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Evaluation of Isavuconazole Activity against *Aspergillus fumigatus* Causing Invasive Infections Worldwide Using the New CLSI Clinical Breakpoints

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Introduction

- Isavuconazole was approved by the US FDA in 2015 and is utilized as a first-line antifungal therapy for the treatment of invasive aspergillosis (IA).
- IA remains a serious, life-threatening infection, with *Aspergillus fumigatus* as the most frequently isolated species.
- The CLSI Subcommittee for Antifungal Susceptibility Testing recently approved clinical breakpoints for isavuconazole against *A. fumigatus*.
- The study objective was to evaluate the *in vitro* activity of isavuconazole and comparator antifungal agents by applying the new CLSI clinical breakpoints against a worldwide collection of *A. fumigatus* causing invasive infections.

Methods

- A total of 846 *A. fumigatus* isolates were collected as part of the 2017–2021 SENTRY Antifungal Surveillance Program from 44 medical centers located in North America (NA; *n*=282; 18 centers), Europe (EU; *n*=449; 17 centers), Asia-Pacific (APAC; *n*=102; 8 centers), and Latin America (LA, *n*=13; 1 center; Figure 1).
- Only 1 isolate per patient was included.
- Isolates were identified by MALDI-TOF MS and/or ITS and β-tubulin sequencing and tested by CLSI broth microdilution.
- CLSI interpretative criteria and epidemiological cutoff criteria (ECV) were applied, including the recently approved isavuconazole breakpoints against *A. fumigatus* (≤1 mg/L, susceptible; 2 mg/L, intermediate; and ≥4 mg/L, resistant; January 2023 meeting, CLSI).
- Posaconazole ECVs of 0.5 mg/L was used against *A. fumigatus*.
- *A. fumigatus* isolates showing non-wildtype MIC values for any azole were submitted to *cyp51* analysis by whole genome sequencing.

Results

A. fumigatus

- Overall, isavuconazole ($MIC_{50/90}$, 0.5/1 mg/L) showed similar activity to other azoles against *A. fumigatus* (Table 1), inhibiting 93.4% at ≤1 mg/L (CLSI-approved susceptible clinical breakpoint), regardless of the region (Figure 2).
- Voriconazole ($MIC_{50/90}$, 0.5/0.5 mg/L) inhibited 91.6% at its susceptible clinical breakpoint (Table 1).
- Itraconazole ($MIC_{50/90}$, 1/1 mg/L; 92.0% WT) and posaconazole ($MIC_{50/90}$, 0.25/0.5 mg/L; 97.2% WT) were also active against all *A. fumigatus* at their respective ECV criteria (Table 1).

Azole-NWT *A. fumigatus*

- Figure 3 displays the distribution of azole-NWT *A. fumigatus* isolates per region and surveillance year.
  - NA showed an increase in the azole-NWT rate over the years, while EU and APAC azole-NWT rates trended lower.
- The azole-NWT phenotype was detected in 88 *A. fumigatus* (10.4%).
  - NA showed the highest frequency of azole-NWT isolates (31; 11.0%), followed by EU (48; 10.7%) and APAC (9; 8.8%; Figure 3).
  - All *A. fumigatus* from LA were WT to azoles.
- Azole activity varied against azole-NWT isolates with and without CYP51 alterations (Table 1 and Figure 4).
- Applying the new isavuconazole CLSI breakpoints, 43.9% of the azole-NWT *A. fumigatus* without CYP51 alteration remained susceptible to isavuconazole and 73.2% were susceptible to voriconazole (Figure 4).
- Isavuconazole and voriconazole inhibited 46.7% and 43.3%, respectively, of azole-NWT *A. fumigatus* isolates displaying CYP51 alterations other than L98H/TR34 at the respective breakpoint (Figure 4).
- *A. fumigatus* isolates carrying L98H/TR34 (17 occurrences) in the CYP51A sequence displayed elevated MIC ranges for all azoles: isavuconazole, 2–>8 mg/L; voriconazole, 1–>8 mg/L; itraconazole, 2–>8 mg/L; and posaconazole, 0.5–4 mg/L.

Conclusions

- Isavuconazole exhibited potent *in vitro* activity against *A. fumigatus*, regardless of the region, when the new CLSI clinical breakpoints were applied.
- Azole-NWT *A. fumigatus* rates increased in NA but slightly decreased in EU and APAC regions.
- Azole activity varied against azole-NWT isolates with and without CYP51 alterations.
- Isavuconazole remained active against >40% of azole-NWT *A. fumigatus* isolates displaying wildtype CYP51 sequences or carrying CYP51 alterations other than L98H/TR34.

