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Epidemiology and Antifungal Susceptibility of Bloodstream Fungal Isolates in Pediatric Patients: a Spanish Multicenter Prospective Survey▽

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Data on fungemia epidemiology and antifungal susceptibility of isolates from children are scarce, leading frequently to pediatric empirical treatment based on available adult data. The present study was designed to update the epidemiological, mycological, and *in vitro* susceptibility data on fungal isolates from children with fungemia in Spain. All fungemia episodes were identified prospectively by blood culture over 13 months at 30 hospitals. Tests of susceptibility to amphotericin B, flucytosine, fluconazole, itraconazole, posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin were performed at participant institutions by a microdilution colorimetric method. New species-specific clinical breakpoints for fluconazole, voriconazole, and echinocandins were also applied. A total of 203 episodes of fungemia in 200 children were identified. A higher proportion of fungal isolates was from general wards than intensive care units (ICU). *Candida parapsilosis* (46.8%), *Candida albicans* (36.5%), *Candida tropicalis* (5.9%), *Candida glabrata* (3.9%), and *Candida guilliermondii* (2.5%) were the leading species. *C. parapsilosis* was the predominant species except in neonates. *C. albicans* was the most frequent in neonatal ICU settings (51.9%). Intravascular catheter (79.3%), surgery (35%), prematurity (30%), and neutropenia (11%) were the most frequent predisposing factors. Most *Candida* isolates (95.1%) were susceptible to all antifungals. When the new species-specific clinical breakpoints were applied, all *C. parapsilosis* isolates were susceptible to echinocandins except one, which was micafungin resistant. This is the largest published series of fungemia episodes in the pediatric setting. *C. parapsilosis* is the most prevalent species in Spain, followed by *C. albicans* and *C. tropicalis*. Resistance to azole and echinocandin agents is extremely rare among *Candida* species. The fluconazole resistance rate in Spain has decreased in the last 10 years.

The incidence of bloodstream fungal infection, in adults and pediatric patients, has risen in the last decade as a result of a combination of several factors, such as increased use of central venous catheters, extensive use of parenteral nutrition, mucosa alteration or prolonged neutropenia due to more aggressive antineoplastic treatments, ever more aggressive surgery and instrumentation techniques, and the widespread use of broad-spectrum antibiotics (8, 9, 17, 18, 24, 25). Currently, *Candida* spp. have become the fourth most frequent causal microorganisms of nosocomial sepsis (17, 25). Furthermore, monitoring programs have detected an increase in the prevalence of infections caused by non-*Candida albicans* (essentially *Candida parapsilosis*, *Candida glabrata*, and *Candida krusei*) and other yeast genera (1, 6, 20). Additionally, significant regional differences have been reported in the distribution and pattern of susceptibility to antifungal agents among the different species (21, 24).

Unfortunately, data about epidemiology or antifungal susceptibility patterns in pediatric patients with fungemia are scarce, and empirical treatment in children with suspicion of invasive fungal infection frequently has to be instituted by extrapolating information from adult patients. The need to update the epidemiological and mycological profiles in pediatric patients with fungemia was one of the aims of the FUNGEMYCA survey, developed prospectively in Spain in 2009. In the present descriptive study, we report the results of this survey in the Spanish pediatric population along with the susceptibility patterns of the fungal isolates recovered, comparing data with a previous study carried out from 1997 to 1999 in Spain (14).

MATERIALS AND METHODS

Study design. The FUNGEMYCA survey was a prospective, sequential, hospital population-based study. Thirty Spanish institutions, widely distributed throughout the country, including the Canary and Baleares Islands, participated in the study. Participating hospitals were required to collect sequentially and

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TABLE 1. Characteristics of candidemia episodes and distribution of the isolated species

