C. albicans, *C. parapsilosis* and *C. tropicalis* invasive infections in the PICU: clinical features, prognosis and mortality

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ABSTRACT

Candida albicans remains the most common agent associated with invasive *Candida* infection (ICI), but with increasing number of non-*albicans* species. An epidemiological, observational study exploring host criteria, clinical characteristics and mortality of ICI was performed in 24 pediatric intensive care units (PICU) in Spain.

Patients were analyzed in global and distributed by infecting species (for groups with ≥15 patients). A total of 125 ICI were included: 47 by *C. albicans*, 37 by *C. parapsilosis*, 19 by *C. tropicalis*, 4 *C. glabrata*, and 18 others. Up to 66% of ICI by *C. albicans* and 75.7% by *C. parapsilosis* occurred in children ≤24 months, while the percentage of children >60 months was higher in ICI by *C. tropicalis*. Bloodstream infection was most common among *C. tropicalis* (78.9%) or *C. parapsilosis* (83.8%) ICI, but urinary infections were almost as common as bloodstream infections among *C. albicans* ICI (31.9% and 38.3%, respectively). Fever refractory to antimicrobials was the most frequent host criterion (46.4% patients), but with equal frequency than prolonged neutropenia in *C. tropicalis* ICI. Thrombopenia was more frequent (p<0.05) in *C. parapsilosis* (60.7%) or *C. tropicalis* (66.7%) ICI than in *C. albicans* ICI (26.5%). Uremia was more frequent (p<0.05) in *C. albicans* (78.3%) or *C. tropicalis* (73.3%) than in *C. parapsilosis* ICI (40.7%). Multiple organ failure and heart insufficiency was higher in *C. tropicalis* ICI. Short duration (≤7 days) of PICU stay was more frequent in *C. albicans* ICI. Mortality rates were: 8.5% (*C. albicans* ICI), 13.5% (*C. parapsilosis* ICI) and 23.3% (*C. tropicalis* ICI).

ICI by different *Candida* species showed different clinical profiles and mortality, making essential identification at species level.

Key words: PICU; Invasive *Candida* infection; *Candida albicans; Candida parapsilosis; Candida tropicalis*

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Infección invasiva por *C. albicans*, *C. parapsilosis* y *C. tropicalis* en la UCI pediátrica: características clínicas, pronóstico y mortalidad

RESUMEN

Candida albicans es el agente más frecuentemente asociado con candidiasis invasiva, pero con un número creciente de casos causados por especies no-*albicans*. Se realizó un estudio epidemiológico observacional explorando criterios del huésped, características clínicas y mortalidad en 24 unidades de cuidados intensivos pediátricas en España.

Se analizó a los pacientes en conjunto y distribuidos por la especie infectante (para aquellos grupos con ≥15 pacientes). Se incluyó un total de 125 candidiasis invasivas: 47 por *C. albicans*, 37 por *C. parapsilosis*, 19 por *C. tropicalis*, 4 por *C. glabrata*, y 18 casos por otras especies. Hasta un 66% de las candidiasis invasivas por *C. albicans* y un 75,7% de las causadas por *C. parapsilosis* ocurrieron en niños ≤24 meses, mientras que el porcentaje de niños con >60 meses fue mayor en el grupo de candidiasis invasiva por *C. tropicalis*. La candidemia fue la infección más frecuente en el grupo de infecciones por *C. tropicalis* (78,9%) o *C. parapsilosis* (83,8%), pero las infecciones del tracto urinario fueron tan frecuentes como la bacteremia entre las infecciones por *C. albicans* (31,9% y 38,3%, respectivamente). La fiebre refractaria a antimicrobianos fue el criterio de huésped más frecuente (46,4% pacientes), pero con igual frecuencia que la neutropenia prolongada en la candidiasis invasiva por *C. tropicalis*. La trombopenia fue más frecuente (p<0,05) en las infecciones por *C. parapsilosis* (60,7%) o *C. tropicalis* (66,7%) que en las producidas por *C. albicans* (26,5%). La uremia fue más frecuente (p<0,05) en las infecciones por *C. albicans* (78,3%) o *C .tropicalis* (73,3%) que en las producidas por *C. parapsilosis* (40,7%). El fallo multiorgánico y la insuficiencia cardiaca fueron más frecuentes en el grupo de infecciones por *C. tropicalis*. La estancia corta (≤7 días) en la unidad fue más frecuente en el caso de infecciones por *C.albicans*. Las tasas de mortalidad fueron: 8,5% (*C. albicans*), 13,5% (*C. parapsilosis*) y 23,3% (*C. tropicalis*). El análisis

de la candidiasis invasiva por las distintas especies de *Candida* mostró perfiles clínicos diferentes y distintas tasas de mortalidad, haciendo esencial la identificación a nivel especie.

