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ANTIFUNGAL SUSCEPTIBILITY OF A COLLECTION OF *ASPERGILLUS FUMIGATUS* STRAINS ISOLATED FROM PATIENTS WITH INVASIVE PULMONARY ASPERGILLOSIS AND COVID-19 ASSOCIATED ASPERGILLOSIS

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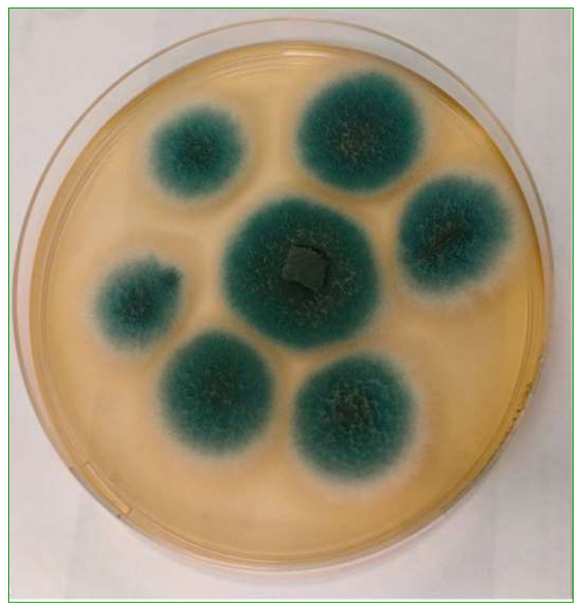
BACKGROUND

Invasive pulmonary aspergillosis (IPA) is a life-threatening fungal disease, mainly affecting immunocompromised patients such as those with haematological malignancies, undergoing hematopoietic stem cells and solid organ transplantation, or receiving immunotherapy with/without corticosteroids Nevertheless, IPA can be diagnosed also in immunocompetent subjects, in particular those with influenza or Sars-Cov-2 (COVID-19) infections (CAPA).

The aim of this study was to investigate the *in-vitro* susceptibility to antifungal drugs on a collection of 86 *Aspergillus fumigatus* strains isolated from patients with probable IPA hospitalized at the IRCCS Policlinico Sant'Orsola in Bologna (Italy) between 2018 and 2023. The pattern of susceptibility/resistance to the antifungal drugs performed by a commercial broth microdilution test was subsequently related to the year of *A. fumigatus* isolation and to the positivity for COVID-19. Moreover, results obtained by the phenotypic assay were compared with real – Time PCR assay, able to detect mutations in the cyp51A gene.



METHODS

86 ***Aspergillus fumigatus*** strains

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Lower respiratory tract specimens of hospitalized patients with probable ***IPA*** & ***Galactomannan positive*** on lower respiratory tract and/or serum specimens

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Isolation on ***Sabouraud Dextrose Agar*** and *identification* by ***MALDI – ToF*** mass spectrometry

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In vitro susceptibility test to ***antifungal drug (MIC mg/ L)***

multiplex RT – PCR test to evaluate the presence of ***azole resistance marker***: ***TR34*** and ***TR46*** , ***mutations*** in the ***Cyp51A*** gene

RESULTS

Table 1 shows the resistance rate, the MIC50 and the MIC90 of all the antifungal drugs tested. Out of the 86 *A. fumigatus* strains analysed, 2 of them (2.3%) showed a resistance to an azole drug (in particular, 1 to itraconazole, MIC = 2 mg/L and 1 to voriconazole, MIC = 8 mg/L), whereas 11 (12.8%) were resistant to amphotericin B (MIC = 2 mg/L). The distribution of MIC values stratified by the years of isolation (2018-2020 vs 2021-2023) is displayed in Figure 1. We observed a slight increasing trend of MIC values for all the azole drugs tested. However, strains isolated from COVID-19 positive patients were characterized by higher MIC values for amphotericin B than those isolated from COVID-19 negative subjects (1.2 ± 0.4 vs 1.0 ± 0.3, p = 0.05). The molecular test for azole resistance markers showed a 100%-agreement with the phenotypic assay.