Patient characteristic	No. (%) of episodes										
	Total	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. glabrata*	*C. guilliermondii*	*C. lusitaniae*	*C. krusei*	*C. famata*	*R. glutinis*	*T. asahii*
Age											
<1 month	72 (35.4)	38 (52.8)	24 (33.3)	3 (4.2)	4 (5.5)		1 (1.4)	1 (1.4)	1 (1.4)		
1–12 months	45 (22.2)	14 (31.1)	26 (63.4)	1 (2.2)	2 (4.4)	1 (2.2)	1 (2.2)				
1–15 years	86 (42.4)	22 (25.6)	45 (52.3)	8 (9.3)	2 (2.3)	4 (4.6)	2 (2.3)	1 (1.2)		1 (1.2)	1 (1.2)
Gender											
Male	123 (60.6)	47 (38.2)	58 (47.2)	8 (6.5)	2 (1.6)	2 (1.6)	1 (0.8)	2 (1.6)	1 (0.8)	1 (0.8)	1 (0.8)
Female	80 (39.4)	27 (33.7)	37 (46.2)	4 (5.0)	6 (7.5)	3 (3.8)	3 (3.8)				
Location at time of fungemia											
NICU	27 (13.3)	14 (51.9)	9 (33.3)	1 (3.7)	1 (3.7)	1 (3.7)			1 (3.7)		
Pediatric ICU	38 (18.7)	15 (39.5)	15 (39.5)	1 (2.6)	2 (5.3)	1 (2.6)	2 (5.3)	1 (2.6)			1 (2.6)
General ward	138 (67.9)	45 (32.6)	71 (51.4)	10 (7.2)	5 (3.6)	3 (2.2)	2 (1.4)	1 (0.7)		1 (0.7)	
Total episodes	203	74 (36.5)	95 (46.8)	12 (5.9)	8 (3.9)	5 (2.5)	4 (2.0)	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)

identify the fungal isolates from blood cultures and to complete, for each fungemia episode, a questionnaire about demographic information, clinical signs of sepsis, and risk factors or predisposing diseases within the preceding 30 days. Approval for the study was obtained from the ethics committees of all participating institutions. All institutions taking part in the study were tertiary hospitals with pediatric departments.

Period of study. The study was carried out over a 13-month period, from January 2009 to February 2010.

Definitions. An episode of fungemia was defined as the isolation of a yeast or mold species from blood culture in a patient with temporally related clinical signs and symptoms. In patients with more than 1 episode of fungemia, an episode was defined as a new case if it occurred more than 30 days after resolution of the previous episode. Outpatient-acquired fungemia was considered when the fungal etiologic agent was isolated in blood in the first 48 h after hospital admission. Neonates were defined as those <1 month of age, infants were defined as those 1 to 12 months of age, and children were defined as those 1 to 15 years old.

Identification of organisms and antifungal susceptibility study. All yeast or mold species isolated from blood cultures were identified at the participating institutions by the routine methods in use at each laboratory. Isolates were stored as suspensions in sterile water at ambient temperature for ulterior studies. Antifungal susceptibility testing was performed, in the first isolate from each fungemia episode, at the participating hospitals by the microdilution colorimetric Sensititre YeastOne SYO-09 panel (TREK Diagnostic Systems). This commercial method determines the MICs of nine antifungal agents: amphotericin B, flucytosine, fluconazole, itraconazole, voriconazole, posaconazole, anidulafungin, caspofungin, and micafungin. Breakpoints applied were those of the Clinical and Laboratory Standards Institute (CLSI) (4). Since no breakpoints have been published for posaconazole and amphotericin B, isolates inhibited by >2 mg/liter and >1 mg/liter, respectively, were considered resistant to these drugs. The recently published species-specific clinical breakpoints for fluconazole, voriconazole, and echinocandins were also applied (5, 15, 16, 19). Isolates of *C. albicans*, *Candida tropicalis*, and *C. parapsilosis* for which fluconazole MICs were ≤2 mg/liter were categorized as susceptible, and those for which MICs were >4 mg/liter were categorized as resistant. *C. glabrata* was considered susceptible dose dependent at MICs of ≤32 mg/liter and resistant at MICs of >32 mg/liter. *C. albicans*, *C. tropicalis*, and *C. parapsilosis* isolates with voriconazole MICs of ≤0.125 mg/liter were classified as susceptible, 0.25 to 0.5 mg/liter as intermediate, and ≥1 mg/liter as resistant. *C. albicans*, *C. tropicalis*, and *C. krusei* isolates with anidulafungin, caspofungin, and micafungin MICs of ≤0.25 mg/liter were classified as susceptible and >0.5 mg/liter as resistant. For *C. glabrata*, isolates with anidulafungin or caspofungin MICs of ≤0.12 mg/liter were categorized as susceptible and MICs of >0.25 mg/liter as resistant, while isolates with micafungin MICs of ≤0.03 mg/liter and >0.12 mg/liter were considered susceptible and resistant, respectively. For *C. parapsilosis* and *Candida guilliermondii*, isolates with MICs of ≤2 mg/liter and >4 mg/liter of the three echinocandins were classified as susceptible and resistant, respectively.

