# Potent *in vitro* activity of Rezafungin (RZF) against *Aspergillus* clinical isolates recovered from lung transplant patients who have received ≥3 months of triazole prophylaxis

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## Background

- The emergence of azole resistance globally among *Aspergillus fumigatus* has major clinical and agricultural implications.
- At our center, isavuconazole (ISA), posaconazole (POS) and voriconazole (VOR) have been used as antifungal prophylaxis or pre-emptive therapy in solid organ transplant (SOT) patients.
- We previously showed that
  - Azole breakthrough (BT) fungi were more likely to be non- *fumigatus Aspergillus* (non-*Af*) spp.
  - Azole BT isolates exhibited higher azole MICs than non-BT isolates, with 7% pan-azole resistance.
- Rezafungin (RZF) is an investigational echinocandin with long serum half-life, suitable for prolonged dosing intervals.
  - It has potent activity against *Aspergillus* spp, including azole-resistant isolates

## Objectives

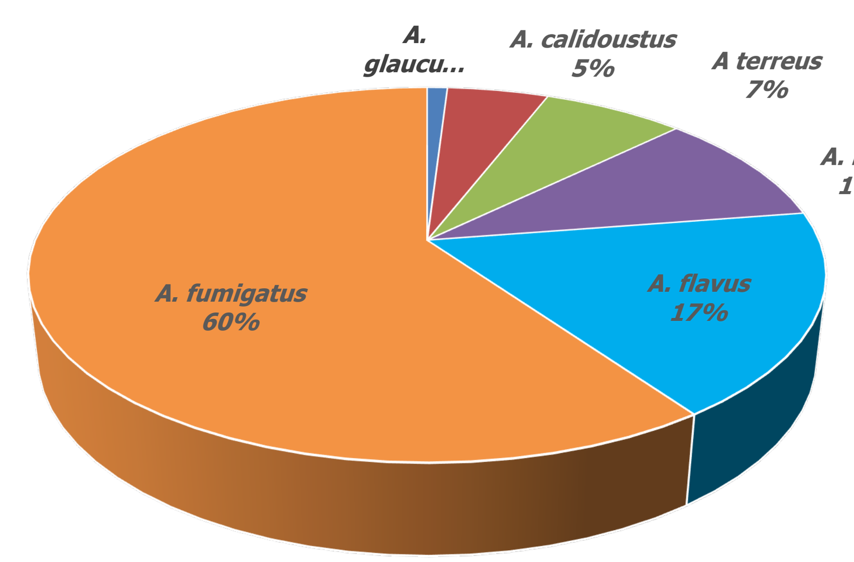
- To determine the azole minimum inhibitory concentrations (MICs) against *Aspergillus* isolates recovered from lung transplant recipients
- To determine the minimum effective concentrations (MECs) of caspofungin (CAS) and RZF against *Aspergillus* clinical isolates from our center.

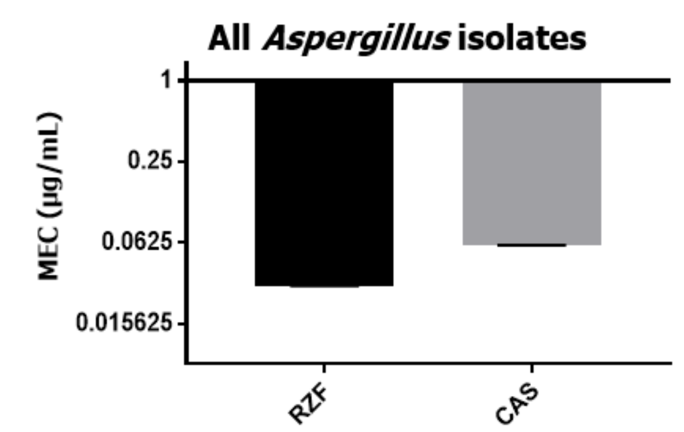
## Methods

- *Aspergillus* clinical isolates: obtained from UPMC lung transplant repository from June 2016 to July 2019
- *Aspergillus* speciation was performed using standard phenotypic analysis, and confirmed by ITS and D1/D2 sequencing
- Determination of antifungal MICs (ISA, POS, VOR, AmB) and MECs (RZF, CAS) was performed using EUCAST methods (Edef 9.3.1).
  - Isolates tested at least in duplicates
- EUCAST proposed clinical breakpoints for susceptibility:
  - ISA/VOR/AmB ≤1 μg/mL
  - POS ≤0.125 μg/mL