Palabras clave: Unidad de Cuidados Intensivos Pediátrica; candidiasis invasiva; *Candida albicans; Candida parapsilosis; Candida tropicalis*

INTRODUCTION

Invasive *Candida* infection (ICI) in the pediatric intensive care unit (PICU) presents as candidemia or disseminated candidiasis, with a reported incidence of 43 cases/100,000 admissions[1]. Epidemiology of *Candida* species depends mostly on the institution, the studied population and host factors, which are quite different in previously healthy children hospitalized in PICUs than in those whose hospitalization is related to malignancies or severe hematological diseases[2]. Over time changes in *Candida* ecology have also been related with the widespread use of azole therapy[3-5]. *Candida albicans* remains the most common fungal agent associated with ICI, but with increasing number of infections due to non-*albicans* species as *Candida parapsilosis* and *Candida tropicalis*[6-8]. ICI by *C. albicans* decreases when increasing the patient's age, a fact probably related with mother-child transmission[9], *C. tropicalis* may be associated with patients with malignancy or neutropenia[2] and *C. parapsilosis* with horizontal transmission through healthcare personnel[9].

Invasive candidiasis has been associated with severe sepsis, septic shock and multiorgan failure, with clinical characteristics resembling those by bacterial pathogens[4,10] since no pathognomonic signs or symptoms are present, especially in children[11,12]. The disease is usually late diagnosed in the course of the PICU stay, making early diagnosis a challenge for intensivists. Together with the shifting trend from *C. albicans* towards non-*albicans* species, there is an associated increase in mortality[11]. In this sense, virulence of non-*albicans* species seems to be greater than that of *C. albicans*, with their isolation (particularly *C. tropicalis*) associated with higher mortality[12,13]. However, previous studies suggest that *C. parapsilosis* is a less fit or virulent species[14,15], and in adults *C. parapsilosis* fungemia is associated with lower mortality than non-*parapsilosis* candidemia[16]. Invasive candidiasis prolongs hospital stay, increases treatment costs and is associated with high crude and attributable mortality[11]. Although the mortality rate is lower in children than in adults[16], the attributed mortality has been reported to be around 10-15% among neonates and infants[17,18], being PICU patients at the highest risk of death due to candidemia[12,19].

The aim of this study was to explore host criteria, clinical characteristics and mortality of a series of pediatric patients with ICI in the PICU in Spain.

MATERIAL AND METHODS

An epidemiological, observational, multicentre study was performed in 24 Spanish PICUs. Patients with diagnosis of ICI aged 7 days to 18 years were included regardless of basal diagnoses. Premature neonates and patients with stay in the PICU for <3 days were excluded. The study consisted of a prospective phase including all children with ICI during one year and a retrospective review of clinical records of children with diagnosis of ICI from January 2008 to December 2009 in order to obtain at least 100 ICI cases with all retrospective and prospective cases included. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments: The study protocol was approved by Research Ethic Committees of all hospitals and informed consent from parents/guardians was obtained before inclusion.

Demographical data, reasons for PICU admission, clinical, analytical and treatment data were recorded. Patients were followed until hospital discharge. Definitions of proven, probable and possible ICI were those of the EORTC/MSG consensus group[20]. Patients were analyzed in global (all patients) and distributed by infecting species, with analysis of groups with ≥15 patients in separate.

Severity was evaluated by the Pediatric Risk of Mortality (PRISM) II score and the age-corrected probability of mortality was obtained using the Pollack equation: [Logit = (0.207*PRISM-(0.005*(age in months))-0.433*1(if postoperative)-4.782]; Predicted Death Rate = e^{logit}/ $(1+e^{logit})$[21,22]. Percentiles 25, 50 and 75 were used as cut-offs.

