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Invasive candidiasis in pediatric intensive care in Greece: a nationwide study

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Abstract *Purpose:* To record the practices for prevention and management of invasive candidiasis in the PICU and investigate the epidemiology of candidiasis and its outcome nationwide. *Methods:* A multicenter national study among PICUs throughout Greece. A questionnaire referring to local practices of prevention and management of candidemia was filled in, and a retrospective study of episodes that occurred during 5 years was conducted in all seven Greek PICUs. *Results:* Clinical practices regarding surveillance cultures, catheter replacement protocols and antibiotic use were similar, although the case mix differed. In all PICUs prophylactic antifungal treatment was administered in transplant and neutropenic oncology patients. Discrepancy existed between PICUs concerning the first-line antifungal agents and treatment duration of candidemia. Twenty-two candidemias were nationally recorded between 2005 and 2009 with a median incidence of 6.4 cases/1,000 admissions. Median age was 8.2 (0.3–16.6) years. *Candida albicans* was isolated in 45.4 % of episodes followed by *Candida parapsilosis* (22.7 %). Common findings were presence of central venous and urinary catheters as well as mechanical ventilation and administration of antibiotics with anti-anaerobic activity in almost all patients with candidemia. Total parenteral nutrition was administered to five (22.7 %) patients. Most of the patients had a chronic underlying disease; five were oncology patients, and two-thirds of those with candidemia were colonized with *Candida* spp. Lipid amphotericin B formulations were the predominant therapeutic choice (54.5 %). Thirty-day mortality was 18.2 %. *Conclusion:* This first national study adds information to the epidemiology of candidemia in critically ill children. In these special patients, candidemia has a relatively low incidence and tends toward non-*albicans Candida* preponderance.

Keywords Candidemia · PICU · Children · Candida · Epidemiology

Introduction

Candida represents the third most common cause of bloodstream infections in hospitalized children [1]; the overall frequency of candidemia has doubled over the last decades [2, 3]. The incidence and mortality of candidemia is higher among severely ill patients; in adults, almost half of the episodes of candidemia occur in patients admitted to the intensive care unit (ICU) [4]. Multicenter large-scale studies have been conducted in adult ICUs [5–7]; however, similar data are lacking in children. Blyth et al. [8] showed in a large population-based study that the incidence and mortality of candidemia were higher in adults than in children (1.8 vs. 0.9/100,000 population and 10 vs. 30 %, $p < 0.001$, respectively); however, patients in the PICU were not studied separately. To our knowledge, very little is specifically known about candidemia in the PICU [9, 10]. The incidence of candidemia in pediatric patients generally ranges between 0.21 and 10.5 cases/1,000 admissions in various studies [2, 8, 11, 12]. Distribution of *Candida* species and outcome also differ widely among reporting centers, a fact that links closely to differences in local prevention, prophylaxis and treatment practices as well as to differences among countries. The lack of specific guidelines concerning the management of *Candida* infections in PICU patients contributes to differences observed among centers and makes interpretation of the results challenging. In order to optimize PICU candidemia management, we conducted a nationwide multicenter study in Greece including virtually all children receiving intensive care in the country and retrospectively recorded candidemia episodes along with local practices of prevention and treatment.

Patients and methods

Survey of clinical practices in PICUs

Seven PICUs (all main PICUs in Greece) were contacted, and five of them finally participated in the study, as the other two did not have any patients with candidemia and/or were not on full operation during the study period. The PICUs participating in the study were: the PICU of Aglaia Kyriakou Children's Hospital (A), PICU of Aghia Sophia Children's Hospital (B), PICU of Penteli Children's Hospital (C) (all three in Athens), PICU of University of Crete Hospital, Heraclion (D), and PICU of Hippokration General Hospital, Thessaloniki (E). The numbers of beds and admissions, the overall mortality and the pathologies of patients (medical, surgical, cardiac, oncology, solid organ and hematopoietic stem cell transplantation) admitted over the time period of the study were recorded, and the clinical practices concerning the management of fungal infections were reviewed in each PICU.

