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Epidemiology, species distribution and *in vitro* antifungal susceptibility of fungaemia in a Spanish multicentre prospective survey

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Objectives: To update the knowledge of the epidemiology of fungaemia episodes in Spain, the species implicated and their *in vitro* antifungal susceptibilities.

Methods: Episodes were identified prospectively over 13 months at 44 hospitals. Molecular methods were used to determine the cryptic species inside the *Candida parapsilosis* and *Candida glabrata* complexes. Susceptibility to amphotericin B, anidulafungin, caspofungin, fluconazole, flucytosine, itraconazole, micafungin, posaconazole and voriconazole was determined by a microdilution colorimetric method. New species-specific clinical breakpoints (SSCBPs) for echinocandins, fluconazole and voriconazole were applied.

Results: The incidence of the 1357 fungaemia episodes evaluated was 0.92 per 1000 admissions. The incidence of *Candida albicans* fungaemia was the highest (0.41 episodes/1000 admissions), followed by *Candida parapsilosis sensu stricto* (0.22). *Candida orthopsilosis* was the fifth cause of fungaemia (0.02), outnumbered by *Candida glabrata* and *Candida tropicalis*. Interestingly, the incidence of fungaemia by *C. parapsilosis* was 11 and 74 times higher than that by *C. orthopsilosis* and *Candida metapsilosis*, respectively. Neither *Candida nivariensis* nor *Candida bracarensis* was isolated. Fungaemia was more common in non-intensive care unit settings (65.2%) and among elderly patients (46.4%), mixed fungaemia being incidental (1.5%). Overall susceptibility rates were 77.6% for itraconazole, 91.9% for fluconazole and 96.5%–99.8% for the other agents. Important resistance rates were only observed in *C. glabrata* for itraconazole (24.1%) and posaconazole (14.5%), and in *Candida krusei* for itraconazole (81.5%).

Conclusions: Fungaemia is more common in non-critical patients. *C. albicans* is the most common species, followed by *C. parapsilosis* and *C. glabrata*. Nearly 90% of yeasts are susceptible to all antifungal agents tested. Resistance rates change moderately when applying the new SSCBPs.

Keywords: candidaemia, *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Candida orthopsilosis*, *Candida dubliniensis*, *Candida metapsilosis*, *Candida nivariensis*, *Candida bracarensis*, incidence, antifungal agents, *in vitro* susceptibility

Introduction

Fungaemia is an important cause of morbidity and mortality closely associated with high healthcare costs in hospitalized patients. Although *Candida albicans* is still the leading cause of fungaemia worldwide, there are important geographical differences in species distribution and patterns of *in vitro* susceptibilities to antifungal agents.[1,2] Thus, performing epidemiological

surveillance studies is important to evaluate potential changes in species distribution and antimicrobial susceptibility, and also to assess the potential impact of new antifungal agents on therapy. In the present study, the main epidemiological characteristics of 1357 fungaemia episodes and the *in vitro* profiles of the susceptibility of isolates to nine antifungal agents are described. Furthermore, we have evaluated the influence of the new species-specific clinical breakpoints (SSCBPs) on resistance rates. To our knowledge, this is the first study reporting the incidence for the newly defined species *Candida metapsilosis*, *Candida orthopsilosis*, *Candida nivariensis* and *Candida bracarensis*.

Patients and methods

Study design

The FUNGEMYCA survey was a prospective, sequential study carried out over a 13 month period, from 1 January 2009 to 31 January 2010, in 44 Spanish tertiary institutions. The distribution of participant hospitals according to the number of beds was >1000 beds (41%), between 600 and 1000 beds (31.8%) and <600 (27.2%). All participating hospitals collected and identified the isolates from blood cultures and completed demographic and clinical questionnaires.

