S.1d Treatment of rare mold infections in 2021: the role of new and old antifungals, September 22, 2022, 10:30 AM - 12:00 PM

Background & Objective: The NRCMA oversees the surveillance of invasive fungal diseases in France. As part of our expertise, we perform antifungal susceptibility testing based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology on all isolates. The antifungal profiles helped us monitor the emergence of resistant isolates, determine the susceptibility patterns of wild-type strains to new antifungals, and in specific cases, determine the relationship between clinical failure and selection/emergence of a less susceptible isolate.

We review the Minimum inhibitory concentrations (MIC) distribution of eight antifungals on clinical isolates of filamentous fungi identified at the NRCMA from 2003 to 2021.

Methods: Species identification was performed by a combination of morphological features and multilocus sequencing. Only strains that produced enough colonies or spores were tested. In vitro susceptibility testing was performed according to the EUCAST procedure. Eight antifungals were used: triazoles (itraconazole, voriconazole, posaconazole, isavuconazole), echinocandins (caspofungin, anidulafungin, micafungin), amphotericin B, and terbinafine. The concentrations inhibiting 50% (MIC50) and 90% (MIC90) of the isolates were determined for species with 9, 10, and 16 isolates, respectively. For Aspergillus fungi, isolates exhibiting highazole MICs, we sequenced the cyp51A gene for mutation screening.

Results: MICs were obtained for 3343 pathogenic strains. We identified Aspergillus spp. with 52%, Paecilomyces spp. (21%), Rhodotorula spp. (18%), Phialophora spp. (10%), Conidiobolus spp., Phialophora spp., Fusarium spp., Alternaria spp., Fusarium spp., and Mucor spp. All isolates from the E. coli group were sensitive to all antifungals tested.

Table 1: Distribution of MICs for each antifungal agent.

| Antifungal Agent | MIC50 (μg/mL) | MIC90 (μg/mL) |
|------------------|--------------|--------------|
| Itraconazole     | 0.25-4       | 1.0-8        |
| Voriconazole     | 0.07-1       | 0.25-2       |
| Posaconazole     | 0.02-0.25    | 0.25-1       |
| Isavuconazole    | 0.015-0.25   | 0.25-1       |
| Caspofungin      | 0.02-0.05    | 0.05-0.25    |
| Anidulafungin    | 0.005-0.02   | 0.02-0.1     |
| Micafungin       | 0.003-0.015  | 0.015-0.05   |
| Amphotericin B   | 0.1-1        | 1-10         |
| Terbinafine      | 0.02-0.25    | 0.25-2       |

Discussion: The results indicate that there is a need for new antifungals, especially for Aspergillus spp., where the MICs are high. The resistance patterns vary by species, and some species may be more susceptible to certain antifungals. The data also highlight the importance of monitoring resistance patterns to ensure effective treatment of rare mold infections.

Conclusion: The results emphasize the need for continued surveillance and research to develop new antifungals and optimize treatment strategies for rare mold infections.
### Table 1. Overall in vitro antifungal activity for species involved in invasive disease as determined by EUCAST methodology (non exhaustive table)

