Background

- Isavuconazole is an azole recently available in Europe as a first-line therapy for invasive aspergillosis.
- Nevertheless, azole resistance in Aspergillus spp. already exists anditraconazole and/or voriconazole-resistant isolates may be cross-resistant to isavuconazole.
- Therefore, we examined the in vitro combination of isavuconazole with caspofungin, micafungin and anidulafungin against azole-susceptible and -resistant Aspergillus fumigatus, A. flavus, A. nidulans, A. terreus, and A. niger.

Material/Methods

- 30 Aspergillus spp. were selected: azole-susceptible A. fumigatus (n=5), azole-resistant A. fumigatus (n=5); 2 isavuconazole-resistant and 3 isavuconazole-resistant), A. flavus (n=5), A. nidulans (n=5), A. terreus (n=5) and A. niger (n=5).
- The in vitro combinations (isavuconazole-caspofungin or micafungin or anidulafungin) were tested using two techniques:
  - a two-dimensional checkerboard microdilution method (based on EUCAST reference method).
  - and an agar based diffusion method (E-test).
- MICs visually determined after 48h of incubation at 35°C.
- In the EUCAST method, a complete (100%) and a partial (50% or MEC) inhibition endpoint was used for isavuconazole, the echinocandins, and the combination. In the E-test method, a complete inhibition (100%) endpoint was determined for isavuconazole, a partial inhibition (50%) for the echinocandins, and a complete and a partial inhibition for the combination.
- Drug interactions were defined as synergistic (Fractional Inhibitory Concentration Index (FICI)≤0.5), indifferent (FICI [0.5-4]) or antagonistic (FICI>4).

Example (E-test): combination of Isavuconazole with Echinocandins against azole-susceptible Aspergillus fumigatus: CB = caspofungin, MF = micafungin, AN = anidulafungin, IVU = isavuconazole.

Results

- **E-test**: These results are similar using a complete or a partial inhibition endpoint.
  - Considering a complete inhibition endpoint: **indifference** for all the strains.
  - Considering a partial inhibition endpoint:

Conclusions

- These in vitro findings mainly showed that combination of isavuconazole and echinocandins is indifferent for azole-susceptible and -resistant A. fumigatus, A. flavus, A. nidulans, A. terreus, and A. niger.
- Antagonism was almost never observed.
- Further in vivo evaluation of these combinations are warranted.