Retrospective observational candidemia study

All patients who had a positive blood culture for *Candida* spp. and were in the PICU for more than 48 h when candidemia was diagnosed were eligible for inclusion in the study. Patients who presented with candidemia on admission were excluded. Cases were identified through the records of the microbiology laboratory of each participating hospital. Identification of *Candida* spp. was performed according to the methods used in each hospital [Vitek 2 automated system in four hospitals and API ID32 in one (both from BioMerieux, Marcy l'Etoile, France)]. The Institutional Review Board of each participating hospital approved the study. As the study was retrospective in nature, the parents did not sign an informed consent form.

Clinical data were collected by reviewing the medical and nursing notes. They included demographic and clinical patient characteristics as well as clinical and treatment details concerning the episode of candidemia. Duration of candidemia was defined as the time elapsed from the day of positive blood culture for *Candida* to the day of first negative blood culture. Cases in which *Candida* spp. was isolated in histology samples or other sterile fluids apart from blood (e.g. peritoneal, pleuritic fluid, bile) or in which there was evidence of chorioretinitis, endophthalmitis or endocarditis were considered as probable disseminated candidemia. Patient mortality was determined 30 days after the diagnosis of candidemia.

Statistical analysis was performed with SPSS (version 19.0). Categorical variables were compared using the x^2 test. Continuous variables were compared using the t test (normally distributed variables) or the Mann-Whitney test (non-normally distributed variables). A two-tailed $p < 0.05$ was considered significant.

Results

Characteristics and policies of PICUs participating in the study

Demographic characteristics of PICUs are shown in Table 1. Patients admitted in PICUs A, B and E were similar as well as those admitted in C and D.

In all five PICUs, surveillance cultures were taken twice weekly from blood, urine and bronchial aspirates, and when there were clinical indications of infection. In most PICUs pharyngeal aspirate cultures were taken once weekly or according to clinical indications. Central venous catheters (CVC), central arterial catheters and peripheral arterial lines were replaced according to clinical indications (obstruction, infection or colonization) in all PICUs as well as urinary and nasogastric catheters. Oral candidiasis was recorded in all PICUs and was treated with oral nystatin.

Table 1 Characteristics of PICUs participating in the study

Characteristics	A	B	C	D	E	Total
No. of beds	6	10	6	6	8	36
Average number of admissions/year	184	243	78	113	128	746
Overall PICU mortality (%)	9.6	12.2	7.9	3.7	13.4	9.4
Candidemia cases/1,000 admissions	6.5	3.3	0	14.1	6.2	6.4
Candidemia cases/1,000 patient days	ND	0.24	0	1.49	0.39	0.36
Candidemia case mortality	0/6	1/4	NA	1/8	2/4	4/22 (18.2 %)
Patient characteristics (%)						
Medical	54.2	39.8	55.6	68.8	54.2	54.5
Surgical	24.7	43	39.4	24.2	32.4	32.7
Oncology	11.3	12.6	1.2	3	6.4	6.9
Cardiology	9.6	1.1	3.7	4	5.5	4.4
Transplantation	0	3	0	0	1.7	0.9

Aglaia Kyriakou Children's Hospital PICU (A), Aghia Sophia Children's Hospital PICU (B), Penteli Children's Hospital PICU (C) (all 3 in Athens), PICU of University Hospital of Heraklion, Crete (D), and PICU of Hippokration General Hospital, Thessaloniki (E)

NA not applicable, *ND* no data available

Antifungal prophylaxis was given to transplant and neutropenic hematological/oncological patients according to prophylactic protocols of the respective transplant and oncology departments. Fluconazole and voriconazole were the most often used antifungal agents. There were no protocols for antifungal prophylaxis in non-neutropenic patients; however, there was a lower threshold for empiric antifungal therapy in critically ill patients with multiple risk factors for candidemia, such as colonization with *Candida* spp. in >1 site, immunocompromise, CVC presence, TPN and long-term antibiotic administration and recent abdominal surgery. Two out of five PICUs considered bronchial aspirates positive for *Candida* spp. as a marker for initiation of pre-emptive therapy. Empiric antifungal treatment was given to septic patients without a focus of infection who did not improve despite broad-spectrum antibiotic coverage in all PICUs. The presence of yeasts in urine was initially dealt with by replacement of the urinary catheter and, if persistent, treatment with fluconazole was initiated in all PICUs.

