# Azole Activity against Filamentous Fungi Causing Invasive Infections in Patients from ICU and Non-ICU Units (2017–2021)

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## Introduction

- · Invasive fungal infection (IFI) is associated with high mortality rates in critically ill patients.
- Appropriate antifungal treatment is crucial for managing IFI.
- · We evaluated the in vitro activity of isavuconazole, itraconazole, posaconazole, and voriconazole against contemporary moulds from ICU and non-ICU patients.

## Methods

- A total of 1,226 filamentous fungal isolates (386/840 from ICU/ non-ICU patients, respectively) were consecutively collected from 2017–2021 as part of the SENTRY Antifungal Surveillance Program.
- A single isolate per patient was collected from 43 worldwide medical centers located in Europe (48.5%; 16 sites in 14 countries), North America (34.0%; 17 sites in 2 countries), Asia-Pacific (15.0%; 8 sites in 5 countries), and Latin America (1.9%; 2 sites in 2 countries).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program, and only those isolates reported to have been collected from ICU or non-ICU patients were evaluated.
- Fungal isolates were identified by MALDI-TOF MS (Bruker Daltonics, Billerica, Massachusetts, USA) or by DNA sequencing analysis when an acceptable identification was not achieved by mass spectrometry.
- Antifungal susceptibility testing was performed in all isolates by broth microdilution following CLSI M38 guidelines.
- · Isolates included Aspergillus spp. (1,014 isolates), Mucorales group (54), Fusarium spp. (43), Scedosporium spp. (40), Lomentospora spp. (14), and other moulds (61; Table 1).
- Organism groups are listed by either ICU or non-ICU setting in Table 1.
- Pneumonia was the predominant infection type among ICU (81.6%) and non-ICU (71.8%) patients, followed by skin/soft tissue infection (7.8%/11.5%) and bloodstream infection (2.8%/1.4%, respectively;
- CLSI interpretative criteria and epidemiological cutoff criteria (ECV) were applied (M59 and M61).

## Results

- · Aspergillus spp. was the most common mould in both ICU (87.6%) and non-ICU (80.5%) settings (Table 1).
- Mucorales group was more common among ICU patients (6.7% vs. 3.3% non-ICU) while Scedosporium spp. was more frequent among non-ICU patients (4.3% vs. 1.0% ICU).
- A. fumigatus (76.0%/65.4% of Aspergillus), A. section Flavi (9.2%/10.9%), and A. section Nigri (7.4%/13.6%) were the top 3 Aspergillus groups in both settings, ICU/non-ICU, respectively.
- Isavuconazole inhibited 94.2%/91.2%, 100.0%/98.6%, and 96.0%/96.7% of A. fumigatus, A. section Flavi, and A. section Nigri from ICU/non-ICU settings, respectively, at the ECVs (Table 2).
- Similar activities (MIC<sub>50/90</sub>) against *A. fumigatu*s from ICU and non-ICU settings were noted for isavuconazole (0.5/1 mg/L vs. 0.5/1 mg/L), posaconazole (0.25/0.5 vs. 0.25/0.5 mg/L), itraconazole (1/1 mg/L vs. 1/2 mg/L), and voriconazole (0.5/0.5 vs. 0.5/0.5 mg/L; Table 3).
- No difference in the azole activities was noted against A. section Flavi isolates from the ICU (MIC<sub>50/90</sub> range, 0.5/0.5–1 mg/L) and non-ICU (MIC<sub>50/90</sub>, 0.5/0.5–1 mg/L) or A. section Nigri isolates from the ICU (MIC<sub>50/90</sub> range, 0.5–2/1–4 mg/L) and non-ICU (MIC<sub>50/90</sub> range, 0.5-2/1-4 mg/L).
- Voriconazole-nonsusceptible (VRC-NS) A. fumigatus isolates were detected in 9.3% of ICU and 9.0% of non-ICU A. fumigatus isolates.
- Among VRC-NS A. fumigatus from ICU/non-ICU, 58.3%/27.5% were wildtype (WT) to isavuconazole, 50.0%/25.0% were itraconazole-WT, and 75.0%/50.0% remained VRC-WT, respectively (Table 2).
- Voriconazole was the most active azole against Scedosporium spp. but was less active against Mucorales than the other azoles (Table 3).
- · All azoles showed limited activity against Fusarium spp.
- No difference was noted in the activities of the azoles between ICU and non-ICU isolates against Scedosporium spp., Mucorales, and Fusarium spp. pathogens.

