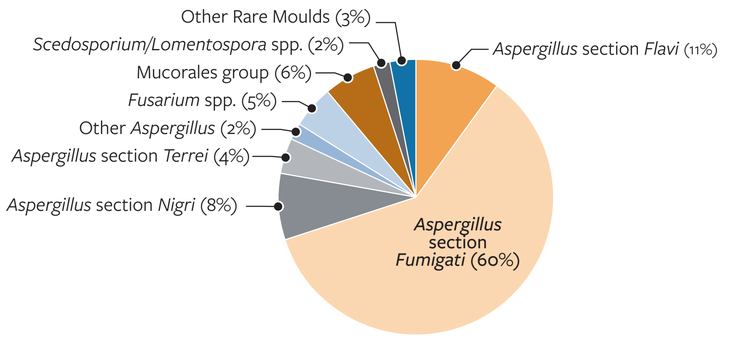
[a] Susceptibility based on CLSI M38M51S, wildtype based on CLSI M57S

Figure 1. Prevalence of mould species found in community-acquired (n=1,252) and nosocomial infections (n=695)

A. Community-acquired



B. Nosocomial



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