Comparisons between proportions in the different groups were performed by the $\chi 2$ test and the Fisher's exact test, when necessary. For quantitative variables, since data did not showed normality in the Kolmogorov – Smirnoff test, the Kruskal-Wallis and Mann-Whitney tests, when necessary, were used.

Statistical analyses were performed using SPSS v 14 programme (SPSS Inc, Chicago IL).

RESULTS

Overall, 125 patients were included, 43 children in the prospective phase and 82 in the retrospective one. Of them, 115 patients had proven ICI, 8 probable ICI and 2 possible ICI.

Forty-seven children were infected by *C. albicans*, 37 by *C. parapsilosis*, 19 by *C. tropicalis*, and 22 children were infected by other species or isolation was reported as *Candida* spp. (14 *Candida* spp., 4 *C. glabrata*, 2 *C. krusei*, 1 *C. lusitaniae* and 1 *C. famata*).

Demographic data are summarized in table 1. Up to 60.8% patients were males; median age was 11 months, without significant differences between the infecting species. Most patients (54.4% of total cases) were ≤12 months old (43.2% were 2-12 months, and 11.2% were ≤1 month), followed by children >60 months old (5 years) that represented 19.2% of total cases. Although non-significant, the percentage of children >60 months of age was higher among patients infected by *C. tropicalis* than among those with ICI by *C. parapsilosis* (31.6%

Table 1 **Demographic data; expressed as n (%) except where indicated**

	All *Candida* n= 125	*Candida albicans* n= 47	*Candida parapsilosis* n= 37	*Candida tropicalis* n= 19
Males	76 (60.8)	27 (57.4)	25 (67.6)	14 (73.7)
Age [median (IQ) in months]	11 (2-36)	9 (3-48)	6 (2.5-30)	12 (3-72)
Living in urban/metropolitan areas	83 (66.4)	39 (83.0)	15 (40.5)[a]	15 (78.9)
Admission to PICU from hospital wards	62 (49.6)	27 (57.4)	12 (32.4)[b]	11 (57.9)
Reason for PICU admission[c]				
Infectious disease	73 (58.4)	25 (53.2)	19 (51.4)	10 (52.6)
Surgery	23 (18.4)	9 (19.1)	9 (24.3)	4 (21.1)
Trauma	3 (2.4)	2 (4.3)	0 (0.0)	0 (0.0)
Chronic disease	23 (18.4)	10 (21.3)	5 (13.5)	4 (21.1)
Cardiovascular disease	35 (28.0)	11 (23.4)	8 (21.6)	10 (5.2)[d]
Malignancy	7 (5.6)	2 (4.3)	2 (5.4)	2 (10.5)

[a]p<0.05 vs. *C. albicans* or *C. tropicalis*; [b]p<0.05 vs. *C. albicans*; [c]More than one reason may be present in a single patient; [d]p<0.05 vs. *C. albicans* or *C. parapsilosis*

Table 2 **Host criteria and type of infection, n (%)**

	All *Candida* n= 125	*Candida albicans* n= 47	*Candida parapsilosis* n= 37	*Candida tropicalis* n= 19
Host criteria	82 (65.6)	30 (63.8)	25 (67.6)	12 (63.2)
Neutropenia >10 days	20 (16.0)	5 (10.6)	5 (13.5)	8 (42.1)[a,b]
Fever refractory to antimicrobials	58 (46.4)	18 (38.3)	20 (54.1)	8 (42.1)
Graft-versus-host disease	2 (1.6)	1 (2.1)	0 (0.0)	1 (5.3)
Prolonged steroid use	22 (17.6)	11 (23.4)	3 (8.1)	3 (15.8)
Body temperature >38ºC or <36ºC	22 (17.6)	9 (19.1)	7 (18.9)	2 (10.5)
No. patients with				
1 criterion	55 (44.0)	21 (44.7)	18 (48.6)	6 (31.6)
≥2 criteria	27 (21.6)	9 (19.1)	7 (18.9)	6 (31.6)
Type of infection				
Bloodstream infections (BSI)	75 (60.0)	18 (38.3)	31 (83.8)[a]	15 (78.9)[a]
Urinary	27 (21.6)	15 (31.9)	1 (2.7)[a]	3 (15.8)
Respiratory	7 (5.6)	5 (10.6)	1 (2.7)	0 (0.0)
Other[c]	16 (12.8)	9 (19.1)	4 (10.8)	1 (5.3)