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Table 1. Activity of isavuconazole and comparator antifungal agents tested against 846 *A. fumigatus* isolates

Organism group (n)	ISC		VRC		ITC		PSC	
	$MIC_{50/90}$	%S[a]	$MIC_{50/90}$	%S[b]	$MIC_{50/90}$	%WT[c]	$MIC_{50/90}$	%WT[d]
A. fumigatus (846)	0.5/1	93.4	0.5/0.5	91.6	1/1	92.0	0.25/0.5	97.2
AZ-NWT (88)	2/8	36.4	1/2	48.9	2/8	22.7	0.5/1	77.0
WT *CYP51* (41)	2/2	43.9	0.5/1	73.2	2/2	36.6	0.5/0.5	90.0
NWT *CYP51* (47)	2/>8	29.8	1/4	27.7	2/>8	10.6	0.5/1	66.0
CYP51 alteration other than L98H/TR34 (30)	2/>8	46.7	1/4	43.3	2/8	16.7	0.5/1	83.3
North America (282)	0.5/1	94.0	0.5/0.5	90.8	1/1	91.8	0.25/0.5	97.5
Europe (449)	0.5/1	92.7	0.5/0.5	91.1	1/1	90.9	0.25/0.5	96.4
Asia-Pacific (102)	0.5/1	94.1	0.5/0.5	95.1	1/1	96.1	0.25/0.5	99.0
Latin America (13)	0.5/1	100.0	0.5/0.5	100.0	0.5/1	100.0	0.25/0.5	100.0

Abbreviations: AZ, azole; NWT, non-wildtype; ISC, isavuconazole; VRC, voriconazole; ITC, itraconazole; PSC, posaconazole.
[a] Isavuconazole breakpoint criteria was approved in the CLSI Jan 2023 meeting but should not be used for clinical laboratories while not published in the M38M51S document.
[b] CLSI (M38M51S, 2022) breakpoints applied.
[c] CLSI (M57S, 2022) epidemiological cut-off value applied.
[d] Posaconazole epidemiological cut-off value of 0.5 mg/L was applied as published by Pfaller et al., 2021.

Figure 1. Distribution *A. fumigatus* collected from 2017–2021 SENTRY surveillance program split by region

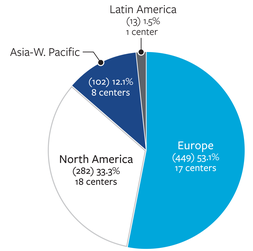
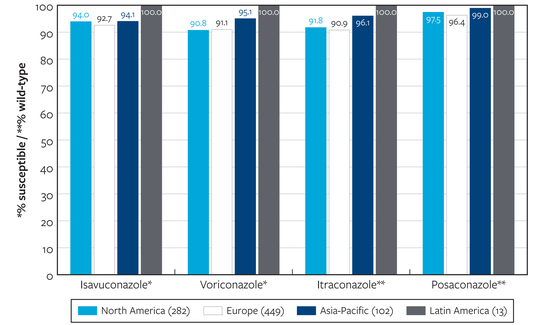


Figure 2. Activity of isavuconazole and other azoles against 846 *A. fumigatus* isolates split by region



* Using CLSI M38M51S (2022) clinical breakpoint criteria.
** Using CLSI M57S (2022) epidemiological cutoff value criteria.

Figure 3. Trend of azole-NWT *A. fumigatus* isolates evaluated by region and surveillance year

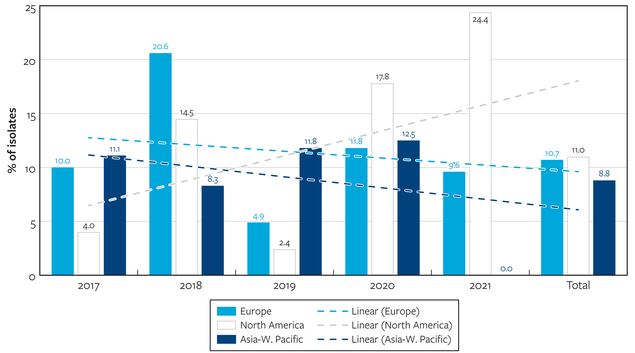
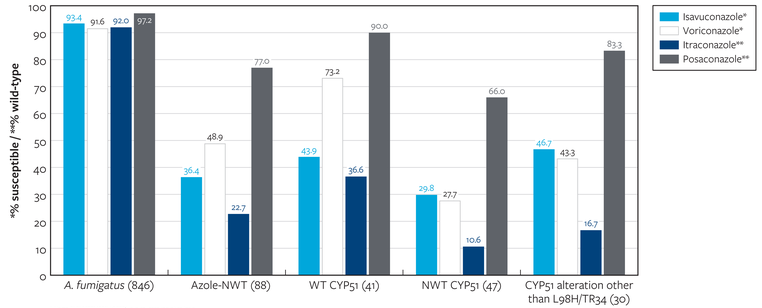


Figure 4. Activity of isavuconazole and other azoles against azole-NWT *A. fumigatus* subgroups



* Using CLSI M38M51S (2022) clinical breakpoint criteria.
** Using CLSI M57S (2022) epidemiological cutoff value criteria.

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