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Letter to the editor

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Non-Candida isolates from blood cultures and intra-abdominal samples: data derived from a multicentre prospective study conducted in Madrid

Judith Díaz-García[1,2]
Ana Gómez[1,2]
Marina Machado[1,2]
Luis Alcalá[1,2,3]
Elena Reigadas[1,2,3]
Carlos Sánchez-Carrillo[1,2,3 †]
Ana Pérez-Ayala[4,5]
Elia Gómez-García de la Pedrosa[6,7,8]
Fernando González-Romo[9,10]
María Soledad Cuétara[11]
Coral García-Esteban[12]
Inmaculada Quiles-Melero[13]
Nelly Daniela Zurita[14]
María Muñoz-Algarra[15]
María Teresa Durán-Valle[16]
Aída Sánchez-García[17]
Patricia Muñoz[1,2,3,18]
Pilar Escribano[1,2,19 *]
Jesús Guinea[1,2,3 *]

on behalf of the CANDIMAD study group

[1]Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
[3]CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain
[4]Hospital Universitario 12 de Octubre, Madrid, Spain
[5]Instituto de Investigación Sanitaria del Hospital 12 de Octubre, Madrid, Spain
[6]Hospital Universitario Ramón y Cajal, Madrid, Spain
[7]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain
[8]CIBER de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain
[9]Hospital Universitario Clínico San Carlos, Madrid, Spain
[10]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos IdISSC, Madrid, Spain
[11]Hospital Universitario Severo Ochoa, Leganés, Spain
[12]Hospital Universitario de Getafe, Getafe, Spain
[13]Hospital Universitario La Paz, Madrid, Spain
[14]Hospital Universitario de La Princesa, Madrid, Spain
[15]Hospital Universitario Puerta de Hierro, Majadahonda, Spain
[16]Hospital Universitario de Móstoles, Móstoles, Spain
[17]Laboratorio Central de la CAM - URSalud - Hospital Infanta Sofía, San Sebastián de los Reyes, Spain
[18]Medicine Department, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain
[19]School of Health, Universidad Camilo José Cela, Madrid, Spain

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Sir,

Since most surveillance studies focus on candidaemia, non-Candida species such as *Saccharomyces cerevisiae*, *Cryptococcus* spp, *Trichosporon* spp, *Rhodotorula* spp, or *Magnusiomyces* spp, among others, have received little attention [1]. Emerging non-Candida spp might account for up to 2.8% of fungaemia episodes [2-6] and are characterised by diminished susceptibilities to systemic antifungal agents. We recently reported the epidemiology and antifungal susceptibility of *Candida* spp sourcing from blood cultures and intra-abdominal samples from patients under care at 16 hospitals in Madrid (Spain) from January 2019 to December 2022 (CANDIMAD study) [7]. Here we describe the non-Candida species distribution and their antifungal susceptibility collected in the CANDIMAD study. Isolates, one per species, patient, and compartment, were identified by molecular methods, and subjected to antifungal susceptibility testing to amphotericin B, azoles, echinocandins and ibrexafungerp according to the EUCAST E. Def 7.3.2 method [8].

We detected a total of 25 non-Candida isolates sourcing from blood cultures (n=12) or intra-abdominal samples (n=13; peritoneal samples [n=11], liver samples [n=2]) that represented 1.1% (n=12/1,101) and 1.3% (n=13/1,031) of isolates from blood cultures and intra-abdominal samples, respectively (Figure 1). Non-Candida yeasts were found in 1.3 % (n=25/1,912) of the patients (*Candida* spp were simultaneously found in 8/25 patients). Interestingly, higher species diversity was found in isolates from blood cultures; the species found in intra-abdominal samples were also found in blood culture isolates except for *S. cerevisiae*, which was exclusively found in intra-abdominal samples. Blood-cultured isolates were mainly sourced from patients in medical (42%) or ICU wards (33%), whereas intra-abdominal isolates were mainly sourced from patients in surgery wards (77%). The number of isolates detected per year were 12 in 2019, 8 in 2020, and 5 in 2021.