The antifungal agents used for empiric and first-line targeted therapies were the same. Two PICUs used fluconazole, whereas three PICUs (A, B and E) used lipid formulations of amphotericin B (LFAMB) as first-line antifungal agents for treatment of candidemia regardless of *Candida* spp. One PICU (D) used an echinocandin for non-*C. albicans* candidemia. Among five PICUs, three treated candidemia for 14 days after negative blood cultures; the other two treated for 21 days. None of the PICUs possessed written protocols for antibiotic use or for management of fungal infections during the study period.

Epidemiology of candidemia episodes

A total of 22 episodes of candidemia were nationally recorded over the 5-year period (2005–2009). The median incidence of candidemia was 6.4 cases/1,000 admissions and 0.36 cases/1,000 inpatient days (the latter being calculated from PICU B, D and E data). There were no patients with candidemia in PICU C over the study period. The demographic data of patients, risk factors, *Candida* spp., duration of candidemia and 30-day mortality are shown in Table 2.

The median age of patients was 8.2 (0.3–16.6) years. The median duration of PICU stay prior to the candidemia episode was 18.5 (4–615) days. Common findings were the presence of CVC and urinary catheters, ventilator support and use of antibiotics with anti-anaerobic activity in almost all patients with candidemia. Most of the patients had a chronic underlying disease, and 5 (22.7 %) were oncology patients. Nine patients had undergone surgery prior to the candidemic episode, and TPN was

Table 2 Demographic and clinical characteristics of children with candidemia

Characteristics	Number (total $n = 22$)
Sex (male)	12 (54.5 %)
Median age (years, range)	8.2 (0.3–17)
Underlying chronic disease	16 (72.7 %)
Median duration of PICU stay prior to infection (days, range)	18.5 (4–615)
Invasive mechanical ventilation	19 (86.3 %)
Urinary catheter	22 (100 %)
Central venous catheter	22 (100 %)
Total parenteral nutrition	5 (22.7 %)
Surgery	9 (45 %)
Malignancy	5 (22.7 %)
Antibiotics with anaerobic activity	22 (100 %)
Prior exposure to antifungal agents	6 (27.2 %)
Prior colonization with *Candida* spp. (≥1 site)	16 (72.7 %)
Non-*C. albicans* candidemia	12 (54.5 %)
Median duration of candidemia (days)	3.5 (1–30)
Central venous catheter removal	18 (81.8 %)
30-day mortality	4 (18.2 %)