[a]p<0.05 vs. *C. albicans*; [b]p<0.05 vs. *C. parapsilosis*; [c]Includes peritonitis, mediastinitis and ICI related to surgical wounds

vs. 10.8%, p=0.073) or *C. albicans* (21.3%, p=0.526). A total of 66.4% patients lived in urban/metropolitan areas, but with differences between groups since patients with ICI by *C. parapsilosis* lived more often in rural/semirural areas. In the group of ICI by *C. albicans* 83.0% patients lived in urban/metropolitan areas, in the group infected by *C. tropicalis* the percentage was 78.9%, whereas in the group of ICI by *C. parapsilosis* the percentage was 40.5% (p<0.001 vs. *C. albicans*, p=0.015 vs. *C. tropicalis*). Cases by *C. albicans* (57.4%) or *C. tropicalis* (57.9%) were admitted to the PICU from other hospital wards

Table 3 **Significant analytical data at time of diagnosis; n (%)**

	All *Candida* n= 125	*Candida albicans* n= 47	*Candida parapsilosis* n= 37	*Candida tropicalis* n= 19
Leukopenia (<2,000/mm^3)	6 (2.1)	0 (0.0)	2 (7.1)	2 (13.3)
Leukocytosis (>11,000/mm^3)	60 (63.8)	23 (67.6)	17 (60.7)	9 (60.0)
Neutropenia (<400/mm^3)	5 (5.4)	0 (0.0)	2 (7.1)	3 (21.4)[a]
Thrombopenia (<10^5/ mm^3)	39 (41.9)	9 (26.5)	17 (60.7)[a]	10 (66.7)[a]
Thrombocytosis (>3 x10^5/mm^3)	25 (26.9)	13 (38.2)	6 (21.4)	1 (6.7)[a]
Urea ≥21 U/L	47 (61.8)	18 (78.3)	11 (40.7)[a]	11 (73.3)[b]
GOT ≥45 U/L	20 (38.5)	8 (42.1)	7 (35.0)	2 (33.3)
GPT ≥50 U/L	14 (26.4)	6 (30.0)	4 (21.1)	2 (33.3)
CRP>40 mg/L	43 (52.4)	15 (44.1)	17 (60.0)	6 (54.5)
Procalcitonin ng/mL (mean±SD)	8.02±16.59	3.48±9.83	7.75±11.17	8.84±5.07

[a]**p<0.05 vs. *C. albicans*;** [b]**p<0.05 vs. *C. parapsilosis***

more often than cases by *C. parapsilosis* (32.4%, p=0.022 vs. *C. albicans*, p=0.066 vs. *C. tropicalis*) that came more often from the emergency room (27.0% for *C. parapsilosis* vs. 19.1% for *C. albicans* vs. 15.8% for *C. tropicalis*), without differences in the percentage of patients coming from surgery or other PICUs. No differences in reasons for PICU admission were found between groups except for cardiovascular disease that were significantly less frequent among cases of ICI by *C. tropicalis* (5.2%) compared to *C. albicans* (23.4%, p=0.039) and *C. parapsilosis* (21.6%, p= 0.033).

Median time of hospitalization prior to PICU admission was 2 days (range 0.5-15.5 days), without differences between ICI by different species. Most common risk factors for ICI were venous catheter (79.2%), urinary catheter (77.6%), use of broad-spectrum antibiotics (76.0%), mechanical ventilation (74.4%), nasogastric intubation (71.2%), enteral nutrition (66.4%), parenteral nutrition (45.6%), arterial catheter (44.8%), and use of systemic steroids (36.0%), without differences by infecting species. However, use of chemotherapeutic agents was more frequent among patients infected by *C. tropicalis* (21.1%) than by *C. albicans* (2.1%, p=0.022) or *C. parapsilosis* (8.1%, p=0.212). At least one risk factor was present in 96.0% patients, and the median number (interquartile range) of risk factors per patient was 6.0 (3-7), with 42.4% patients presenting eight or more risk factors. Up to 65.6% patients presented at least one host criterion for ICI, and 21.6% presented two or more (table 2). The most frequent criterion was fever refractory to antimicrobials (46.4%) followed by prolonged use of steroids (17.6%). Differences by infecting species were only found for neutropenia lasting >10 days, which was more frequent among patients infected by *C. tropicalis* (42.1%) than among those with ICI by *C. albicans* (10.6%, p=0.006) or *C. parapsilosis* (13.5%, p=0.022).

