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# Evaluation of Isavuconazole MIC Strips for Susceptibility Testing of *Aspergillus* and *Scedosporium* Species

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## Background

- Invasive fungal disease (IFD) is a major cause of mortality and morbidity in immunocompromised patients.[1,2]
  - Aspergillosis is the most common infection type caused by moulds in patients undergoing haematopoietic stem cell transplant or solid organ transplant, and is associated with high mortality in these patient groups.[1,2]
  - Rare fungal species, such as *Scedosporium* spp., have limited treatment options and are associated with high mortality rates.[3,4]
- Isavuconazonium sulfate, the water-soluble prodrug of the broad-spectrum, triazole antifungal, isavuconazole, was developed for the treatment of IFD.
  - Based on the results from Phase 3 clinical trials,[5,6] isavuconazonium sulfate has been approved by the U.S. Food and Drug Administration for the treatment of adults with invasive aspergillosis (IA) and invasive mucormycosis.[7]
  - In addition, the European Commission has approved isavuconazole for the treatment of adults with IA and adults with mucormycosis for whom amphotericin B is not appropriate.[8]
- The objective of this study was to assess the *in vitro* activity of isavuconazole comparing gradient minimum inhibitory concentration (MIC) strips with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution reference method.

## Methods

- 62 *Aspergillus* spp. (19 *A. flavus*, 18 *A. fumigatus*, 9 *A. terreus* and 8 *A. niger*) and 8 *Scedosporium apiospermum* clinical isolates were obtained from bronchoalveolar lavage, sputum and bronchial aspirate.
- All isolates were tested for susceptibility to isavuconazole using the EUCAST broth microdilution method (E. Def 9.3).
  - Isolates were cultured for 48 hours at 35°C; MIC was judged by visual evidence of no growth.
- 45 isolates were tested using a "MIC Test Strip isavuconazole" (Liofilchem, Italy).
  - Cultures were prepared in a MacFarland 0.5 conidia suspension and grown on RPMI1640 2% glucose agar gel.
  - MICs from the strips were read at 80% growth inhibition after 48 hours incubation at 35°C.
  - For the analysis of essential agreement, values from the MIC strips were rounded up to the next corresponding dilution for the broth microdilution.
  - The percent of essential agreement between the two methods was calculated within a ±1-fold dilution.

## Results

- A summary of all isolates tested in the study is provided in **Table 1**.

**Table 1. Isolate summary and susceptibility test result**

| Pathogen | Clinical sample | Ward | MIC test strip (mg/L) | EUCAST (mg/L) |
|---|---|---|---|---|
| *A. flavus* | Bronchoalveolar lavage | ICU | 0.75 | 0.5 |
| *A. flavus* | Bronchoalveolar lavage | Pneumology | - | 0.5 |
| *A. flavus* | Sputum | Haematology | 1 | 0.5 |
| *A. flavus* | Sputum | Medicine | - | 0.5 |
| *A. flavus* | Sputum | Paediatric haematology | 0.75 | 1 |
| *A. flavus* | Sputum | Pneumology | - | 1 |
| *A. flavus* | Bronchoalveolar lavage | Pneumology | - | 1 |
| *A. flavus* | Sputum | Medicine | - | 2 |
| *A. flavus* | Sputum | Medicine | 0.75 | 0.5 |
| *A. flavus* | Sputum | Paediatric haematology | 0.75 | 1 |
| *A. flavus* | Sputum | Paediatric haematology | 0.75 | 1 |
| *A. flavus* | Sputum | Pneumology | - | 1 |
| *A. flavus* | Bronchoalveolar lavage | Medicine | 0.75 | 1 |
| *A. flavus* | Sputum | Medicine | 0.25 | 0.125 |
| *A. flavus* | Bronchial aspirate | Pneumology | 0.38 | 0.25 |
| *A. flavus* | Bronchial aspirate | Medicine | 1 | 1 |
| *A. flavus* | Sputum | Pneumology | 1 | 1 |
| *A. flavus* | Sputum | Pneumology | 0.75 | 1 |
| *A. flavus* | Sputum | Medicine | 1 | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.38 | 0.25 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.38 | 0.25 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.50 | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | - | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | Pneumology | 0.50 | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | - | 1 |
| *A. fumigatus* | Bronchial aspirate | ICU | - | 1 |
| *A. fumigatus* | Bronchial aspirate | Pneumology | 0.125 | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.75 | 1 |
| *A. fumigatus* | Bronchoalveolar lavage | Medicine | 0.50 | 1 |
| *A. fumigatus* | Bronchoalveolar lavage | Pneumology | 1 | 1 |
| *A. fumigatus* | Bronchoalveolar lavage | Medicine | 1 | 1 |
| *A. fumigatus* | Bronchial aspirate | ICU | 1 | 1 |

