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Use of Voriconazole to Predict Susceptibility and Resistance to Isavuconazole for *Aspergillus fumigatus* by Using the CLSI Methods and Interpretive Criteria

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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.
- The CLSI Subcommittee for Antifungal Susceptibility Testing approved clinical breakpoints for isavuconazole and voriconazole against *Aspergillus fumigatus*.
- Since antifungal susceptibility testing for filamentous fungi is cumbersome, we initiated this study to confirm if voriconazole MIC values can be used to predict the susceptibility of isavuconazole for *A. fumigatus* when using the CLSI testing method.
- Voriconazole and isavuconazole MIC values were compared to determine the percentage of essential agreement (EA), categorical agreement (CA) and very major (VME), major (ME), and minor error rates, and the ability to detect Cyp51 alterations.

Methods

- A total of 976 *A. fumigatus* isolates were collected as part of the SENTRY Antifungal Surveillance Program from 2017 to 2022.
- The isolates were collected in Europe (n=514), USA (n=318), Asia-Pacific (n=128), and Latin America (n=16).
- Only 1 isolate per patient episode was included.
- All isolates were identified by MALDI-TOF MS and/or ITS and β-tubulin sequencing.
- All isolates were tested by CLSI reference broth microdilution method.
- CLSI approved breakpoints for *A. fumigatus* versus voriconazole (≤0.5/1/≥2 mg/L for susceptible/intermediate/resistant; M38M51S CLSI document) and isavuconazole (≤1/2/≥4 mg/L for susceptible/intermediate/resistant; January 2023 meeting, CLSI) were applied.
- Non-susceptible *A. fumigatus* isolates were submitted to *cyp51* analysis by whole genome sequencing as previously described.

Results

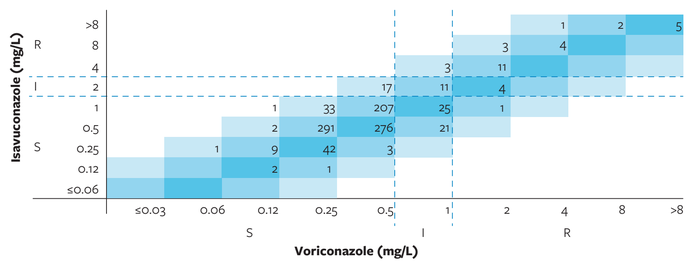
- A total of 354 (36.3%) of the 976 *A. fumigatus* isolates tested displayed the same MIC results for voriconazole and isavuconazole (Figure 1).
- The essential agreement of isavuconazole MIC values to voriconazole was 93.9% for ±1-dilution and 99.9% for ±2-dilutions.
- The categorical agreement was 92.7% with no very major errors, 1 (0.1%) major error, and 70 (7.2%) minor errors.
- Most (46/70; 65.7%) isolates displaying minor errors had a voriconazole intermediate MIC result at 1 mg/L and isavuconazole susceptible MIC values (0.5 or 1 mg/L).
  - 17 isolates exhibited intermediate isavuconazole MIC results (2 mg/L) but susceptible voriconazole (0.5 mg/L).
  - The remaining minor errors were 3 isolates displaying voriconazole at 1 mg/L (intermediate) and a resistant isavuconazole MIC at 4 mg/L and 4 isolates displaying voriconazole at 2 mg/L (resistant) and intermediate isavuconazole MIC values (2 mg/L).
- 37 isolates harbored Cyp51 alterations and 28/37 (75.7%) followed in the same MIC interpretative category for both azoles (Table 1).
  - 22/37 (59.5%) isolates were categorized as resistant to isavuconazole and voriconazole.
- Among 18 isolates harboring a L98H/TR34 Cyp51A genotype, 16 were resistant to both azoles and 2 isolates had MIC values in the intermediate category for one agent and resistant to the other agent.
- Three isolates were isavuconazole-susceptible and either voriconazole-resistant (2 isolates; major error) or -intermediate (1 isolate, minor error).
  - These isolates carried I124V Cyp51A or Cyp51B Q42L alone or in combination.

Table 1. Isavuconazole and voriconazole MIC values for *A. fumigatus* isolates carrying CYP51 mutations

MIC (mg/L)				
Isavuconazole	Voriconazole	CYP51A	CYP51B	State, Country
1	1	I242V	Wild type	IN, USA
1	1	I242V	Q42L, S501Q	IN, USA
1	2	Wild type	Q42L	Australia
2	0.5	F46Y, M172V, N248T, D255E, E427K	Q42L	Thailand
2	1	Wild type	K82Q, F149V, P383L	Australia
2	1	Wild type	Q42L	NJ, USA
2	1	Wild type	Q42L	NJ, USA
2	1	I242V	Q42L, S501Q	IN, USA
2	1	F46Y, M172V, E427K	Wild type	VT, USA
2	1	F46Y, M172V, N248T, D255E, E427K	Wild type	Czech Republic
2	2	Wild type	Q42L	NJ, USA
2	2	K67Q	Wild type	MI, USA
2	2	TR34, L98H	Wild type	Italy
4	1	Wild type	Q42L	France
4	1	TR34, L98H	Wild type	Italy
4	2	TR34, L98H	Wild type	Belgium
4	2	TR34, L98H	Wild type	Italy
4	2	TR34, L98H	Wild type	Italy
4	2	TR34, L98H	Wild type	Slovenia
4	2	TR34, L98H	Wild type	UK
4	2	TR34, L98H	Wild type	Italy
4	2	TR34, L98H	Wild type	UK
4	2	TR34, L98H	Wild type	UK
4	2	TR34, L98H	Wild type	Czech Republic
8	2	TR34, L98H	Wild type	Italy
8	2	TR34, L98H	Wild type	UK
8	4	TR34, L98H	Wild type	Germany
8	4	TR34, L98H	Wild type	Belgium
8	4	TR34, L98H	Wild type	France
>8	4	G448S	Wild type	VA, USA
>8	8	G138C	Wild type	New Zealand
>8	8	TR34, L98H	Wild type	Belgium
>8	>8	G448S	Q42L	VA, USA
>8	>8	H147Y	Wild type	France
>8	>8	TR34, L98H	Wild type	Italy
>8	>8	TR46, Y121F, M172I, T289A, G448S	Wild type	Belgium
>8	>8	Y121F, T289A	Wild type	New Zealand

Resistant Intermediate Susceptible

Figure 1. Scattergram for isavuconazole MIC vs voriconazole MIC using CLSI MIC breakpoints *Aspergillus fumigatus*



Essential agreement	Number of Isolates	%
Same MIC	354	36.3
± 1 dilution	916	93.9
± 2 dilutions	975	99.9
Categorical agreement	905	92.7

Interpretation	Number of Isolates	Very major (%)	Major (%)	Minor (%)
R	29	0 (0.0%)	N/A	3 (10.3%)
I	32	N/A	N/A	21 (65.6%)
S	915	N/A	1 (0.1%)	46 (5.0%)
Total	976	0	1 (0.1%)	70 (7.2%)

Conclusions

- Voriconazole and isavuconazole had excellent essential agreement at ±1-dilution (93.9%) and ±2-dilutions (99.9%) and categorical agreement (>95%).
- Voriconazole and isavuconazole MIC values were within ±1-dilution for 35/37 (94.6%) isolates harboring Cyp51 alterations but the categorical agreement was 59.5% (just one major error and 8 minor errors).
- In summary, voriconazole can predict the isavuconazole susceptibility testing interpretation results when testing *A. fumigatus* using the CLSI reference broth microdilution method.

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