Antifungal MIC ranges against the isolates were: amphotericin B, 0.125 – 4 mg/L; fluconazole 0.5 - >64 mg/L; voriconazole, 0.008 – 8 mg/L; posaconazole, 0.016 – 2 mg/L; isavuconazole, 0.016 - 2 mg/L; micafungin, 0.03 - >8 mg/L; anidulafungin, 0.016 - >8 mg/L; and ibrexafungerp, 0.25 - >8 mg/L. MIC distributions broken down per species is shown in Table 1. Clinical breakpoints to classify these species as resistant or susceptible according to EUCAST methodology are absent with the exception of amphotericin B against *Cryptococcus neoformans*; ECOFFS are only available for amphotericin B against *Saccharomyces cerevisiae*, and amphotericin B, voriconazole and posaconazole against *Cryptococcus neofor-*

Correspondence:
Jesús Guinea
Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo, 46, 28007 Madrid, Spain.
E-mail: jguineaortega@yahoo.es

*Both authors contributed equally

†In Memoriam

Table 1 **Minimum inhibitory concentration (MIC) distributions of the eight antifungal drugs used against the species tested**

	MIC distributions (no. of isolates at each MIC, in mg/L)													No. isolates (%)	
	≤0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	≥8	16	32	≥64	Non-wild type	Resistant
Saccharomyces cerevisiae (n= 9)															
Amphotericin B	-	-	0	4	3	2	0	0	0	0	-	-	-	0 (0)	ND
Fluconazole	-	-	0	0	0	0	1	2	3	1	1	0	1	ND	ND
Voriconazole	0	1	6	0	1	0	1	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	1	1	4	2	1	0	0	0	-	-	-	ND	ND
Isavuconazole	1	3	3	0	2	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	1	1	6	1	0	0	0	0	0	-	-	-	ND	ND
Anidulafungin	1	0	2	5	1	0	0	0	0	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	1	6	2	0	0	0	-	-	-	ND	ND
Trichosporon spp (n= 5)															
Amphotericin B	-	-	0	0	0	1	0	2	2	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	1	1	0	2	0	0	1	0	ND	ND
Voriconazole	2	1	1	0	0	1	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	3	0	0	1	1	0	0	0	-	-	-	ND	ND
Isavuconazole	2	0	1	0	0	0	1	1	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	5	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	5	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	1	0	0	3	1	-	-	-	ND	ND
Magnusiomyces capitatus (n= 4)															
Amphotericin B	-	-	0	0	0	2	2	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	2	0	1	0	ND	ND
Voriconazole	0	0	0	3	0	1	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	0	1	2	1	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	1	1	0	1	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	1	0	3	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	2	2	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	1	0	1	1	0	1	-	-	-	ND	ND
Rhodotorula mucilaginosa (n= 3)															
Amphotericin B	-	-	0	1	2	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	0	0	0	0	3	ND	ND
Voriconazole	0	0	0	0	0	0	0	2	0	1	-	-	-	ND	ND
Posaconazole	0	0	0	0	1	0	0	2	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	0	1	1	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Cryptococcus neoformans (n= 2)															
Amphotericin B	-	-	0	0	2	0	0	0	0	0	-	-	-	0 (0)	0 (0)
Fluconazole	-	-	-	0	0	1	0	2	0	0	0	0	0	ND	ND
Voriconazole	1	1	0	0	0	0	0	0	0	0	-	-	-	0 (0)	ND
Posaconazole	1	0	1	0	0	0	0	0	0	0	-	-	-	0 (0)	ND
Isavuconazole	0	1	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	2	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	2	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	1	1	0	-	-	-	ND	ND
Kodamaea ohmeri (n= 1)															
Amphotericin B	-	-	0	0	1	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	0	0	0	0	ND	ND
Voriconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	0	1	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	1	0	0	0	0	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	1	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	1	0	0	0	-	-	-	ND	ND
Exophiala dermatitidis (n= 1)															
Amphotericin B	-	-	0	0	1	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	0	0	0	0	ND	ND
Voriconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Anidulafungin	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	0	1	0	-	-	-	ND	ND