## Results

**Figure 1 – Distribution of *Aspergillus* spp. tested and overall RZF and CAS MECs**



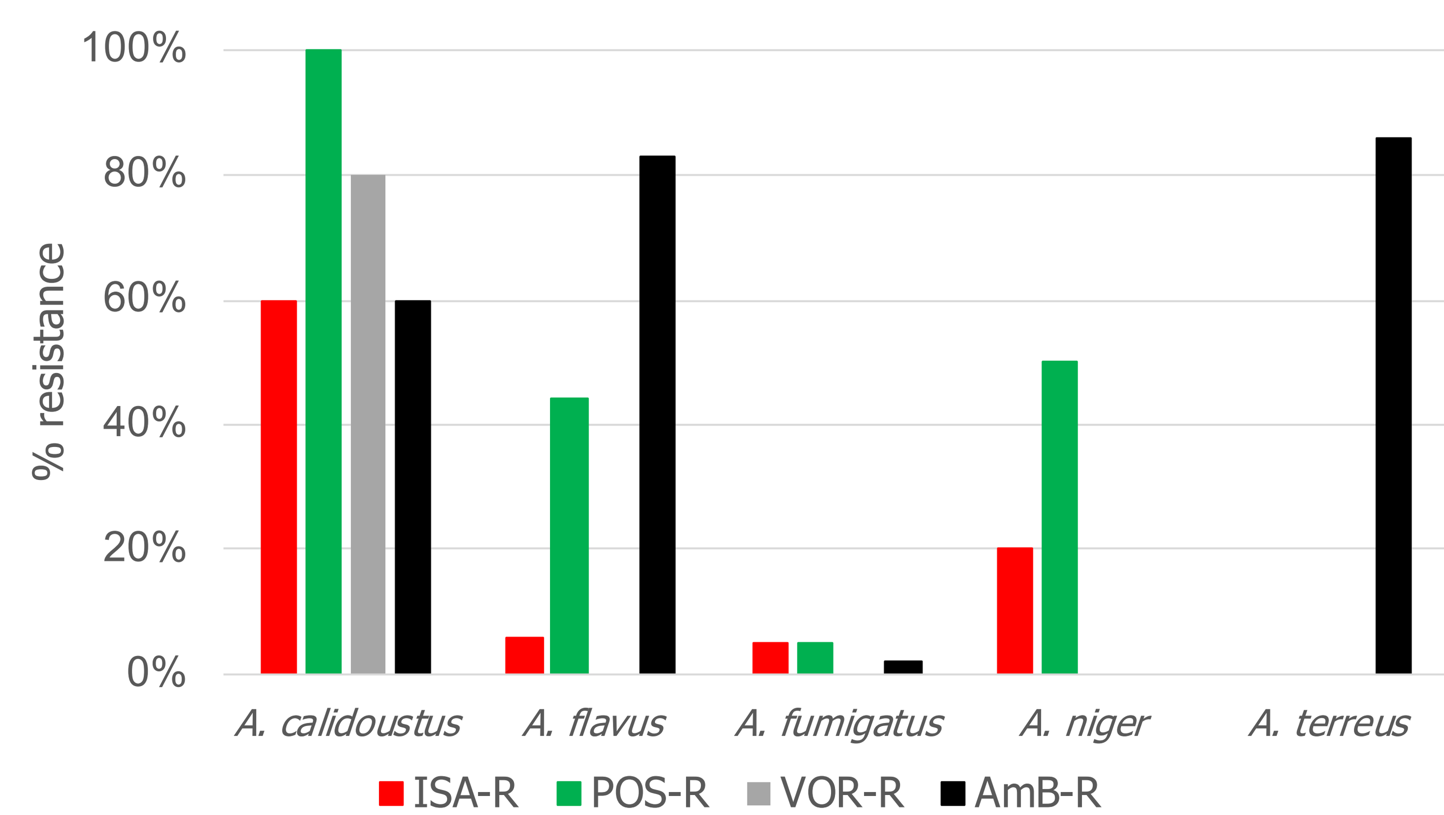

There was no difference in RZF and CAS MECs (p=0.86)

**Table 1 – Antifungal MICs against *Aspergillus* isolates (median MICs)***

| *Aspergillus spp* | # isolates | ISA | POSA | VORI | AmB | Caspo | RZF |
|---|---|---|---|---|---|---|---|
| *A. calidoustus* | 5 | 8 | 2 | 8 | 2 | 0.03 | 0.03 |