#### Table 1. Distribution of filamentous fungi isolates collected worldwide from ICU and on ICII cottings (2017, 2021)

non-ICU settings (2017–2021)			
Organisms / Organism groups	ICU	Non-ICU	Total
Aspergillus spp.	338 (87.6%)	676 (80.5%)	1,014
Aspergillus section Fumigati	76.6%	66.0%	705
Aspergillus fumigatus	76.0%	65.4%	699
VRC-NS A. fumigatus	9.3%	9.0%	64
Aspergillus section Nigri	7.4%	13.6%	117
Aspergillus section Flavi	9.2%	10.9%	105
Aspergillus section Terrei	4.4%	4.3%	44
Other Aspergillus spp.	2.4%	5.2%	43
Fusarium spp.	11 (2.8%)	32 (3.8%)	43
Fusarium solani species complex	54.5%	34.4%	17
Gibberella fujikuroi species complex	18.2%	37.5%	14
Fusarium oxysporum species complex	27.3%	15.6%	8
Fusarium incarnatum-equiseti species complex	0.0%	9.4%	3
Fusarium dimerum species complex	0.0%	3.1%	1
Mucorales group	26 (6.7%)	28 (3.3%)	54
Rhizopus spp.	53.8%	46.4%	27
Lichtheimia spp.	15.4%	25.0%	11
Mucor spp.	11.5%	21.4%	9
Rhizomucor spp.	15.4%	3.6%	5
Syncephalastrum spp.	3.8%	3.6%	2
Scedosporium spp.	4 (1.0%)	36 (4.3%)	40
Lomentospora prolificans	4 (1.0%)	10 (1.2%)	14
Other moulds	3 (0.8%)	58 (6.9%)	61
Total	386	840	1,226

The percentage in parentheses is related to the total number of organisms, and the percentage without parentheses is related to the number of isolates in that specific organism group.

#### Figure 1. Distribution of filamentous fungi from ICU and non-ICU settings per infection type

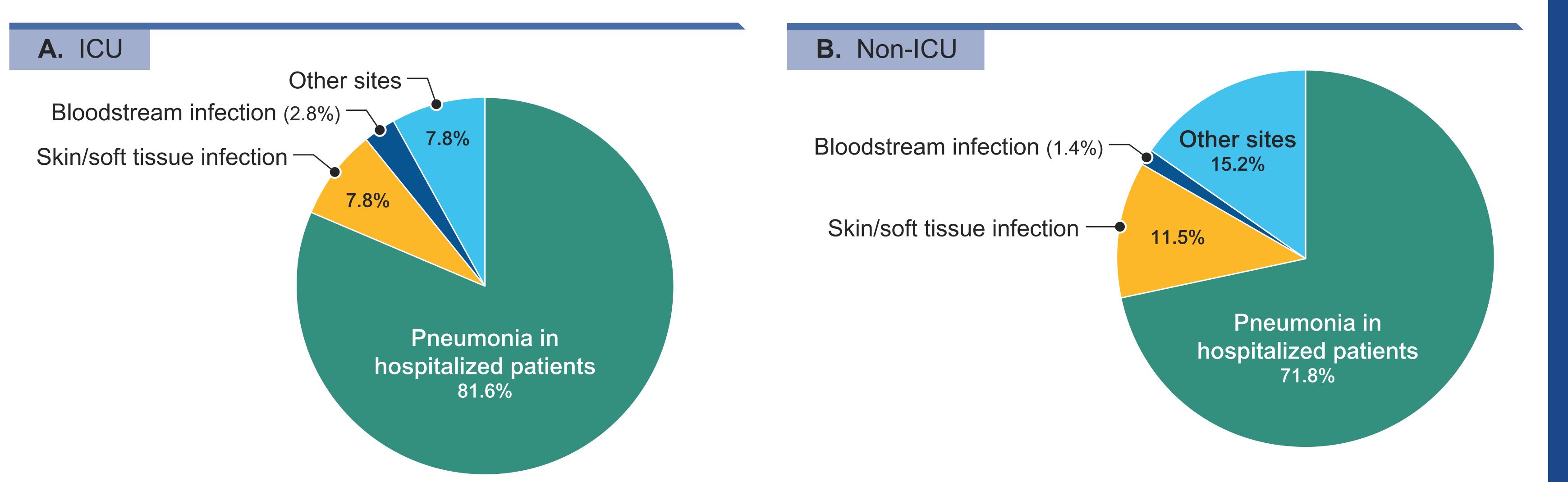


Table 2. Azole activity against Aspergillus spp. from ICU and non-ICU settings using CLSI epidemiological cutoff values