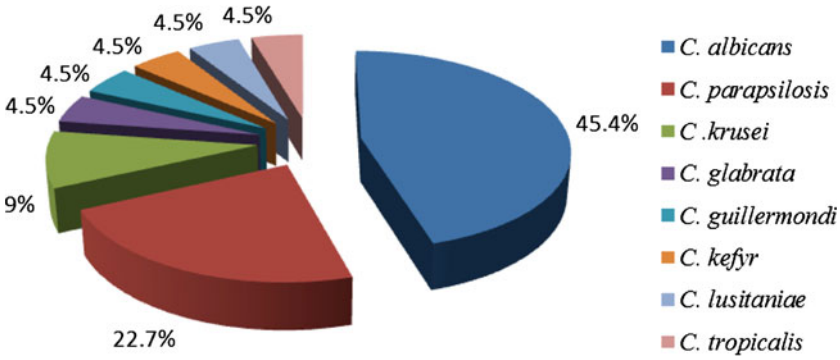

Fig. 1 *Candida* spp. distribution in PICUs in Greece

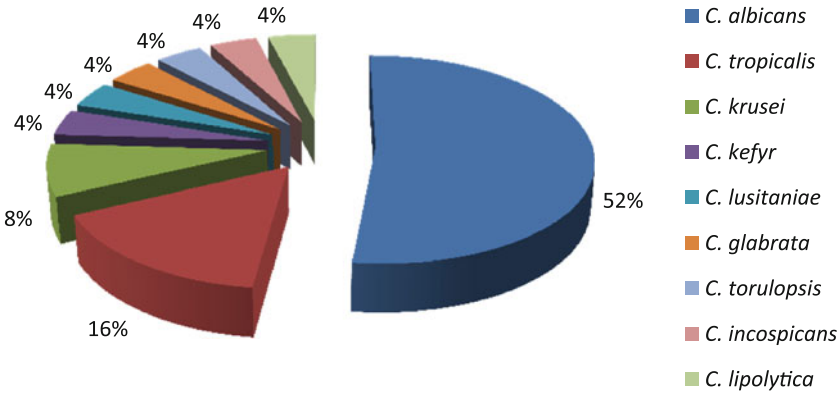

Fig. 2 Distribution of *Candida* spp. recovered from colonized sites

administered in five (22.7 %) patients. Six patients had received antifungal agents prior to the episode, and in 5/6 patients candidemia represented a breakthrough infection. Non-*albicans Candida* spp. was isolated in 54.5 % of cases mostly in patients with previous exposure to antifungal agents, although due to the small number of cases, this did not reach statistical significance. The distribution of *Candida* species that caused candidemia is shown in Fig. 1.

Seventy-three percent of patients with candidemia had *Candida* spp. isolated from at least one sterile or non-sterile body site prior to the episode and eight were colonized at ≥2 sites. Species-specific data regarding colonization were missing in 4 patients, but 10/16 patients were colonized by the same *Candida* species that was isolated from blood cultures. The distribution of *Candida* spp. isolated from colonized sites is shown in Fig. 2. Follow-up blood cultures were taken until negative in all PICUs. Eye examinations and echocardiograms were not routinely performed except in cases of protracted candidemia. The median duration of candidemia was 3.5 (1–30) days, while in three cases with protracted candidemia, disseminated candidiasis and fatal outcomes were recorded. All but two patients received antifungal therapy. Among 20 patients treated with antifungal agents, a LFAMB was the most frequent initial choice of therapy (12 cases), followed by fluconazole (5 cases) and caspofungin (3 cases), while combination therapy was given as a second line therapy to four patients, all of whom had a fatal outcome. Due to the retrospective nature of the study, antifungal susceptibility data were not available from all departments; nevertheless, all *C. albicans* isolates were susceptible to fluconazole.

In most cases CVCs were removed (18 cases) after diagnosis of candidemia. The patients who did not receive treatment were initially managed by removal of pre-existing CVC, and subsequent blood cultures were negative. Thirty-day mortality was 18.2 %. On analysis, outcome did not seem to correlate with the presence of chronic underlying disease, malignancy, *Candida* species or CVC removal.

Discussion

This is the first epidemiological study of candidemia in Greek PICUs nationwide. We found that clinical practices are similar among PICUs although no written protocols exist. Case mix and patient mortality somehow differs. The median incidence of candidemia was 6.4 cases/1,000 admissions. Administration of broad-spectrum antibiotics, mechanical ventilation, presence of CVC and urinary catheters and prior *Candida* colonization are recognized as common risk factors. A lipid formulation of

amphotericin B was the preferred first choice of therapy. The 30-day mortality was 18.2 %.