Bloodstream infections represented 60.0% of total cases, one-third of them being catheter-associated. Bloodstream infections were more frequent (p<0.001) among patients with ICI by *C. parapsilosis* (83.8%) or *C. tropicalis* (78.9%) than among those infected by *C. albicans* (38.3%) (table 2). Urinary tract infections represented 21.6% of total cases, being more frequent among ICI by *C. albicans* (31.9%) than among those by *C. parapsilosis* (2.7%, p<0.001) or *C. tropicalis* (15.8%, p=0.182).

Table 3 shows analytical data at time of diagnosis. Leukocytosis was present in 63.8% patients, thrombopenia in 41.9% patients and thrombocytosis in 26.9% patients. Patients with ICI by *C. tropicalis* presented more often neutropenia than those with ICI by *C. albicans* (21.4% vs. 0.0% p=0.021). Thrombopenia was more frequent (p≤0.008) among patients with ICI by *C. tropicalis* (66.7%) or *C. parapsilosis* (60.7%) than among those with ICI by *C. albicans* (26.5%). Uremia was more frequent among patients with ICI by *C. albicans* (78.3%) or *C. tropicalis* (73.3%) than among those with ICI by *C. parapsilosis* (40.7%, p=0.007 vs. *C. albicans* and p=0.042 vs. *C. tropicalis*).

During their stay in the PICU, 50.4% of patients had at least one episode of fever, with a median duration of 3.5 days (interquartile range 2-6 days). Multiple organ failure occurred in 15.2% patients (31.6% for ICI by *C. tropicalis*, 13.5% for ICI by *C. parapsilosis* and 12.8% for ICI by *C. albicans*), and heart insufficiency in 8.8% patients (21.1% for *C. tropicalis*, 8.1% for *C. parapsilosis* and 8.5% for *C. albicans*). Forty percent of patients required mechanical ventilation, and 11.2% renal replacement therapy, without differences by infecting species.

Ninety-five (76.0%) patients received antibiotics during PICU admission, with a median duration of 12 days (interquartile range 6-25.3 days). Most frequent compounds were cephalosporins and glycopeptides (in 45.0% patients each), carbapenems and aminoglycosides (in 40.0% patients each), penicillins (25.0%) and macrolides (7.5%). Antifungal treatment last-

Table 4 **PRISM II median values, probability of death and mortality; expressed as n (%) except where indicated**

	All *Candida*	*Candida albicans*	*Candida parapsilosis*	*Candida tropicalis*
	n= 125	n= 47	n= 37	n= 19
PRISM II value, median (IQ)	5.03 (3.24-12.30)	4.90 (3.23-6.39)	5.10 (3.72-18.68)	5.39 (2.28-21.87)
% probability of death				
< 3.23	30 (24.0)	11 (23.4)	8 (21.6)	7 (36.8)
3.23 - 5.02	28 (22.4)	15 (31.9)	6 (16.2)	2 (10.5)
5.03 - 12.30	36 (28.8)	15 (31.9)	10 (27.0)	4 (21.1)
≥12.31	31 (24.8)	6 (12.8)	13 (35.1)[a]	6 (31.6)
Mortality	17 (13.6)	4 (8.5)	5 (13.5)	5 (26.3)

[a]p<0.05 vs. *C. albicans*

ed for a median of 16 days (interquartile range 11-24.8 days); azoles being used in 48.0% patients, amphotericin B in 46.4% and echinocandins in 16.8%, without differences by infecting species except for voriconazole that was more often administered in cases of ICI by *C. tropicalis* (18.7%) than in those by *C. albicans* (0.0%, p=0.022) or *C. parapsilosis* (7.1%, p=0.336).

Median length of PICU stay was 24 days (interquartile range 13-44.5 days); short duration (≤7 days) was more frequent among patients with ICI by *C. albicans* (21.3%) than among those with ICI by *C. parapsilosis* (2.7%, p=0.011) or *C. tropicalis* (10.5%, p=0.484). PICU stay longer than 21 days was found in 56.0% patients, without differences by infecting species.