Definitions

A fungaemia episode was defined as the isolation of fungi from blood cultures in a patient with temporally related clinical signs and symptoms. Outpatient-acquired fungaemia was considered when the fungal aetiological agent was isolated in blood in the first 48 h after hospital admission. Age groups were neonates (<30 days of age), children (1 month–15 years old), adults (16–64 years old) and the elderly (>64 years old).

Identification and antifungal susceptibility study

All isolates were identified and their susceptibility to antifungal agents tested at the participating institutions and stored as suspensions in sterile water at room temperature. Antifungal susceptibility testing to nine agents was performed by the microdilution colorimetric Sensititre YeastOne® SYO-09 panel (TREK Diagnostic Systems, Cleveland, OH, USA). On the basis of the good correlation between SensititreYeastOne® and CLSI results,[3] CLSI clinical breakpoints and the recently published SSCBPs and epidemiological cut-off values (ECVs) were applied.[4–9] For posaconazole and amphotericin B, isolates inhibited by >1 mg/L were considered resistant. Quality controls were performed in each centre using *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258.

Molecular identification of the C. parapsilosis complex

The identities of *C. parapsilosis sensu stricto*, *C. orthopsilosis* and *C. metapsilosis* isolates were confirmed in a reference laboratory as described by Miranda-Zapico *et al.*[10] Furthermore, the identities of these species were confirmed by DNA amplifying and further sequencing of ITS1 and ITS4 regions of rRNA genes.

Molecular identification of the Candida glabrata complex

The molecular re-identification of all *C. glabrata sensu lato* isolates into the species *C. glabrata sensu stricto*, *C. nivariensis* and *C. bracarensis* was performed in a reference laboratory as previously described by Alcoba-Flórez *et al.*[11]

Statistical analyses

Incidences for each participating centre were calculated as the number of fungaemia episodes per 1000 admissions. Data were analysed with SPSS 10.0.7 for statistics (SPSS Inc., Chicago, IL, USA). Continuous variables were compared with Student's *t*-test and categorical variables with the χ^2 or Fisher's exact test. Comparison of antifungal susceptibility was carried out with $\log_2$ MIC. Differences in antifungal susceptibility patterns among species and age groups were evaluated using non-parametric Kruskal–Wallis analysis of variance followed by a Mann–Whitney *U*-test with Bonferroni correction for multiples comparison. A P value <0.05 was considered significant.

Results and discussion

Fungaemia incidence varies depending on hospital characteristics, geographical area and denominator used, which makes comparisons among studies difficult. However, an increase in incidence is being observed worldwide. In our study, the overall incidence (0.92 episodes/1000 admissions, range 0.18–2.2) is similar to recent studies in Europe (0.41–1.09 episodes/1000 admissions),[12] but lower than that observed in Brazil (2.49 episodes/1000 admissions).[13] Table 1 shows the incidence of episodes caused by the six most common species. Of the total of 1357 episodes of fungaemia reported in the current survey, of note is that *C. orthopsilosis* was the fifth most common cause of fungaemia (0.020). More fungaemia occurred amongst patients hospitalized in general wards (65.2%) than in those from intensive care units (ICUs) and among elderly patients (46.4%). The main yeasts isolated were *C. albicans* (44.66%), *C. parapsilosis* (26.58%), *C. glabrata* (11.47%), *Candida tropicalis* (8.21%), *C. orthopsilosis* (2.18%), *C. krusei* (1.96%), *Candida lusitaniae* (0.94%), *Cryptococcus neoformans* (0.73%), *Candida guilliermondii* (0.65%), *Candida famata* (0.44%), *Trichosporon asahii* (0.36%), *Candida dubliniensis* (0.29%), *C. metapsilosis* (0.29%), *Rhodotorula glutinis* (0.29%), *Rhodotorula mucilaginosa* (0.22%), *Candida kefyr* (0.15%), *Candida pseudotropicalis* (0.07%), *Blastoschizomyces capitatus* (0.07%), *Saccharomyces cerevisiae* (0.07%), *Trichosporon mucoides* (0.07%) and *Debaryomyces etchellsii* (*Pichia etchellsii*) (0.07%). Neither *C. nivariensis* nor *C. bracarensis* was isolated. In agreement with Pfaller *et al.*[14] and our previous national survey,[15] the global rank order of species isolated in ICU and non-ICU settings was the same. Of note, *C. glabrata* was the third most common species in Spain, prevailing over *C. tropicalis*. The rank order of species in the ICU was characteristic of each institution, possibly being related to the different antifungal practices (prophylaxis and/or treatment) and to the patient management in each of these settings.