| *A. flavus* | 18 | 0.25 | 0.25 | 0.25 | 4 | 0.25 | 0.25 |
| *A. fumigatus* | 61 | 0.125 | 0.06 | 0.125 | 0.5 | 0.06 | 0.015 |
| *A. glaucus* | 1 | 0.5 | 0.5 | 0.25 | 0.5 | 0.03 | 0.03 |
| *A. niger* | 10 | 0.25 | 0.125 | 0.25 | 4 | 0.125 | 0.03 |
| *A. terreus* | 7 | 0.25 | 0.125 | 0.25 | 4 | 0.06 | 0.06 |

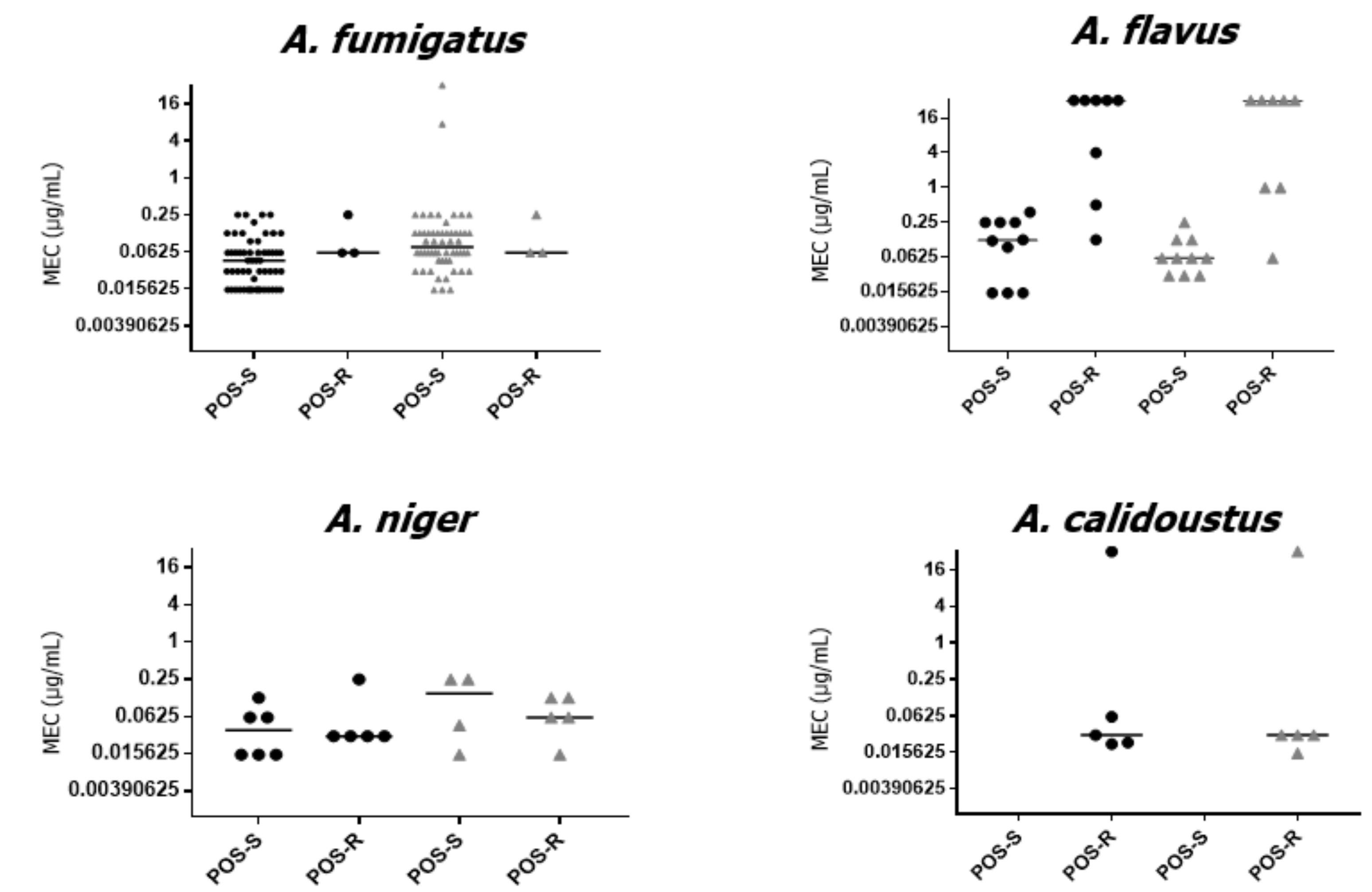
*MEC values are listed for echinocandins; MIC and MEC values are listed in μg/mL