PRISM II values and predictive mortality rates are shown in table 4. Median PRISM II value was 5.03 (interquartile range 3.24-12.30), without differences by infecting species; however, the percentage of patients with a probability of death ≥12.31% (percentile 75) was lower among patients with ICI by *C. albicans* (12.8%) than among those with ICI by *C. parapsilosis* (35.1%, p=0.030) or *C. tropicalis* (31.6%, p=0.089).

Overall mortality was 13.6%, without significant differences between species, although ICI by *C. tropicalis* showed higher mortality rate (26.3%) than ICI by *C. albicans* (8.5%, p=0.106) or *C. parapsilosis* (13.5%, p=0.281). Mortality rates were lower than those predicted using a probability of death cut-off ≥12.31 for *C. parapsilosis* (13.5% vs. 35.1%, p=0.057) but not for *C. albicans* (8.5% vs. 12.8%, p=0.738) or *C. tropicalis* (26.3% vs. 31.6%, p=1.000).

DISCUSSION

Candida species, frequent colonizers occasionally producing infection, are not especially invasive organisms. Nevertheless, while *C. glabrata* is always a yeast and *C. parapsilosis* may present also pseudohyphae, *C. tropicalis* and *C. albicans* may produce true hyphae with intrinsic virulence factors regulating the transition from yeast to the filamentous phenotype[23,24].

In most studies, *C. albicans* remains the most common fungal agent associated with ICI (55% of all *Candida* isolates) followed by *C. parapsilosis* (17.5% isolates), *C. tropicalis* (10% isolates) and *C. glabrata* (2-3%)[2,8]. However, in recent years the proportion of cases due to species other than *C. albicans* has increased markedly[5,25]. In our series, ICI by *C. albicans* accounted for 37.6% of all cases, ICI by *C. parapsilosis* for 29.6% and ICI by *C. tropicalis* for 15.2% of all cases, with only 3.2% of cases caused by *C. glabrata*. The elevated percentage of cases by non-*albicans Candida* (62.4%) in the present study confirms the importance of these species in the PICU and supports previous reports showing percentages as high as 70% for non-*albicans* species[12]. Identification at species level results crucial[26] because resistance to amphotericin B and to fluconazole is higher in non-*albicans* species (3.04% and 10.29%, respectively) than in *C. albicans* (0.41% and 1.27%, respectively)[27]. The shift towards higher percentages of non-*albicans* species has been partially attributed to the widespread use of azoles for antifungal therapy or prophylaxis[3,4,8,28], mainly affecting the susceptibility to these agents in *C. parapsilosis* or to the use of azoles and amphotericin B that affects susceptibility in *C. glabrata*[8,29]. In addition, the increase in the incidence of *C. parapsilosis* has been partially explained by the extensive use of indwelling catheters and the tendency of this species to adhere to foreign materials, with documented transmissions from patient-to-patient or from healthcare workers to patients[8].

C. albicans has more often been described in young infants due to mother-child transmission[9] and *C. parapsilosis* in children ≤2 years[6]. In the present study 66% of ICI cases by *C. albicans* and 75.7% of ICI by *C. parapsilosis* occurred in children ≤24 months of age, while the percentage of children >60 months was higher among patients infected by *C. tropicalis*. This could be related with the lower percentage of cardiovascular disease and the higher percentage of children with malignancies and/or prolonged neutropenia among patients infected by *C. tropicalis*.

Bloodstream infection was the most frequent type of ICI accounting for 60% of cases; however, while it was the most

common type among ICI cases by *C. tropicalis* or *C. parapsilosis* (confirming these two species[11,12] as predominant species causing candidemia in children, as occurs also in neonatal units[30]), in cases by *C. albicans*, urinary infections were almost as common as bloodstream infections.

It is well known that there are no pathognomonic clinical signs/symptoms for ICI, especially in children, being unexplained fever or fever refractory to antibiotics critical clues for diagnosis of ICI[11]. In the present series, fever refractory to antimicrobials was the most frequent host criterion (46.4% patients), but interestingly, this criterion and prolonged neutropenia were present as host criteria with equal frequency among patients with ICI by *C. tropicalis*. Other differences were found in relation to thrombopenia, a sign previously described as unspecific for candidemia[31], which was more frequent among patients with ICI by *C. parapsilosis* or by *C. tropicalis* than among those with ICI by *C. albicans*. In addition, neutropenia at time of diagnosis was significantly more frequent in patients with ICI by *C. tropicalis*, as has been previously described[2], whereas uremia was significantly more frequent in ICI cases by *C. albicans* than in *C. parapsilosis* (with only one case of urinary infection by this species in the present series).