Recently *C. metapsilosis* and *C. orthopsilosis* have been described as causes of candidaemia in Spain,[10] but the incidence of these species is not well known. Notably, in our survey, *C. orthopsilosis* was the fifth most common cause of candidaemia, with 0.020 episodes per 1000 admissions being caused by this species. *C. metapsilosis* fungaemia was anecdotal: four isolates (0.3%, 0.003 episodes per 1000 admissions). However, the incidence of fungaemia by *C. parapsilosis* was 11 and 74 times higher than that by *C. orthopsilosis* and *C. metapsilosis*, respectively.

Mixed fungaemia has been a matter of concern for its potentially poorer prognosis. However, in our study mixed fungaemia was uncommon, as only 20 episodes (1.5%) were caused by two or more fungal species and were reported mainly in ICU settings (50%), confirming the report of Jensen *et al.*[16] for a single

Table 1. Demographic characteristics of patients with fungaemia and species distribution

	Location at time of fungaemia, no. (%)			
	ICU	non-ICU	Total, no. (%)	Incidence per 1000 admissions
C. albicans	230 (48.0)	385 (42.9)	615 (44.7)	0.412
C. parapsilosis	127 (26.5)	239 (26.6)	366 (26.6)	0.222
C. glabrata	45 (9.4)	113 (12.6)	158 (11.5)	0.107
C. tropicalis	41 (8.6)	72 (8.0)	113 (8.2)	0.076
C. orthopsilosis	7 (1.5)	23 (2.6)	30 (2.2)	0.020
C. krusei	6 (1.3)	21 (2.3)	27 (2.0)	0.018
Other *Candida* spp.	13 (2.7)	26 (2.9)	39 (2.8)	0.025
Other yeasts	10 (2.1)	16 (1.8)	26 (1.9)	0.019
Fusarium spp.	0	3 (0.3)	3 (0.2)	0.002
Total	479 (34.8)	898 (65.2)	1377	0.925

Table 2. *In vitro* susceptibility of 1377 fungaemia isolates to nine antifungal agents

Species (no. of isolates tested)	Drug	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percentage of susceptible isolates M27-S3	Percentage of resistant or non-susceptible isolates according to	
						M27-S3	SSCBPs
C. albicans (615)	AND	0.016–8	0.03	0.12	99.8	0.2	0.8
	CAS	0.008–1	0.03	0.12	100	0	0.2
	MCF	0.008–8	0.016	0.03	99.7	0.4	1.1
	FLC	0.06–256	0.5	1	98.4	1.5	2.6
	ITC	0.016–16	0.06	0.12	93.3	2.1	ND
	VOR	0.008–8	0.008	0.016	98.3	1.6	1.6
	POS	0.008–8	0.03	0.12	98	1.9	10.1[a]
	AMB	0.12–1	0.25	0.5	100	0	ND
	5FC	0.06–64	0.06	0.5	98.8	0.7	ND
C. parapsilosis (366)	AND	0.016–8	1	2	98.1	1.6	0.5
	CAS	0.008–8	0.5	1	99.7	0.3	0.3
	MCF	0.008–8	1	2	97.4	2.2	1.1
	FLC	0.06–32	1	2	98.1	0	4.1
	ITC	0.016–1	0.06	0.12	90.7	0.3	ND
	VOR	0.008–1	0.016	0.06	100	0	0.5
	POS	0.008–2	0.03	0.12	99.7	0.3	0.8[a]
	AMB	0.12–2	0.25	0.5	99.6	0.3	ND
	5FC	0.06–8	0.06	0.25	99.7	0	ND
C. glabrata (158)	AND	0.016–4	0.03	0.06	99.4	0.6	2.5
	CAS	0.008–1	0.06	0.12	100	0	1.9
	MCF	0.008–8	0.016	0.03	98.7	1.2	3.2
	FLC	0.12–256	8	16	65.8	6.3	6.3
	ITC	0.016–16	0.5	1	19.4	24.1	ND
	VOR	0.008–8	0.12	0.5	95.5	1.2	8.9[a]
	POS	0.008–8	1	2	85.7	14.5	5.7[a]
	AMB	0.12–2	0.5	1	99.3	0.6	ND
	5FC	0.06–8	0.06	0.06	99.3	0	ND
C. tropicalis (113)	AND	0.016–8	0.06	0.25	99.1	0.9	0.9
	CAS	0.008–0.25	0.06	0.12	100	0	0