Statistical analyses. Data were analyzed with SPSS 10.0.7 (SPSS Inc., Chicago, IL). Continuous variables were compared with Student's *t* test, and categorical variables were compared with the chi-square or Fisher's exact test. A *P* value of <0.05 was considered significant.

RESULTS

A total of 203 episodes of fungemia in 200 patients <16 years of age were identified during the study period. *Candida* species accounted for 99% of the fungal isolates. Most fungemia occurred among males (60.6%) and patients less than 1 year old (57.6%), and more fungemia occurred among those hospitalized in general wards (67.9%), including hematology/oncology departments, than in intensive care units (ICUs) (18.7%) or neonatal ICUs (NICUs) (13.3%) (Table 1). *C. parapsilosis* (46.8%), *C. albicans* (36.5%), *C. tropicalis* (5.9%), *C. glabrata* (3.9%), *C. guilliermondii* (2.5%), *Candida lusitaniae* (2%), *C. krusei* (1%), *Candida famata* (0.5%), *Trichosporon asahii* (0.5%), and *Rhodotorula glutinis* (0.5%) were the species causing fungemia during the study period. Mixed infections occurred in three episodes (*C. guilliermondii* and *T. asahii*, *C. albicans* and *C. lusitaniae*, and *C. parapsilosis* and *C. lusitaniae*), all of them in male ICU patients more than 1 year of age. No *Cryptococcus*, *Fusarium*, or *Acremonium* species were isolated throughout the study. The causal agents of fungemia varied according to age, gender, or patients' locations in the hospital (Table 1) and their underlying conditions (Table 2). *C. parapsilosis* was the predominant species in patients over 1 month of age, while *C. albicans* was the predominant species in neonates (52.8% versus 31.1% in the group 1 to 12 months old [$P = 0.02$]). *C. glabrata* was identified more frequently from females than it was from males (7.5% versus 1.6% [$P = 0.03$]), and *C. albicans* was more common in the NICU setting (51.9%) than in the pediatric ICU (39.5%) or other hospital locations (32.6%).

Presence of intravascular catheter (79.3%), surgery (35%), prematurity (30%), and neutropenia (11%) were the predisposing factors most frequently associated with fungemia (Table 2). *C. parapsilosis* was the prevalent species related to all the predisposing factors analyzed, except for premature or neutropenic children, in whom *C. albicans* was the most com-

TABLE 2. Major predisposing factors among children with fungemia and species distribution

Predisposing factor	No. of isolates (% for each predisposing factor)										
	Total[a]	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. glabrata*	*C. guilliermondii*	*C. lusitaniae*	*C. krusei*	*C. famata*	*R. glutinis*	*T. asahii*
Intravascular line	161 (79.3)	62 (38.5)	73 (45.3)	10 (6.2)	5 (3.1)	3 (1.9)	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.6)
Surgery	70 (35.0)	29 (41.4)	34 (48.6)	3 (4.3)	4 (5.7)						
Prematurity	60 (30.0)	33 (55.0)	22 (36.7)	2 (3.3)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)			
Neutropenia	22 (11.0)	10 (45.4)	4 (18.2)	4 (18.2)	1 (4.5)	1 (4.5)		2 (9.0)			
HSCT	18 (9.0)	4 (22.2)	9 (50.0)	4 (22.2)						1 (5.5)	
Burns	5 (2.5)	2 (40.0)	3 (60.0)								
SOT	4 (2.0)	2 (50.0)	1 (25.0)		1 (25.0)						
HIV	1 (0.5)				1 (100)						

[a] Some patients have more than one risk factor. HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant.

mon species isolated. No outpatient-acquired fungemia episodes were observed during the study period.