The mortality of ICI is estimated to be around 10-15% among neonates and infants[17,18], being PICU patients at the highest risk of death due to candidemia[12,19]. In the present study we used the PRISM II score since it was developed for PICU mortality risk assessment[21]. No differences in median PRISM II values were found according to the infecting species; however, the percentage of patients presenting a predictive mortality rate ≥12.31 was higher among those with ICI by *C. parapsilosis* (35.1%) and *C. tropicalis* (31.6%) than among those with ICI by *C. albicans* (12.8%). Mortality rates were similar to these predicted percentages in the case of ICI by *C. albicans* (8.5%) and *C. tropicalis* (23.3%), but not in ICI by *C. parapsilosis* (13.5%). The mortality rates found in our series are in accordance with data in the literature, with mortality rates of ICI by *C. parapsilosis* lower than those of ICI by other species[6,16,32], and the highest mortality for ICI by *C. tropicalis*[13]. The higher frequency of multiple organ failure and heart insufficiency among patients with ICI by *C. tropicalis* in our series may have influenced mortality rates of ICI by this species. While median length of PICU stay was similar for the three species, short duration (≤7 days) was more frequent in ICI by *C. albicans* than in ICI by *C. parapsilosis* or *C. tropicalis*, the two species with approximately one-third of patients showing death probabilities ≥12.31.

Although this is a large series of ICI, distribution of patients by infecting species may have limited conclusions obtained from comparisons between them due to the reduction of the number of cases, mainly affecting ICI by *C. tropicalis*. However, our results suggest different clinical profiles, prognosis and mortality according to the specific species. These facts, together to the different susceptibility profiles described in the literature, make essential from the clinical perspective identification at species level of the genus *Candida* causing the ICI.

ACKNOWLEDGEMENTS

Part of this study was presented at the 31st ESPID (Milan, Italy, May 28 - June 1, 2013)

Other members of the ERICAP group are:

M.C. Goñi (H. Virgen del Camino, Pamplona), J.M. Sánchez (H. Clínico Universitario, Salamanca), A. Rodríguez (H. Clínico Universitario, Santiago de Compostela), S. Pantoja (H. Universitario Puerta del Mar, Cádiz), M. Ortiz-Pallarés (H. Xeral Vigo, Vigo), A. Bustinza (H. General Universitario Gregorio Marañón, Madrid), S. Brió (H. Sant Pau, Barcelona), J.S. León (H. Universitario Nuestra Sra. de la Candelaria, Sta. Cruz de Tenerife), S. Sánchez (Corporación Parc Taulí, Barcelona), M. Benito-Garcia (H. Clínico Universitario, Valladolid), JC Flores-González (H Puerta del Mar, Cádiz), J.M. Espinosa (H. Universitario Infanta Cristina, Badajoz), M. Nieto (H. Cruces, Bilbao) P.M. Roselló (H. Clínico Universitario, Valencia), P Maduga (H. Infantil Miguel Servet, Zaragoza), C. Ramil (Complexo Hospitalario Universitario, A Coruña), D. Arjona (H. Virgen de la Salud, Toledo), A. Sancho (H. Universitario de Canarias, Tenerife), M.J. Arroyo (H. Reina Sofía, Córdoba), J.J. Granizo (Grana Datos SL) and M.J. Giménez (Microbiology Unit, Medicine Dpt., School of Medicine, Univ. Complutense, Madrid).

CONFLICTS OF INTEREST

I. Jordan has received consulting fees, payments for lectures and support for travel to meetings from Astellas Pharma S.A.; M. Balaguer and Ll Hernandez has received support for travel to meetings from Astellas Pharma S.A.; L Casanueva and C. Shuffelman has received fees for participation in review activities from Astellas Pharma S.A; M-A Garcia-Teresa has received support for travel to meetings from Astellas Pharma S.A.; P. Anguita is an employee of Astellas Pharma S.A., Madrid, Spain. For the remaining authors none to declare.

FUNDING

This study was supported in part by an unrestricted grant from Astellas Pharma S.A. (Madrid, Spain).

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