| Species (no. of isolates tested) | AMB | ITZ | VCZ | PSZ | CSF | MCF | TERR |
|----------------------------------|-----|-----|-----|-----|-----|-----|------|
| Cunninghameilla bertholletiae (n=17) | 0.5 | 2/8 | 2/8 | 2/8 | 0.5/1 | ≥8/28 | ≥8/28 | 0.12/0.2 |
| Cunninghameilla spp. (n=8) | 4/8 | 2/8 | 2/8 | 1/8 | ≥8/28 | 0.12/0.2 |
| Lichthaima corymbifera (n =78) | 0.5/0.5 | 1/4 | ≥8/28 | 0.5/0.5 | ≥8/28 | 0.5/1 |
| Lichthaima ramosa (n=74) | 0.12/0.2 | 2/8 | ≥8/28 | 0.5/1 | ≥8/28 | 1/2 |
| Macor cinctelloides (n=75) | 0.03/0.1 | ≥8/28 | ≥8/28 | 1/8 | ≥8/28 | ≥8/28 |
| Macor spp. (n=10) | 0.12/0.2 | ≥8/28 | ≥8/28 | 2/2 | ≥8/28 | ≥8/28 |
| Rhizomucor pusillus (n=57) | 0.06/0.1 | 0.5/1 | ≥8/28 | 0.25/0.5 | ≥8/28 | ≥8/28 | 0.25/0.5 |
| Rhizopus nigricans (n =111) | 0.12/0.2 | 1/8 | ≥8/28 | 0.5/2 | ≥8/28 | ≥8/28 |
| Syncephalastrum racemosum (n=5) | 0.03/0.1 | ≥8/28 | ≥8/28 | 0.5/1 | ≥8/28 | 0.5/1 |
| Sclerotinia vosiiformis complex (n=5) | 8/8 | 0.25/0.5 | 0.12/0.5 | ≥8/28 | ≥8/28 |
| Alternaria alternata complex (n=34) | 0.5 | 0.5/1 | 4/8 | 0.12/0.5 | 0.5/1 | 0.06/0.12 |
| Alternaria alternata complex (n=28) | 0.25/0.5 | 0.5/1 | 4/8 | 0.12/0.5 | 0.5/1 | 0.06/0.12 |
| Aspergillus fumigatus (n=293) | 0.25/0.5 | 0.25/0.5 | 0.25/1 | 0.06/0.1 | ≥8/28 | 0.1/0.5 | 0.015/0.03 | 2/2 |
| Aspergillus lentui (n=5) | 8/8 | 1/8 | 1/8 | 0.25/0.1 | 2/8 | ≥8/28 |
| Aspergillus hirsutus (n=6) | 0.5/0.1 | 0.5/0.2 | 0.25/0.5 | 0.25/0.5 | 0.5/0.5 | ≥8/28 |
| Aspergillus niger (n=21) | 2/8 | 0.12/0.5 | 0.12/0.2 | 0.06/0.2 | 0.25/0.5 | 0.5/0.5 | 0.015/0.03 |
| Aspergillus quadrijugatus (n=17) | 0.5/1 | 0.12/0.5 | 0.12/0.2 | 0.12/0.1 | 2/2 | ≥8/28 |
| Curvularia spp. (n=26) | 0.12/0.5 | 0.12/0.5 | 0.12/0.2 | 0.12/0.1 | 2/2 | ≥8/28 |
| Exophiala dermatitidis (n=33) | 0.12/0.2 | 0.12/0.2 | 0.12/0.2 | 0.12/0.1 | 2/2 | ≥8/28 |
| Exophiala jeaneslei (n=10) | 0.5/1 | 0.12/0.5 | 0.12/0.2 | 0.12/0.1 | 2/2 | ≥8/28 |
| Exophiala oligosperma (n=5) | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 2/2 | ≥8/28 |
| Exophiala spinifera (n=12) | 0.12/0.2 | 0.03/0.2 | 0.12/0.2 | 0.25/0.2 | 2/2 | ≥8/28 |
| Fonsecaea monophora (n=9) | 0.25/0.5 | ≤0.01/0.1 | 0.06/0.1 | 0.06/0.1 | 0.5/0.5 | 0.5/0.5 | 0.03/0.2 |
| Fonsecaea pedrosoi (n=8) | 0.25/0.5 | 0.12/0.5 | 0.12/0.5 | 0.06/0.1 | 1/1 | 1/1 | 0.03/0.2 |
| Fonsecaea nigricans (n=12) | 0.5/1 | 0.01/0.0 | 0.06/0.1 | 0.06/0.1 | 1/1 | 1/1 | 0.03/0.2 |
| Fusarium fujikuroi complex (n=161) | 4/8 | ≥0.01/0.0 | 4/8 | 4/8 | 4/8 | ≥8/28 | 1/2 |
| Fusarium dimerum complex (n=37) | 0.25/0.5 | ≥8/28 | ≥8/28 | 2/8 | ≥8/28 | ≥8/28 | 0.5/1 |
| Fusarium oxysporum complex | 2/4 | ≥8/28 | 2/8 | ≥8/28 | ≥8/28 | 2/4 |
| Fusarium solani complex (n=247) | 4/8 | ≥8/28 | 8/8 | ≥8/28 | ≥8/28 | ≥8/28 |
| Lomentospora prolificans (n=59) | 8/8 | ≥8/28 | 8/8 | ≥8/28 | 4/8 | 4/8 | ≥8/28 |
| Microascus circulus (n=7) | 8/8 | ≥8/28 | ≥8/28 | ≥8/28 | 4/8 | 4/8 | ≥8/28 |
| Phaeoacremonium parasiticum (n=20) | 0.5/2 | ≥8/28 | ≥8/28 | 1/2 | 1/2 | 1/2 | 0.12/0.2 |
| Pleurostomophora richardsiae (n=7) | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 |
| Scedosporium sp. (n=19) | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 |
| Scedosporium boydii (n=45) | 8/8 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 |
| Scedosporium apiospermum (n=108) | 8/8 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 |
| Scedosporium aurantiacum (n=6) | 8/8 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 |
| Scedosporium dehoogii (n=10) | 8/8 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 |
| Scedosporium minutum (n=5) | 8/8 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 | 0.5/0.5 |
| Scopulariopsis brevicollis (n=20) | 8/8 | ≥8/28 | ≥8/28 | ≥8/28 | 1/4 | 0.25/0.5 | 2/8 |
| Hormographia aspersihalata (n=6) | 0.06/0.5 | ≥8/28 | 1/2 | ≥8/28 | 4/4 | 4/4 | 8/8 |

Source: Annual activity report NRCMA 2020-Institut Pasteur