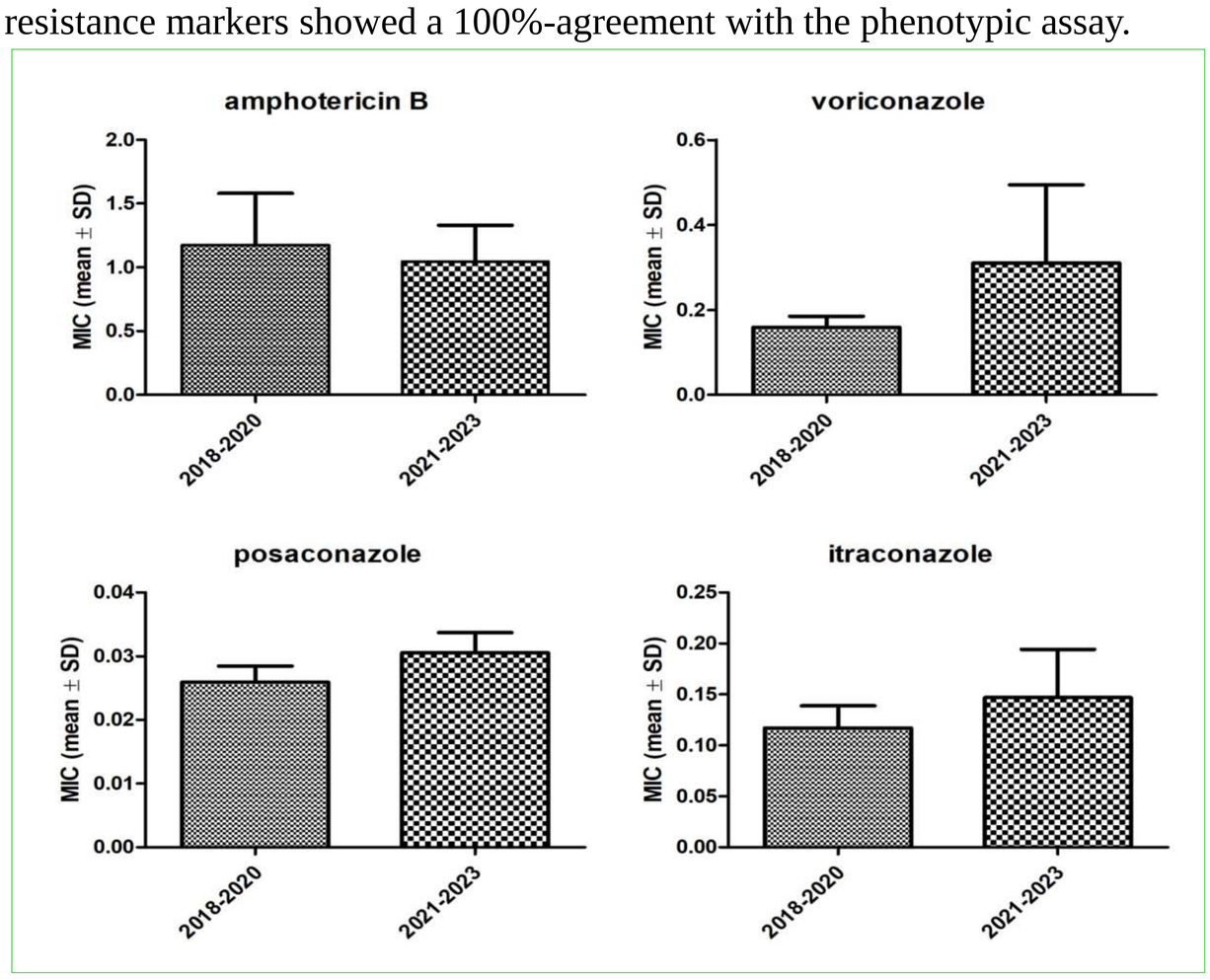

Figure 1. Distribution of MIC values for AMB B and azoles stratified by the period of *A. fumigatus* strain isolation. Data are expressed as mean MIC values ± SD. The period 2018-2020 was compared to the period 2021-2023.

Amphotericin B			5-flucytosin			Fluconazole		
Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90
12,8 % (11/86)	1 µL	2 µL	/	4 µL	8 µL	/	>128 µL	>128 µL
Voriconazole			**Posaconazole**			**Itraconazole**		
Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90
1,2 % (1/86)	0,0625 µL	0,5 µL	0 % (0/86)	0,03 µL	0,0625 µL	1,2 % (1/86)	0,0625 µL	0,25 µL
Micafungin			**Anidulafungin**			**Caspofungin**		
Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90	Resistance rate	MIC 50	MIC 90
/	4 µL	>8 µL	/	1 µL	>8 µL	/	4 µL	8 µL

Table 1. Resistance rate, MIC50 and MIC90 for all the antifungal drugs tested on the collection of 86 *A. fumigatus* strains. The resistance rate is reported only for the antifungals for which EUCAST set clinical breakpoints (www.eucast.org).

CONCLUSIONS

We observed that in our setting the rate of azole-resistance in *A. fumigatus* strains remains quite limited, although in presence of a slight MIC drift over time. Nonetheless, it is crucial to continue monitoring the trend of azole resistance in *Aspergillus* strains for proper clinical management and implementation of effective antimicrobial stewardship programs In this context, the use of PCR-based resistance testing may help to improve antifungal stewardship programs.