All PICUs are multi-disciplinary, admitting medical and surgical patients, while oncology and cardiac patients constitute a minority. PICUs A, B and E have more admissions/year and seem to have higher mortality rates, probably due to the fact that they accept sicker patients as they are referral centers in southern (PICUs A and B) and northern (PICU E) Greece. The overall mortality (mean 9.4 %) is somewhat higher than that reported in other centers in the USA and Europe (2.1–6.2 %) [13–15]. To our knowledge, only one recent study focusing on mortality in PICU patients in Greece has been published. In this report, mortality was found to be in accordance with predicted mortality as estimated by the PRISM score (III) and thus proportionate to the disease severity of the population studied [16]. There are no outstanding differences in the clinical practices followed among PICUs throughout the country. The frequency of changing indwelling catheters is similar among PICUs and in general accordance with published guidelines [17, 18].

The latest Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases guidelines, which refer to the management of invasive candidiasis in adults and children, do not have graded recommendations for the management of candidemia in critically ill children specifically, a fact that reflects the lack of evidence about this patient population [19, 20]. Consequently, prophylactic and empirical treatment strategies regarding non-neutropenic critically ill children largely depend on clinical judgment. It is suggested, however, that fungicidal agents such as polyenes and echinocandins would be preferable as a first line treatment option in critically ill patients. The clinical practices reported by all PICUs were similar. There was a discrepancy in policies concerning the duration of treatment in 2/5 PICUs where therapy lasted longer; uncertainties about treatment end points might be accountable. Almost all the patients with candidemia had CVC and urinary catheters in place, received mechanical ventilation and broad-spectrum antibiotics, and in a significant number of them the presence of malignancy, prior surgery and administration of TPN were also recorded. All are well-described risk factors for candidemia [1, 9, 21–23].

Table 3 summarizes the epidemiology of invasive candidiasis as outlined in various previous studies including a number of critically ill children (references). While this table includes the studies including PICU patients, its main limitation is that it also includes neonates and non-PICU pediatric patients as well. In a recent European epidemiologic study of candidemia in children, although relatively more oncology patients were included, the results were similar [25]. In our study, 16/22 (72 %) patients suffered from chronic underlying conditions, only 5 of which were related to malignancy. Associated comorbidities such as long hospitalization, malnutrition and long-term antibiotic therapy may account as risk factors for candidemia.

Previous colonization with *Candida* spp. is a well-established risk factor for candidemia in adults and has been included in scoring systems predicting candidemia [28–30]. In a PICU study the presence of colonization was an independent predictor of candidemia [31]. In accordance with this study, most of our patients were colonized with *Candida* prior to candidemia episode. Although *Candida* colonization data concerning all patients admitted in PICUs were not available, in a recent study conducted in one of the participating PICUs (PICU E), overall patient colonization with *Candida* spp. in $\geq$1 site was 34.2 % (Vogiatzi et al. 30th ESPID, Thessaloniki Greece, 2012, abstract no. 1174). Notably, the lower respiratory system was the most common site of colonization, probably justifying "early" decisions of pre-emptive antifungal therapy in cases of existing bronchial *Candida* colonization.

The median incidence of candidemia nationally is 6.4 cases/1,000 admissions (range 0–14.1 cases/1,000 admissions). A similar Italian study in adults admitted to the ICU reported a median incidence of 10.1 cases/1,000 admissions [6], while in the study of Zaoutis et al. [9], candidemia in PICU patients was 3.5 cases/1,000 admissions during the 1997–2004 period. Candidemia due to non-*albicans Candida* spp. exceeded 50 % of the cases, in accordance with the global trend of increasing frequency of non-*albicans Candida* spp. [8, 12, 27, 32, 33].

Lipid formulations of amphotericin B were prescribed as initial treatment to most of our patients (73.7 %). In one of the largest studies including children, Blyth et al. [8] found that 61.3 % of children received treatment with some form of AMB. In two other studies of pediatric patients beyond the neonatal period, the rates of AMB treatment were similar [11, 26]. Of note, our study referred to exclusively PICU patients, who are a priori sicker than children admitted in other wards, so a small percentage of them were expected to be candidates for fluconazole treatment. The use of echinocandins was limited in treating patients because of non-*albicans Candida* spp. (three patients) during the study period. Two of the patients did not receive any treatment, apart from CVC removal, and had a favorable outcome, probably representing cases of CVC colonization.