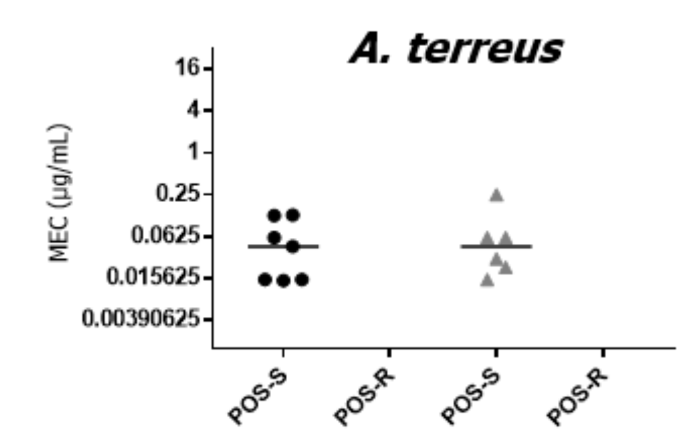
**Table 2 – Antifungal resistance against *Aspergillus* isolates**




## Results

**Figure 2 – MECs of RZF and CAS against selected POS-susceptible (POS-S) and –resistant (POS-R) *Aspergillus* spp.**
Black circles denotes RZF MECs and gray triangles denote CAS MECs




- Overall, there was no difference in RZF and CAS MECs among *Aspergillus* isolates with azole-S or azole-R, except for *A. flavus*, where the RZF and CAS MECs were higher for POS-R than for POS-S isolates (p=0.0008 and 0.001, respectively)
- High RZF and CAS MECs (>1 μg/mL were predominantly observed among *A. flavus* and to a lesser extent, *A. calidoustus* isolates

## Conclusions

- **Azole resistance was most prevalent among non-*A. fumigatus* spp.**
  - ***A. calidoustus, A. flavus and A. niger* were the most common *Aspergillus* spp. associated with azole resistance**
- **The rate of 26% of amphotericin B resistance is of concern, and might reflect the common and prolonged use of inhaled amphotericin B at our center for lung transplant recipients**
- **The excellent activity of RZF and CAS suggests that these drugs are potential therapeutic options for patients infected with azole-resistant or azole-breakthrough *Aspergillus* isolates.**
- **The long-half-life and high tolerability of RZF make this agent an attractive consideration for antifungal prophylaxis**