Table 3 summarizes the results of *in vitro* susceptibility testing of bloodstream fungal isolates. Overall, the rate of resistance to amphotericin B and flucytosine was very low; only one isolate (0.49%) of *C. tropicalis* was resistant (MIC of 2 mg/liter) to amphotericin B, and one *C. albicans* isolate was resistant to flucytosine (MIC of 32 mg/liter). Among *Candida* spp., only three isolates showed multiresistance when applying the CLSI clinical breakpoints: one *C. albicans* and one *C. tropicalis* isolate resistant to all azole agents, and one *C. tropicalis* isolate resistant to amphotericin B and azoles.

Of all *Candida* species isolated, 95.1% were susceptible to the nine antifungal agents tested (96% of *C. albicans* isolates, 98% of *C. parapsilosis* isolates, 87.5% of *C. glabrata* isolates, 83.4% of *C. tropicalis* isolates, 100% of infrequent *Candida* species [*C. lusitaniae*, *C. guilliermondii*, and *C. famata*]), including the two *C. krusei* isolates, intrinsically resistant to fluconazole. The resistance rates for *Candida* species and antifungal agents range from 0% (caspofungin) to 2% (itraconazole). *C. tropicalis* was the species most resistant to antifungals: two isolates (16.6%) were resistant to fluconazole and itraconazole (Table 3).

Applying the new species-specific clinical breakpoints for fluconazole, voriconazole, and echinocandins (5, 15, 16, 19), the resistance rates were equal to those obtained by applying the CLSI breakpoints (4), except for *C. albicans* and micafungin and fluconazole, where one isolate was categorized as resistant. For voriconazole, one *C. tropicalis* isolate shifted from intermediate to resistant. In contrast, all *C. parapsilosis* isolates were classified as susceptible with the species-specific clinical breakpoints except one micafungin-resistant isolate (Table 3).

DISCUSSION

Studies on epidemiology and susceptibility of fungemia are more frequent in adult populations and are based on large samples; thus, pediatricians often have to rely on data from these studies when applying treatment. To our knowledge, this is one of the largest multicenter prospective series of fungemia reported in pediatric patients, having a total of 200 patients from 30 Spanish tertiary hospitals. Data were collected in 13 months and incorporate results of *in vitro* susceptibility to nine systemic antifungal agents, including those most recently commercialized (posaconazole and micafungin). Furthermore, we have applied not only the clinical breakpoints from CLSI but also the new species-specific clinical breakpoints for fluconazole, voriconazole, and echinocandins.

As in adults, fungemia occurs more frequently in males (60.6%) (2, 3, 13). Among pediatric patients, fungemia is more frequent in children over 1 year of age (42.4%) and neonates (35.4%). In our study, a higher proportion (67.9%) of fungemia episodes occurs in patients admitted to a general pediatric or surgical ward, which is in contrast to other pediatric series, where the ICU is the most prevalent hospital unit with fungemia (10, 26). As in other studies, the most frequent predisposing factor associated with fungemia is an indwelling intravenous catheter (79.3%), in accordance with that reported by Stamos and Rowley (87%) and Neu et al. (89%) (10, 23).

Overall, the predominant fungal species isolated in Spain is *C. parapsilosis*, which causes 46.8% of episodes. But species distribution varies according to patients' comorbidities, with *C. albicans* being isolated most frequently in neonates (52.8%) and in patients admitted in NICUs (51.9%).

When comparing these data with those from our previous study from 1997 to 1999 (14), no significant differences in global species distribution has been observed; nevertheless, the percentage of *C. parapsilosis* isolation has decreased in all age groups, mainly in patients less than 1 year old (53% versus 42.7%), while the prevalence of *C. albicans* has increased, although without statistical significance.

The overall species distribution observed in our national survey contrasts with other studies where *C. albicans* is the first species isolated in children, followed by *C. parapsilosis* (2, 3, 23, 26). However, in the study published by Neu et al., *C. parapsilosis* is the predominant species regardless of the patients' comorbidity or age group (10).

In our study, polyfungal infections occurred in three cases (1.5%), all of them involving two species. This rate of mixed infection is similar to those reported in other series (2, 3). Interestingly, in two of the four fungemia episodes concerning *C. lusitaniae*, this species was isolated in combination with another yeast. Additionally, no *Cryptococcus*, *Fusarium*, or *Acremonium* species have been isolated as causal agents of fungemia.