"-", antifungal concentration not tested. "ND", not determined as either breakpoints or ECOFFs were not available

[a]Underlined values indicate non-wild-type isolates according to ECOFFs, and values in bold indicate resistant isolates [9]

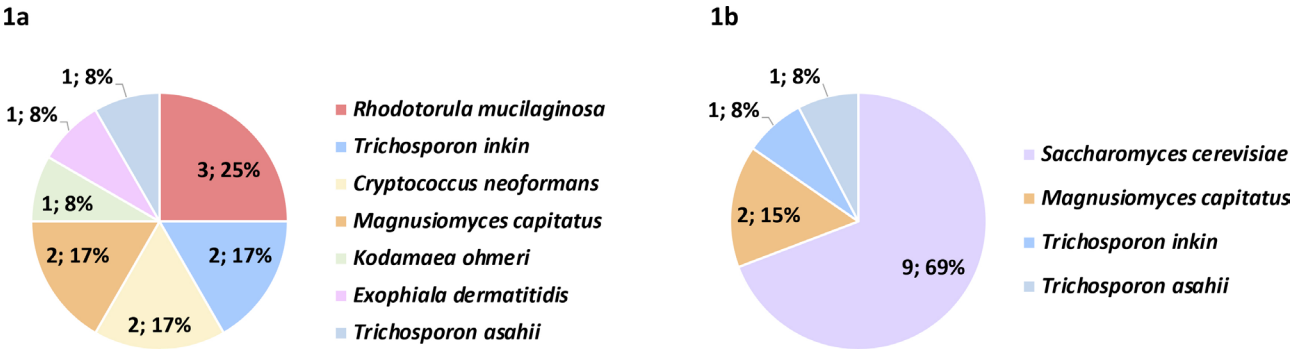

Figure 1 | **Non-Candida species found in blood cultures (1a) or intra-abdominal samples (1b)**

mans [9]. In those cases we did not find any resistant/non-wild type isolate but echinocandins and ibrexafungerp presented high MICs against the *Trichosporon*, *Magnusiomyces*, *Rhodotorula*, and *Cryptococcus* isolates studied (Table 1). If all isolates are considered intrinsically echinocandin-resistant, then the overall echinocandin resistance rate would rise from 0.5% to 1.5% ($P<0.05$) in blood cultures, and from 1.0% to 2.2% ($P<0.05$) in intra-abdominal samples. Likewise, adopting the non-species-specific fluconazole EUCAST breakpoint (resistant >4 mg/L) [10], a total of n=10 isolates should be considered fluconazole-resistant (*Magnusiomyces capitatus* [n=3], *Rhodotorula mucilaginosa* [n=3], *Saccharomyces cerevisiae* [n=3], and *Trichosporon asahii* [n=1]), and the overall fluconazole resistance rate would also rise slightly from 9.1% to 9.5% ($P>0.05$) in blood cultures, and from 8.2% to 8.4% ($P>0.05$) in intra-abdominal samples.

In conclusion, we observed that non-Candida yeasts represented 1.1% and 1.3% of isolates from blood cultures and intra-abdominal samples, respectively. Considering these species as a cause of fungaemia will lead to increased rates of echinocandin resistance given the intrinsically diminished susceptibility of the species to these drugs. The future setting of ECOFF and clinical breakpoints may offer clinicians better guidance in the management of patients with invasive infections caused by non-Candida yeasts.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of the Gregorio Marañón Hospital (CEim; study no. MICRO.HGUGM.2019-001).

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CONFLICT OF INTEREST

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