Continued

Table 2. *Continued*

Species (no. of isolates tested)	Drug	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percentage of susceptible isolates M27-S3	Percentage of resistant or non-susceptible isolates according to	
						M27-S3	SSCBPs
	MCF	0.008–8	0.03	0.06	99.1	0.9	0.9
	FLC	0.12–256	1	4	94.7	5.3	9.9
	ITC	0.016–16	0.25	1	49.6	10.6	ND
	VOR	0.008–8	0.06	0.5	93.8	5.3	6.2
	POS	0.008–8	0.12	0.5	92.9	7.1	49.6[a]
	AMB	0.12–2	0.5	1	99.1	0.9	ND
	5FC	0.06–32	0.06	0.12	99.1	0.9	ND
C. orthopsilosis (30)	AND	0.12–2	0.5	1	100	0	0[a]
	CAS	0.12–1	0.25	0.5	100	0	10[a]
	MCF	0.12–2	0.5	1	100	0	6[a]
	FLC	0.25–16	0.5	2	100	0	3[a]
	ITC	0.016–0.25	0.12	0.25	100	0	ND
	VOR	0.008–0.25	0.16	0.03	100	0	3[a]
	POS	0.016–0.25	0.06	0.12	100	0	0[a]
	AMB	0.12–0.5	0.25	0.5	100	0	ND
	5FC	0.06–4	0.06	0.12	100	0	ND
C. krusei (27)	AND	0.016–8	0.06	0.12	96.2	3.7	3.7
	CAS	0.03–8	0.25	0.5	92.3	7.4	7.4
	MCF	0.03–8	0.12	0.12	96.2	3.7	7.4
	FLC	4–64	32	64	11.5	—	—
	ITC	0.016–4	0.25	0.5	15.4	81.5	ND
	VOR	0.03–2	0.25	0.25	96.2	0	3.7
	POS	0.016–1	0.25	0.5	100	0	3.7[a]
	AMB	0.12–1	0. 5	1	100	0	ND
	5FC	0.06–16	8	16	46.2	0	ND
C. lusitaniae (13)	AND	0.03–1	0.12	0.5	100	0	0[a]
	CAS	0.06–1	0.12	0.5	100	0	7.7[a]
	MCF	0.008–0.5	0.06	0.25	100	0	0[a]
	FLC	0.12–2	0.5	1	100	0	0[a]
	ITC	0.016–0.25	0.12	0.12	92.3	0	ND
	VOR	0.008–0.03	0.008	0.016	100	0	0[a]
	POS	0.016–0.12	0.03	0.06	100	0	0[a]
	AMB	0.12–0.5	0.12	0.25	100	0	ND
	5FC	0.06–0.25	0.06	0.06	100	0	ND
Other *Candida*[b] (26)	AND	0.03–2	0.5	2	100	0	ND
	CAS	0.016–8	0.25	1	92.0	8.0	ND
	MCF	0.008–4	0.5	1	96	4.0	ND
	FLC	0.12–16	1	8	95.8	0	ND
	ITC	0.03–1	0.12	0.5	54.2	4.2	ND
	VOR	0.008–0.5	0.03	0.12	100	0	ND
	POS	0.008–0.5	0.12	0.5	100	0	ND
	AMB	0.12–1	0.25	0.5	100	0	ND
	5FC	0.06–4	0.06	0.25	100	0	ND
Overall *Candida* (1348)	AND	0.016–8	0.06	2	99.2	0.8	ND
	CAS	0.008–8	0.06	0.5	99.6	0.4	ND
	MCF	0.008–8	0.016	1	98.9	1.1	ND

