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Activity of mold-active azole agents against *Aspergillus fumigatus* clinical isolates nonwildtype to azoles and isolates displaying CYP51 alterations

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Introduction

- *Aspergillus fumigatus* is the leading cause of invasive aspergillosis.
- Triazoles are considered the first-line therapy for invasive aspergillosis; however, azole resistance among *A. fumigatus* has increased in Europe and North America over the past two decades.
- Azole resistance is usually caused by alterations in CYP51A, which is involved in the ergosterol biosynthesis pathway.
- There are recognized discrete changes in the CYP51A from environmental exposure or due to the prolonged clinical use.
  - Additionally, alterations in the homologue CYP51B have been described in association with azole resistance.
- We analyzed 1,262 *A. fumigatus* isolates collected globally from 2017–2024 and reported the rates of azole nonwildtype (NWT) isolates and presence of CYP51 alterations.

Materials and Methods

- A total of 1,262 *A. fumigatus* isolates from respiratory and invasive infections were collected in 56 hospitals from 2017–2024.
- Isolates were identified by MALDI-TOF and/or DNA sequencing methods.
- Antifungal susceptibility testing was performed using the reference broth microdilution method described by CLSI M38 guidelines.
- Breakpoints and epidemiological cutoff values (ECVs) were published on CLSI documents (M38M51S and M57S) or by Pfaller et al. for posaconazole.

Results

- Among 1,262 *A. fumigatus* isolates, 112 (8.9%) were NWT to isavuconazole (n=105; 8.3% overall), itraconazole (n=108; 8.6%) and/or voriconazole (n=65; 5.2%).
  - Four (3.2% overall) isolates were nonwildtype to posaconazole using an ECV of 0.5 mg/L.
- The 116 azole NWT *A. fumigatus* isolates were collected from Europe (n=62), North America (n=39) and Asia-Pacific (n=15) in similar rates (9.7%, 9.8% and 7.4%, respectively).
  - These isolates were not observed in Latin America.
- Among 116 azole NWT *A. fumigatus* isolates, susceptibility to voriconazole and isavuconazole was 44.0% and 37.1% respectively (Figure 2).
- A total of 49 isolates displayed CYP51A alterations (Figure 1), including 20 isolates displaying the TR34/L98H genotype that has been associated with environmental use of azoles.
- All but one isolate displaying the TR34/L98H genotype were collected in Europe (Figure 1).
- Thirteen other CYP51A alterations were detected alone or in combination (Figure 1).
- Voriconazole and isavuconazole susceptibility rates against isolates harboring CYP51A alteration were 20.8% and 24.5%, respectively (Figure 2).
- Isolates carrying the TR34/L98H genotype were resistant to isavuconazole and voriconazole, all were NWT to itraconazole and 20.0% were NWT to posaconazole (Figure 2).
- Non-TR34/L98H isolates and non-CYP51A mutants displayed higher susceptibility rates to azoles (Figure 2).
- CYP51B alterations were noted in 9 isolates, all also having CYP51A alterations.

Conclusions

- The rates of azole-NWT *A. fumigatus* were similar in Asia-Pacific, Europe and North America; however, a large number of European isolates harbored the TR34/L98H genotype that displayed high resistance to all azoles.
- Emerging azole-resistant *A. fumigatus* is worrisome and there is a critical role for antifungal surveillance in tracking emerging resistance since a small number of laboratories test these isolates.

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Figure 1. Distribution of (A) azole NWT *A. fumigatus* isolates and (B) CYP51A alterations by geographic regions