In our study, CVC removal did not affect patient outcome; however, the time of CVC removal was not recorded. On the other hand, CVC removal appeared sufficient in two of our cases despite the lack of antifungal treatment. When and whether CVCs need to be removed, in which cases a "wait and see" approach is justifiable and the role of antifungal lock therapy are questions that remain to be answered.

Outcomes were variable among PICUs, and the small number of cases did not allow comparisons. Overall 30-day mortality was not related to *Candida* species in our study, in agreement with the finding of Dutta et al., who in a cohort of

Table 3 Studies on invasive candidiasis including critically ill children

Author [ref]	Time period	*n*	Candidemia incidence	Patient characteristic	First-line treatment	Mortality (%)	*Candida* species (%)					
							Albicans	*Parapsilosis*	*Tropicalis*	*Glabrata*	*Krusei*	Other
Singhi et al. [10]	1993–1996	64	43/1000 admissions	PICU	Oral itraconazole (37/48)	28.1	29.7	0	48.4	1.6	6.3	14.1
Rodriguez-Nunez [24]	1996–1998	116	6.9/1000 admissions	PICU	NR	22	48	18.9	4.3	5.2	0.8	20.6
Abelson et al. [2]	1991–1996	32	1.8/1000 admissions	Children[a]	NR	52	60	6	9	9	<3	16
	1997–2001	65	6.4/1000 admissions	Children[a]	NR	41	48	25	11	2	3	11
Zaoutis et al. [9]	1997–2004	101	3.6/1000 admissions	PICU	NR	44	NR	NR	NR	NR	NR	NR
Celebi et al. [11]	1997–2005	102	5.1/1000 admissions	Children/20 PICU, 22 NICU	Amphotericin B 75.2 %	25.5	39.2	21.6	15.7	6.9	4.9	11.7
Tortorano et al. [6]	2006–2008	238	6.31/1000 admissions	ICU-multicenter study[b]	Fluconazole 63 %	46.2	60	13	8	13.4	1.8	3.2
Tragiannidis et al. [25]	1998–2008	35	0.47/1000 admissions	Children[a]	Fluconazole (7/23)	11.4	46	17	5.7	14	0	17.1
Dotis et al. [12]	1997–2009	406	2.5/1000 admissions	Children/164 ICU	Polyenes	13.8	49	24	6	4	2	1
Dutta and Palazzi [26]	2000–2009	226	0.06-0.3/1000 inpatient days	Children[a]	Amphotericin B	9.3	44.2	23.9	14.8	6.5		
Steinbach et al. [27]	2007–2011	196	NR	Children[a]	Amphotericin B 30 %	19	44	22	NR	11	3	22
Present study	2005–2009	22	6.4 cases/1000 admissions	PICU	Lipid amphotericin B 60 %	18.2	45.4	22.7	4.5	4.5	9	13.9

NR not reported

[a] PICU patients included

[b] Mostly adult ICU patients and PICU patients included

226 children did not find any difference in mortality between *C. albicans* and non-*albicans Candida* spp. candidemia [26]. Others, however, show conflicting results, probably depending on the contribution of particular non-*albicans Candida* spp. included in the studies [10, 12, 27, 34].

There are two limitations in our study. First, the small number of cases that occurred in each PICU as well as the pooled sample during the 5-year study period makes statistical analysis difficult. Second, due to the retrospective nature of the study, severity of illness was not documented, as not all PICUs used the same scoring system. Nevertheless, our study outlines the epidemiology and management of candidemia in a very distinct population not well studied previously (children in the PICU) on a national level, which is reported for the first time. We hope to offer an insight into existing candidemia data and practices nationwide and provide a background for future prospective studies.

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Conflicts of interest The authors have no conflict of interest.

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