Among *Candida* species, 95.1% of all isolates are susceptible to the nine antifungal agents tested. Despite the extensive use of fluconazole, the susceptibility rate to this agent remains very high (99.4% of *C. albicans* and *C. parapsilosis* isolates), similar

TABLE 3. *In vitro* susceptibility of 203 fungemia isolates to nine antifungal agents[a]

Species (no. of isolates tested)	Drug	MIC (mg/liter)			No. (%) of resistant isolates	
		Range	50%	90%	CLSI	Species-specific clinical breakpoint[c]
C. parapsilosis (95)	AND	0.016–4	1	2	2	0
	CAS	0.008–2	0.5	0.5	0	0
	MCF	0.016–8	1	2	1 (1.1)	1 (1.1)
	FZ	0.12–8	1	2	0	0
	ITZ	0.016–0.25	0.06	0.12	0	ND
	VOR	0.008–0.12	0.008	0.03	0	0
	POS	0.008–1	0.03	0.12	0	ND
	AMB	0.12–1	0.25	0.5	0	ND
	FLC	0.06–1	0.06	0.25	0	ND
C. albicans (74)	AND	0.016–0.5	0.016	0.12	0	0
	CAS	0.008–0.5	0.03	0.12	0	0
	MCF	0.008–1	0.016	0.03	0	1 (1.4)
	FZ	0.06–256	0.5	0.5	1 (1.4)	2 (2.7)
	ITZ	0.016–8	0.06	0.12	1 (1.4)	ND
	VOR	0.008–8	0.008	0.016	1 (1.4)	1 (1.4)
	POS	0.008–8	0.03	0.12	1 (1.4)	ND
	AMB	0.12–0.5	0.25	0.5	0	ND
	FLC	0.06–32	0.06	0.5	1 (1.4)	ND
C. tropicalis (12)	AND	0.016–8	0.12	0.25	1 (8.3)	1 (8.3)
	CAS	0.03–0.25	0.06	0.25	0	0
	MCF	0.016–8	0.03	0.06	1 (8.3)	1 (8.3)
	FZ	0.5–256	1	256	2 (16.6)	2 (16.6)
	ITZ	0.03–16	0.25	8	2 (16.6)	ND
	VOR	0.03–8	0.06	2	1 (8.3)	2 (16.6)
	POS	0.03–4	0.25	4	1 (8.3)	ND
	AMB	0.25–2	0.5	0.5	1 (8.3)	ND
	FLC	0.06–2	0.06	2	0	ND
C. glabrata (8)	AND	0.016–0.03	0.03		0	0
	CAS	0.008–0.12	0.03		0	0
	MCF	0.008–0.016	0.016		0	0
	FZ	1–16	4		0	0
	ITZ	0.12–1	0.25		1	ND
	VOR	0.03–0.25	0.06		0	ND
	POS	0.06–1	0.25		0	ND
	AMB	0.12–1	0.25		0	ND
	FLC	0.06	0.06		0	ND
C. guilliermondii (5)	AND	0.5–2	1		0	0
	CAS	0.12–0.5	0.25		0	0
	MCF	0.25–1	0.5		0	0
	FZ	0.5–8	4		0	ND
	ITZ	0.03–0.5	0.25		0	ND
	VOR	0.008–0.12	0.06		0	ND
	POS	0.016–0.5	0.12		0	ND
	AMB	0.25–0.5	0.25		0	ND
	FLC	0.06	0.06		0	ND
C. lusitaniae (4)	AND	0.12–0.5	0.25		0	ND
	CAS	0.06–0.25	0.12		0	ND
	MCF	0.008–0.5	0.06		0	ND
	FZ	0.25–1	0.25		0	ND
	ITZ	0.03–0.12	0.12		0	ND
	VOR	0.008–0.016	0.008		0	ND
	POS	0.03–0.06	0.03		0	ND
	AMB	0.12–0.5	0.25		0	ND
	FLC	0.06	0.06		0	ND
C. krusei (2)	AND	0.016–0.06	0.016		0	0
	CAS	0.25	0.25		0	0
	MCF	0.12	0.12		0	0
	FZ	64	64		2 (100)	2 (100)
	ITZ	0.25	0.25		0	ND
	VOR	0.25			0	ND
	POS	0.25–0.5	0.25		0	ND
	AMB	0.5	0.5		0	ND
	FLC	02–8	2		0	ND