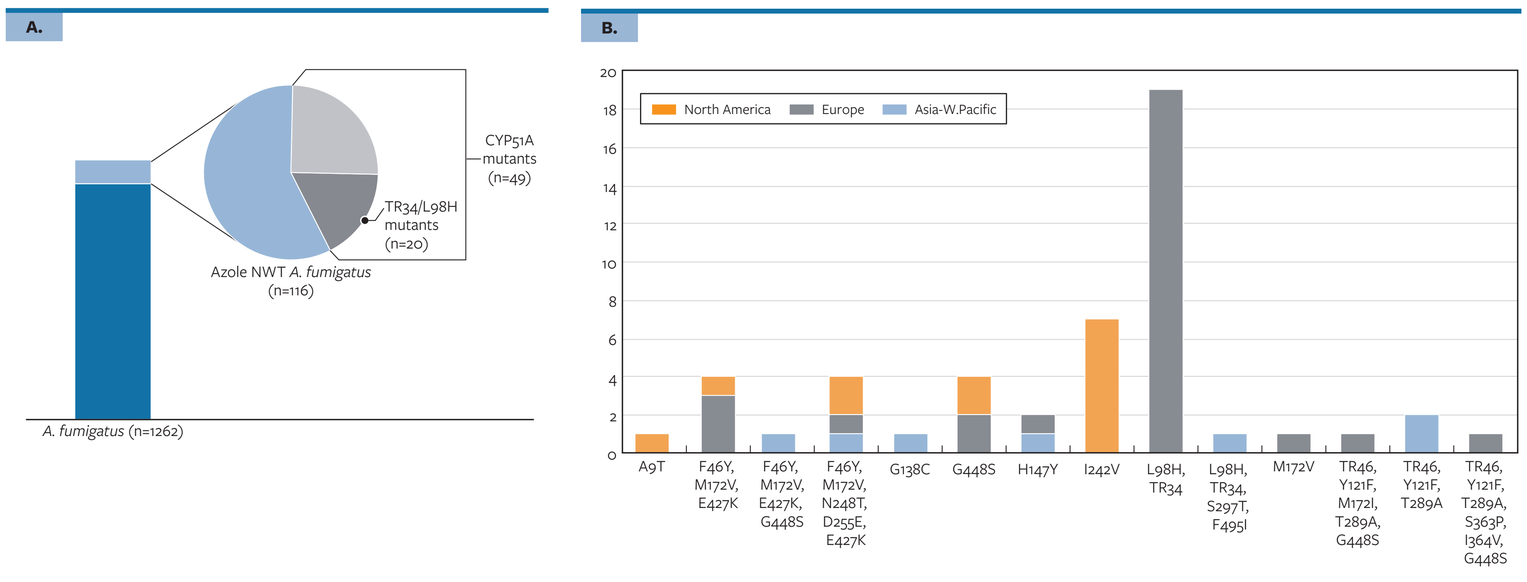
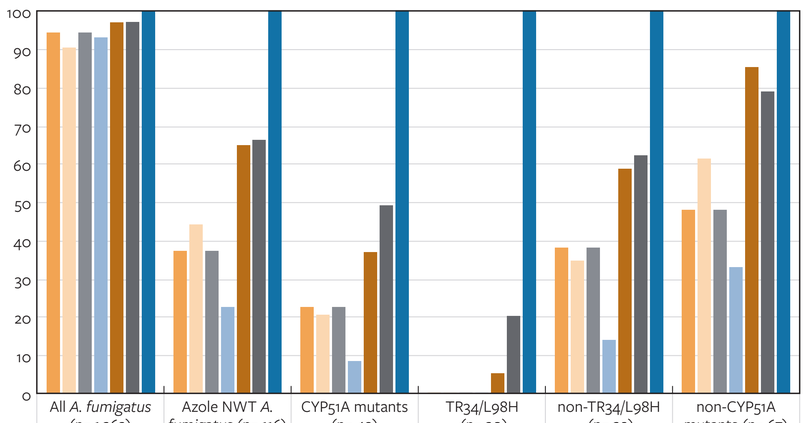


Figure 2. Activity of azole agents against azole NWT *A. fumigatus*



	All *A. fumigatus* (n= 1,262)	Azole NWT *A. fumigatus* (n= 116)	CYP51A mutants (n= 49)	TR34/L98H (n= 20)	non-TR34/L98H (n= 29)	non-CYP51A mutants (n= 67)
Isavuconazole % S	94.2	37.1	22.4	0.0	37.9	47.8
Voriconazole % S	90.2	44.0	20.4	0.0	34.5	61.2
Isavuconazole % WT	94.2	37.1	22.4	0.0	37.9	47.8
Itraconazole % WT	92.9	22.4	8.2	0.0	13.8	32.8
Voriconazole % WT	96.8	64.7	36.7	5.0	58.6	85.1
Posaconazole % WT	96.9	66.1	49.0	20.0	62.1	78.8
Amphotericin B % WT	99.8	100.0	100.0	100.0	100.0	100.0

% S = percentage susceptible isolates when applying CLSI M38M51S breakpoints.
% WT = percentage of wildtype isolates when applying CLSI M57S ECVs.

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