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Antifungal Drug Susceptibility Profile of *Pichia anomala* Isolates from Patients Presenting with Nosocomial Fungemia▽

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In vitro susceptibility of 58 isolates of *Pichia anomala* to five antifungal drugs using two broth microdilution methods (CLSI and EUCAST) was analyzed. Low susceptibility to itraconazole was observed. Fluconazole, voriconazole, amphotericin B, and caspofungin showed good antifungal activity, although relatively high drug concentrations were necessary to inhibit the isolates.

Several reports have pointed to *Pichia anomala* (anamorph *Candida pelliculosa*) as a cause of a large spectrum of invasive infections (13, 20, 23, 35), fungemia being the most common presentation (2, 6, 17, 26, 41). Usually, the patients have been treated with amphotericin B (with or without 5-flucytosine) or fluconazole with good clinical outcomes (3, 6, 12, 16, 26, 38). Nonetheless, treatment failures may occur (1, 6, 43), as may cases of breakthrough fungemias in immunocompromised patients receiving prophylaxis with fluconazole (14).

Although *P. anomala* is considered an emergent hematogenous yeast pathogen, data on the susceptibility of *P. anomala* to antifungal drugs are scarce (4, 5, 19, 29, 33). The aim of this study was to determine the in vitro susceptibility profile to five antifungal drugs of a large collection of *P. anomala* isolates from blood cultures of patients with nosocomial fungemia.

For this purpose, 52 nonrelated bloodstream isolates of *P. anomala* (36 from Brazil, 13 from Argentina, and 3 from Spain) and 6 from unknown clinical specimens (United States) were tested by two broth microdilution methods, those of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) (21) and the European Committee on Antibiotic Susceptibility Testing (EUCAST) (37) guidelines.

We evaluated the activity of amphotericin B (Sigma), itraconazole (Janssen Pharmaceutica), voriconazole (Pfizer, Inc.), and caspofungin (Merck & Co.) at concentrations ranging from 0.015 to 8 μg/ml and of fluconazole (Pfizer, Inc.) at concentrations ranging from 0.12 to 64 μg/ml.

The inhibition criterion adopted to determine the MIC for amphotericin B was the lowest drug concentration which produced complete or nearly complete (≥95%) inhibition compared with the drug-free control well (25). For azoles (21) and caspofungin (24), the lowest concentration which produced ≥50% inhibition was used.

All MICs were determined spectrophotometrically (530 nm) after incubation for 24 h (EUCAST) or 48 h (CLSI). To categorize the isolates as susceptible, we employed the CLSI (21) interpretive criteria for fluconazole (≤8 μg/ml) and itraconazole (≤0.12 μg/ml); for voriconazole, we used a recently established breakpoint (BP) of ≤1 μg/ml (30). Based on pharmacokinetic data, a BP of ≤1 μg/ml was assumed for caspofungin (40) and for amphotericin B (22, 29). The CLSI interpretive criteria were also adopted for EUCAST results for comparison only, as EUCAST BPs have not been defined yet.

In our study, we found an excellent agreement (≤2-fold dilutions) between MIC results generated by the EUCAST and CLSI methods for all antifungal drugs (Table 1). The lowest agreement rate was observed for itraconazole assays, as reported in a previous study testing other *Candida* species (10). In evaluations of the differences among MICs obtained by the two methods, EUCAST produced statistically significant lower MICs for voriconazole, amphotericin B, and caspofungin (Table 1). However, despite these differences, all isolates were categorized as susceptible by both methods, according to the assumed BPs. Although both methods were suitable to test *P. anomala*, the 24 h of incubation with the EUCAST method provided a clear spectrophotometric endpoint reading, which represents an advantage by reducing the incubation time.

No remarkable differences were observed when the geographic distribution of the isolates was considered (data not shown), and so Table 2 presents in a continuous fashion the cumulative percentages of all 58 *P. anomala* isolates that were found to be susceptible at each dilution throughout the serial dilutions. We could observe that MICs tended to concentrate

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TABLE 1. Distribution of *P. anomala* isolates according to differences in MIC results obtained by the EUCAST and CLSI methods

Antifungal drug	No. of iolates for which EUCAST MICs differed from CLSI MICs by indicated no. of dilutions[a]							Agreement within indicated no. of dilutions (%)		Mean difference (log_2 values)	95% Confidence interval
	−3	−2	−1	0	1	2	3	±1	±2		
Fluconazole		6	8	33	9	2		86	100	−0.12	−0.36 to 0.12
Itraconazole	1	2	14	30	10		1	93	96	−0.14	−0.38 to 0.11
Voriconazole		3	23	28	4			95	100	−0.43	−0.62 to −0.25
Amphotericin B		1	22	27	8			98	100	−0.28	−0.46 to −0.90
Caspofungin		8	32	16	2			86	100	−0.80	−0.98 to −0.60

[a] Fifty-eight *P. anomala* isolates were tested with each drug.

from the middle to the high end of the range for all the drugs. Although almost all isolates were categorized as being susceptible to fluconazole (Table 2), similar to results from other investigators (19, 29, 33, 42), some studies showed different results (5, 36). Indeed, the modal values, MIC_{50} and MIC_{90}, of our collection were close to those reported for *C. glabrata* (8, 9, 11, 27, 28, 34), a species of *Candida* that is considered to be less susceptible to azoles than *Candida albicans*.