Continued on following page

TABLE 3—*Continued*

Species (no. of isolates tested)	Drug	MIC (mg/liter)			No. (%) of resistant isolates	
		Range	50%	90%	CLSI	Species-specific clinical breakpoint[c]
Other yeasts[b] (3)	AND	8	8		2 (66.6)	ND
	CAS	8			2 (66.6)	ND
	MCF	8	8		2 (66.6)	ND
	FZ	4–256	4		1 (33.3)	ND
	ITZ	0.03–2	0.03		1 (33.3)	ND
	VOR	0.06–4	0.06		1 (33.3)	ND
	POS	0.25–8	0.25		1 (33.3)	ND
	AMB	0.5	0.5		0	ND
	FLC	0.06–2	0.06		0	ND
Overall (203)	AND	0.015–8	0.12		5 (2.48)	
	CAS	0.008–8	0.12		2 (1)	
	MCF	0.008–8	0.25		4 (2)	
	FZ	0.06–256	0.5		6 (3)	
	ITZ	0.016–16	0.06		4 (2)	
	VOR	0.008–8	0.008		3 (1.5)	
	POS	0.008–8	0.03		3 (1.5)	
	AMB	0.12–2	0.25		1 (0.5)	
	FLC	0.06–32	0.06		1 (0.5)	

[a] AND, anidulafungin; CAS, caspofungin; MCF, micafungin; FZ, fluconazole; ITZ, itraconazole; VOR, voriconazole; POS, posaconazole; AMB, amphotericin B; FLC, flucytosine; ND, not defined.
[b] One isolate each of *C. famata*, *T. asahii*, and *R. glutinis*.
[c] Defined in Materials and Methods.

to that reported by other authors (3, 10), and it has even increased since our last study 10 years ago (14). Furthermore, as *C. glabrata* and *C. krusei* are very infrequent in the pediatric setting (2, 3, 10, 12, 14, 22, 23, 26), fluconazole is still a reasonable option for fungemia treatment before species identification, except in children with prior azole exposure, as is recommended by the latest guidelines published (7, 11).

Except intrinsically resistant species (*T. asahii* and *R. glutinis*), echinocandins show a broad antifungal activity; only two *C. parapsilosis* isolates and one *C. tropicalis* isolate were resistant to micafungin or/and anidulafungin. Of note, all *C. parapsilosis* isolates were susceptible to the three echinocandins when applying the new species-specific clinical breakpoints, and only one isolate was resistant to micafungin. Regarding amphotericin B and flucytosine, as in other series, both agents present the lowest rate of resistance (0.5%). With respect to the newly commercialized systemic antifungal agents, micafungin and posaconazole, both show excellent *in vitro* activity against *Candida* species isolates.

Despite the increasing use of antifungal agents in the last decade, when comparing the present results with those obtained in our previous national study 10 years ago (14), a decrease in a percentage of isolates resistant to amphotericin B, flucytosine, fluconazole, itraconazole, and voriconazole is observed. One of the limitations of this study is the lack of data on antifungal use or severity of illness; nevertheless, the large size of the sample gives pediatricians valuable information about susceptibility when deciding on appropriate treatment.

This descriptive study is one of the largest multicenter series of fungemia episodes in the pediatric setting. *C. parapsilosis* is the most frequently implicated species in Spain, followed by *C. albicans* and *C. tropicalis*. The risk factors observed for fungemia are in accordance with those reported by other authors in different countries. In the Spanish pediatric population evaluated, resistance to azole and echinocandin agents is extremely rare among *Candida* species, confirming the utility of these agents for the empirical treatment of fungemia in children. The percentage of fluconazole-resistant isolates in the pediatric population in Spain has decreased in the last 10 years. This study confirms the importance of epidemiological surveillance studies on fungemia for evaluating changes in species distribution and antimicrobial susceptibility patterns and for assessing the potential impact of new antifungal agents.

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