Continued

Table 2. *Continued*

Species (no. of isolates tested)	Drug	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percentage of susceptible isolates M27-S3	Percentage of resistant or non-susceptible isolates according to	
						M27-S3	SSCBPs
	FLC	0.06–256	0.5	8	92.3	2.9	ND
	ITC	0.016–16	0.12	0.5	48.5	5.1	ND
	VOR	0.008–8	0.008	0.25	98.1	1.4	ND
	POS	0.008–8	0.03	0.5	96.7	3.3	ND
	AMB	0.12–2	0.25	0.5	99.8	0.2	ND
	5FC	0.06–64	0.06	0.25	98.1	0.4	ND
C. neoformans (10)	AND	8–>8	8	>8	0	100	ND
	CAS	8–>8	8	>8	0	100	ND
	MCF	8–>8	8	>8	0	100	ND
	FLC	0.5–8	4	8	100	0	0[a]
	ITC	0.016–0.12	0.06	0.12	100	0	ND
	VOR	0.008–0.06	0.03	0.06	100	0	0[a]
	POS	0.016–0.25	0.12	0.25	100	0	0[a]
	AMB	0.12–0.5	0.12	0.5	100	0	ND
	5FC	0.5–4	4	4	100	0	ND
Other yeasts[c] (16)	AND	0.016–>8	8	>8	12.5	87.5	ND
	CAS	0.06–>8	8	>8	12.5	87.5	ND
	MCF	0.03–>8	8	>8	12.5	87.5	ND
	FLC	1–256	8	256	56.3	37.5	ND
	ITC	0.003–16	0.25	4	43.8	37.6	ND
	VOR	0.008–8	0.06	4	62.5	18.8	ND
	POS	0.008–8	0.25	8	75	25	ND
	AMB	0.12–1	0.5	1	100	0	ND
	5FC	0.06–32	0.12	16	87.5	6.3	ND
Overall yeasts (1374)	AND	0.016–>8	0.06	2	97.6	2.4	ND
	CAS	0.008–>8	0.06	0.5	98	2.0	ND
	MCF	0.008–>8	0.03	1	97.3	2.7	ND
	FLC	0.06–256	0.5	8	91.9	3.3	ND
	ITC	0.016–16	0.12	0.5	77.6	5.4	ND
	VOR	0.008–4	0.016	0.25	97.7	1.6	ND
	POS	0.008–8	0.06	0.5	96.5	3.5	ND
	AMB	0.12–2	0.25	0.5	99.8	0.2	ND
	5FC	0.06–64	0.06	0.25	98	0.5	ND
Fusarium spp. (3)	AND	0.015–8	0.12	—	ND	ND	ND
	CAS	0.008–8	0.12	—	ND	ND	ND
	MCF	0.008–8	0.25	—	ND	ND	ND
	FLC	0.06–256	0.5	—	ND	ND	ND
	ITC	0.016–16	0.06	—	ND	ND	ND
	VOR	0.008–8	0.008	—	ND	ND	ND
	POS	0.008–8	0.03	—	ND	ND	ND
	AMB	0.12–2	0.25	—	ND	ND	ND
	5FC	0.06–32	0.06	—	ND	ND	ND