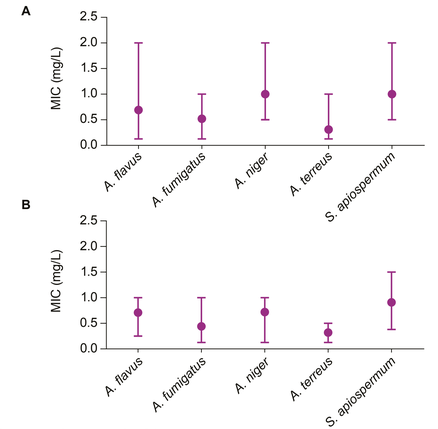
**Table 1 *(continued)***

| Pathogen | Clinical sample | Ward | MIC test strip (mg/L) | EUCAST (mg/L) |
|---|---|---|---|---|
| *A. fumigatus* | Sputum | Paediatric haematology | 0.19 | 0.125 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.125 | 0.125 |
| *A.fumigatus* | Sputum | Paediatric Pneumology | 0.38 | 0.5 |
| *A. fumigatus* | Bronchoalveolar lavage | ICU | 0.38 | 0.5 |
| *A. fumigatus* | Bronchial aspirate | Paediatric Pneumology | 0.75 | 0.5 |
| *A. niger* | Sputum | Haematology | 0.125 | 0.5 |
| *A. niger* | Sputum | Paediatric haematology | - | 0.5 |
| *A. niger* | Sputum | Haematology | 1 | 1 |
| *A. niger* | Sputum | Medicine | 0.75 | 1 |
| *A. niger* | Sputum | Paediatric Pneumology | - | 2 |
| *A. niger* | Sputum | Medicine | 1.50 | 2 |
| *A. niger* | Sputum | Medicine | 1 | 1 |
| *A. niger* | Sputum | Paediatric Pneumology | 1 | 1 |
| *A. terreus* | Sputum | Haematology | 0.38 | 0.25 |
| *A. terreus* | Sputum | Medicine | - | 0.25 |
| *A. terreus* | Bronchoalveolar lavage | Medicine | 0.125 | 0.25 |
| *A. terreus* | Bronchoalveolar lavage | Pneumology | - | 0.125 |
| *A. terreus* | Sputum | Haematology | 0.25 | 0.5 |
| *A. terreus* | Sputum | Haematology | - | 0.5 |
| *A. terreus* | Bronchoalveolar lavage | Pneumology | 0.50 | 1 |
| *A. terreus* | Sputum | Pneumology | 0.50 | 0.5 |
| *A. terreus* | Sputum | Paediatric Pneumology | 0.125 | 0.125 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | 1.50 | 2 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | - | 0.5 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | - | 1 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | 0.38 | 0.5 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | - | 0.5 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | 1.50 | 2 |
| *S. apiospermum* | Bronchial aspirate | Paediatric Pneumology | 0.50 | 1 |
| *S. apiospermum* | Sputum | Paediatric Pneumology | 1.50 | 2 |

ICU, intensive care unit.

- Using the EUCAST broth microdilution method, the geometric means and MIC ranges for *A. niger* and *S. apiospermum* were comparable (**Figure 1**).

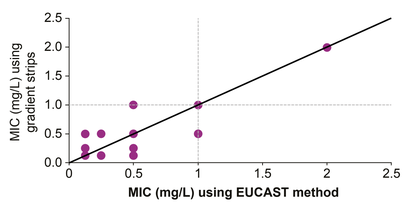
**Figure 1. Geometric means and MIC ranges for EUCAST reference method (A) and isavuconazole MIC strips (B)**




Data are expressed as mean ± upper/lower limit.

- The essential agreement between the isavuconazole MIC strips and the EUCAST reference method was 93.3%, regardless of the species tested (**Figure 2**).

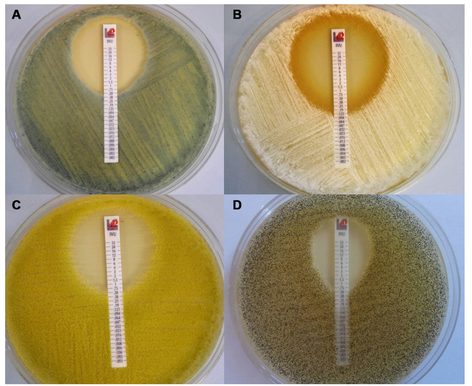
**Figure 2. Essential agreement between the EUCAST reference method and MIC strips**




MIC test strip values were rounded up to match the EUCAST dilutions for direct comparison.
Three isolates differed by > ±1-fold dilution (all 3 isolates differed by ± 2-fold dilution).

- Growth inhibition of isolates tested using the isavuconazole MIC strips was comparable to that tested using the EUCAST broth microdilution method (**Table 1** and **Figure 1**); examples of MIC test strips are displayed in **Figure 3**.

**Figure 3. Examples of isavuconazole activity demonstrated using MIC strips against *A. fumigatus* (A), *A. terreus* (B), *A. flavus* (C) and *A. niger* (D)**




## Conclusions

- In this study, isavuconazole MICs against *S. apiospermum* were comparable with those obtained for *A. niger.*
- Isavuconazole MIC strips showed good agreement with the EUCAST reference method.
- Isavuconazole MIC strips could be a useful alternative for susceptibility testing of *Aspergillus* spp. and *S. apiospermum.*

**References**

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**Disclosures**

L. Trovato, A.P. Di Giovanni, and S. Oliveri: no conflicts of interest to disclose.
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