	ICU			Non-ICU				
Organism group (no. of isolates ICU/non-ICU)	CLSI %WT <sup>a</sup>				CLSI %WT <sup>a</sup>			
	ISC	ITC	PSC	VRC	ISC	ITC	PSC	VRC
Aspergillus fumigatus (257/442)	94.2%	91.8%	NA	97.7%	91.2%	89.4%	NA	95.5%
VRC-NS AFM a (24/40)	58.3%	50.0%	NA	75.0%	27.5%	25.0%	NA	50.0%
Aspergillus section Flavi (31/74)	100.0%	100.0%	100.0%	100.0%	98.6%	100.0%	100.0%	100.0%
Aspergillus section Nigri (25/92)	96.0%	92.0%	100.0%	100.0%	96.7%	93.4%	100.0%	96.7%
Aspergillus section Terrei (15/29)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

<sup>a</sup> Criteria published by CLSI M61 (2020). ECV criteria published in CLSI M59 (2020).

#### Table 3. Activity of antifungal agents against filamentous fungi isolates from ICU and non-ICU settings

	ICU				Non-ICU				
Organism group (no. of isolates ICU/non-ICU)	MIC <sub>50</sub> /MIC <sub>90</sub> (mg/L)					MIC <sub>50</sub> /MIC <sub>90</sub> (mg/L)			
	ISC	ITC	PSC	VRC	ISC	ITC	PSC	VRC	
Aspergillus fumigatus (257/442)	0.5/1	1/1	0.25/0.5	0.5/0.5	0.5/1	1/2	0.25/0.5	0.5/0.5	
VRC-NS AFM a (24/40)	1/4	1/>8	0.5/1	1/2	2/8	2/8	0.5/1	1/4	
Aspergillus section Flavi (31/74)	0.5/1	0.5/1	0.5/0.5	0.5/1	0.5/1	0.5/1	0.5/0.5	0.5/1	
Aspergillus section Nigri (25/92)	1/4	2/4	0.5/1	1/2	2/4	2/4	0.5/1	1/2	
Aspergillus section Terrei (15/29)	0.5/0.5	0.5/1	0.25/0.5	0.5/0.5	0.25/0.5	0.5/0.5	0.25/0.25	0.25/0.5	
Fusarium spp. (11/32)	>8/>8	>8/>8	>8/>8	8/>8	>8/>8	>8/>8	>8/>8	4/>8	
Mucorales (26/28)	2/>8	1/>8	0.5/>8	>8/>8	2/>8	2/8	1/8	>8/>8	
Scedosporium spp. (4/36)	8/—	8/—	2/—	0.5/—	8/>8	8/>8	2/>8	0.5/2	

ICU, intensive care unit; ISC, isavuconazole; ITC, itraconazole; PSC, posaconazole; VRC, voriconazole; NA, not available; VCR-NS AFM, voriconazole-nonsusceptible A. fumigatus. <sup>a</sup> Using CLSI M61 (2020 "—", MIC<sub>oo</sub> not calculated due to <10 isolates.

### Conclusions

- · Aspergillus spp. was the most common filamentous fungi group of pathogens in ICU and non-ICU settings.
- Mucorales group was more frequently recovered from ICU patients while Scedosporium spp. was more commonly recovered from non-ICU
- Pneumonia was the most frequent type of infection caused by filamentous fungi in both settings.
- Isavuconazole was active against Aspergillus isolates from ICU and non-ICU settings, including against VRC-NS A. fumigatus.
- VRC-NS A. fumigatus rates were similar between ICU and non-ICU
- All azoles displayed similar activity against moulds from ICU and non-ICU settings.

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