AND, anidulafungin; CAS, caspofungin; MCF, micafungin; FLC, fluconazole; ITC, itraconazole; VOR, voriconazole; POS, posaconazole; AMB, amphotericin B; 5FC, flucytosine; ND, not defined.
[a]Isolates above ECV.
[b]Nine isolates of *C. guilliermondii*, six of *C. famata*, four each of *C. dubliniensis* and *C. metapsilosis*, two of *C. kefyr* and one *C. pseudotropicalis*.
[c]Five isolates of *T. asahii*, four of *R. glutinis*, three of *R. mucilaginosa*, and one isolate each of *B. capitatus*, *S. cerevisiae*, *T. mucoides* and *D. etchellsii*.

institution. Finally, there were three episodes caused by *Fusarium solani*, *Fusarium verticilloides* and *Fusarium* sp.

Fungaemia aetiology varied according to age, gender, hospitalization ward or underlying conditions of the patients. *C. albicans* was the most prevalent species in neonates (53.6%), adults (44.8%) and elderly patients (47.3%), while *C. parapsilosis* was predominant in children (48.9%), with statistically significant differences between both species ($P<0.05$).

Table 2 summarizes the results of *in vitro* susceptibility, applying both current and new CLSI SSCBPs. Overall, 88.9% of yeast isolates were susceptible to the nine antifungal agents tested. Although there has been wide use of fluconazole in the last decade in Spain, the susceptibility rate to this agent continues to be very high (91.9%). These findings have also been reported by other authors.[14] More than 95% of *C. glabrata* and *C. krusei* isolates were highly susceptible to anidulafungin, micafungin and voriconazole. Conversely, itraconazole was the least active drug, 5.4% of yeast isolates being resistant and 77.6% susceptible. Important resistance rates were only observed in *C. glabrata* for itraconazole (24.1%) and posaconazole (14.5%), and in *C. krusei* for itraconazole (81.5%).

Resistance rates changed moderately when applying the new SSCBPs, and the most remarkable increases were observed in *C. parapsilosis* for fluconazole (from 0% to 4.1%), and in *C. krusei* for voriconazole (from 0% to 3.7%). Echinocandin resistance increased between 0 and 4.1 times depending on the fungal species and the specific drug, *C. glabrata* being the most affected species.

For the four most common species, the percentage of isolates above the posaconazole ECV ranged from 0.8% for *C. parapsilosis* to 49.6% for *C. tropicalis*. While the percentage of isolates inhibited by >1 mg/L posaconazole ranged from 0.3% for *C. parapsilosis* to 14.5% for *C. glabrata*, this latter species was the only one where the percentage of non-wild-type isolates diminished with the application of the ECV.

Amphotericin B and flucytosine were the agents with the lowest overall resistance rates (0.2% and 0.5%, respectively). Thus the overall resistance rates to antifungal agents in our study were very low, being even lower in ICU settings.

Excluding those intrinsically resistant species, echinocandins show a broad antifungal activity. Moreover, resistance rates (≤1.1%) varied slightly when applying the revised SSCBPs for most species. However, increased resistance rates were observed in *C. glabrata* (from 1.9% to 3.2%) and *C. krusei* (from 3.7% to 7.4%), rates similar to those reported by other authors.[14]

In summary, we present the largest multicentre fungaemia study conducted in Spain and provide the incidence of the cryptic species included in the *C. parapsilosis* and *C. glabrata* complexes and the *in vitro* susceptibility of blood isolates to nine of the currently most used systemic antifungal agents. Furthermore, we have determined the repercussions of the recent ECVs and SSCBPs on resistance rates. The large size of this study minimizes its clinical limitations, thus providing valuable information for clinicians before establishing empirical treatment in patients with fungaemia.

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Transparency declarations

None to declare.

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