Itraconazole was the triazole with the lowest in vitro activity against *P. anomala*, as more than 60% of all isolates showed reduced sensitivity to the drug (Table 2). Also, the MIC_{50} and MIC_{90} for itraconazole were much higher than those frequently obtained for *C. albicans* (8, 11, 25, 34) and were similar to those determined for *Candida glabrata*, *Candida krusei*, and *Candida guilliermondii* (4, 10, 11, 18, 25, 34).

Voriconazole was very active against all *P. anomala* isolates (Table 2), but MICs were usually higher than those reported for *C. albicans*, *Candida parapsilosis*, and *Candida tropicalis* (7, 18, 28, 29, 31, 33). Actually, they were similar to MIC results obtained by other investigators testing *C. glabrata* and *C. krusei* (7, 18, 28, 29, 31).

In our study, amphotericin B MICs were tightly clustered between 0.12 and 1.0 μg/ml, and all isolates were considered susceptible to the drug (Table 2). In fact, the resistance of *Candida* species to amphotericin B is a rare phenomenon that may be associated with the low sensitivity of broth microdilution methods in identifying resistant strains.

Caspofungin presented good in vitro activity against *P. anomala*, as all isolates were inhibited by ≤1 μg/ml (Table 2). However, their MICs were higher than those usually necessary to inhibit most isolates of *C. albicans*, *C. tropicalis*, and *C. glabrata.* (7, 15, 25, 32). The only other study on the susceptibility of *P. anomala* to caspofungin generated MIC_{50} values eight times lower than those in our report. This finding may be explained partially by differences in the incubation times used in the two studies, as we read the CLSI MICs at 48 h instead of 24 h as suggested by Pfaller et al. (32). In fact, we were not able to determine MICs with confidence at 24 h by using the CLSI inoculum, in contrast with the 100-fold-higher EUCAST inoculum. Finally, neither trailing nor paradoxical growth was seen in our series of *P. anomala* isolates with caspofungin, as observed for some *Candida* species (25, 39).

In summary, *P. anomala* did not show intrinsic resistance to any of the drugs studied. Nonetheless, susceptibility to itraconazole was poor. In contrast, fluconazole, voriconazole, amphotericin B, and caspofungin presented good activity against *P. anomala*, although relatively high drug concentrations were necessary to inhibit the isolates. Altogether, the susceptibility

TABLE 2. Antifungal drug susceptibility profile of *P. anomala* determined by CLSI and EUCAST broth dilution methods

Antifungal drug and microdilution method	Cumulative % of susceptible isolates[a] at MIC (μg/ml) of:											Mode	Geometric mean, MIC	% Susceptibility[b]
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16			
Fluconazole														
CLSI	0	0	0	0	0	0	0	15.5	56.8	93	100	4	5.08	96.6
EUCAST	0	0	0	0	0	0	0	22.4	55.1	96.5	100	8	4.79	93
Itraconazole														
CLSI	1.7	0	12	36.1	74.1	96.5	100					0.25	0.21	36.2
EUCAST	0	0	7	39.5	91.2	98.2	100					0.25	0.19	39.6
Voriconazole														
CLSI	0	3.4	18.9	39.6	96.5	100						0.25	0.16	100
EUCAST	0	3.4	29.3	65.5	100							0.12	0.12	100
Amphotericin B														
CLSI	0	0	0	12	36	88	100					0.5	0.45	100
EUCAST	0	0	0	15.5	55.1	94.7	100					0.25	0.37	100
Caspofungin														
CLSI	0	1.7	17.2	84.5	100							0.12	0.12	100
EUCAST	0	12	70.6	100								0.06	0.07	100

[a] $n = 58$.

[b] EUCAST and CLSI MICs were interpreted according to CLSI breakponts for fluconazole and itraconazole. For voriconazole, amphotericin B, and caspofungin, the adopted breakpoint was ≤1 μg/ml.

profile of *P. anomala* was more similar to that of *C. glabrata* than to that of *C. albicans*. Trailing and paradoxical growth were not observed in the presence of any antifungal drug tested.

Finally, our study analyzed the largest series studied to date of *P. anomala* bloodstream isolates tested against five antifungal drugs by two different methods and could establish a reliable susceptibility profile for *P. anomala*, as an attempt to guide the choice of antifungal drugs for therapy in cases of invasive infections.

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