mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Candidaemia in a paediatric centre and importance of central venous catheter removal

Eda Karadag-Oncel,[1] Ates Kara,[1] Yasemin Ozsurekci,[1] Sevtap Arikan-Akdagli,[2] Ali Bulent Cengiz,[1] Mehmet Ceyhan,[1] Deniz Gur,[2] Melda Celik[1] and Aslinur Ozkaya-Parlakay[1]

[1]*Pediatric Infectious Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey and* [2]*Department of Medical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey*

Summary

The aim of this study is to identify differences in distribution of *Candida species*, resistance to antifungals and clinical outcome, as well as the identification of potential risk factors associated with candidaemia in children. We conducted a retrospective analysis in children ≤18 years with blood culture proven candidaemia identified between 2004 and 2012. Patients were divided into two groups (Group 1, <3 months, $n = 51$; Group 2, ≥3 months, $n = 197$) to identify any potential difference between the neonatal and early infantile periods in terms of risk factors and distribution of *Candida* species. A total of 248 distinct episodes of candidaemia were identified over the study period. The most frequently isolated *Candida* species were *C. albicans* (53.2%), followed by *C. parapsilosis* (26.2%), *C. tropicalis* (8.1%). Of the 248 episodes, 71 episodes (28.6%) resulted in death within 30 days from the onset of candidaemia. In Group 1, failure of central venous catheter (CVC) removal was found to be associated with a 20.5-fold increase in mortality [95% CI (3.9, 106.5); $P < 0.001$], compared to a 5.9-fold increased risk with hypoalbuminaemia [95% CI (1.03, 34.1); $P = 0.046$]. For Group 2, the increased risk was 23-fold for failure of CVC removal [95% CI (7.48, 70.77); $P < 0.001$], 7.4-fold for mechanical ventilation [95% CI (2.64, 21.08); $P < 0.001$], 4.4-fold for hypoalbuminaemia [95% CI (1.56, 12.56); $P = 0.005$], 3.1-fold for neutropaenia [95% CI (1.31, 7.69); $P = 0.010$] and 2.2-fold for male gender [95% CI (1.02, 4.71); $P = 0.043$]. Therapeutic choices should be guided by sound knowledge of local epidemiological trends in candidaemia. Removal of CVC significantly reduces mortality and is an essential step in the management of candidaemia.

Key words: Candidaemia, children, mortality, risk factors, central venous catheter.

Introduction

Recent years have witnessed an increase in the incidence of candidaemia, which may be attributed to several factors that increase the risk of infection, such as more invasive surgical procedures, widespread use of broad-spectrum antibiotics and longer durations of hospital stay. The few population-based studies that have focused on children have demonstrated a similar trend in younger patients, mainly attributable to high-risk groups such as premature infants requiring intensive care and immunocompromised children (e.g. those with malignancies and a history of transplantation requiring immunosuppressive therapy).[1,2]

Correspondence: E. Karadag-Oncel, MD, Pediatric Infectious Diseases Unit, Hacettepe University Faculty of Medicine, Sıhhiye, 06100 Ankara, Turkey.
Tel.: +90 312 3051166. Fax: +90 312 3108241.
E-mail: dredakaradag@gmail.com

This trial was presented in ICAAC 2014 as a poster presentation.The trial was registered to ClinicalTrials.gov (http://www.clinicaltrials.gov) under identifier NCT02088476.

Submitted for publication 30 September 2014
Revised 30 November 2014
Accepted for publication 11 December 2014

doi:10.1111/myc.12288

Childhood candidaemia is associated with significant morbidity, with reported mortality rates of 13%–30% in general paediatric populations, and 43%–54% in infants.[3–5] Candidaemia, which is often difficult to diagnose, is frequently associated with signs and symptoms of the sepsis syndrome. Any delay in initiation of appropriate antifungal treatment, including inappropriate initial therapy, has been shown to be associated with increased mortality.[6,7] Different *Candida* species are associated with varying degrees of disease severity, which underlines the importance of institution-specific surveillance studies for better understanding age distribution and risk factors facilitating candidaemia.[5] Furthermore, susceptibility patterns of different *Candida* species may show great variability, which in turn has major implications on the initial choice of empirical antifungal therapy. Initiation of appropriate therapy in different age and risk groups has been shown to have a significant impact on outcome.[8]

The main aim of this study was to identify the distribution of *Candida* species, as well as to determine the outcome of candidaemia episodes and associated risk factors.

Materials and methods

Patient selection and study design

This study was approved by the Institutional Review Board of the Hacettepe University Faculty of Medicine with a waiver of informed consent for data collection. The trial was registered with ClinicalTrials.gov (http://clinicaltrials.gov) under identifier NCT02088476. We conducted a retrospective cohort study by reviewing the medical records of children who were admitted to Hacettepe University Ihsan Dogramaci Children's Hospital, a tertiary care, 269-bed paediatric referral hospital. The electronic records of the microbiology laboratory were screened and patients with blood cultures positive for Candida between January 2004 and December 2012 were identified. Among these years, 42.046 patients were hospitalised. Medical records of patients with confirmed candidaemia were reviewed and information regarding demographics (age and gender), underlying diagnoses and history of surgery/transplantation were recorded. Febrile neutropaenic patients and premature infants who were using empirical or prophylactic antifungal agents were excluded from the analysis. The presence or absence of potential risk factors for candidaemia such as an indwelling central venous catheter (CVC), use of antibiotics (administered for >72 h), use of antifungals (administered for >24 h), immunosuppressants, total parenteral nutrition, admission to the intensive care unit (ICU), mechanical ventilation, neutropaenia, hypoalbuminaemia and hypophosphataemia was also noted for each patient. Relevant details regarding each candidaemia episode, such as the number of the days the CVC was retained, the choice and duration of antifungal therapy, susceptibility pattern of isolated *Candida* species, and outcome of candidaemia, were also recorded. In patients with recurrent candidaemia, each episode was evaluated separately for risk factors and outcome.

Case definitions

Candidaemia is defined as the presence of growth of any *Candida* species in at least one blood culture obtained by either peripheral venipuncture or through an indwelling CVC. In the event that the same isolate is detected in a peripheral blood culture and catheter-drawn blood culture obtained at least 2 h apart, candidaemia is considered a CVC related bloodstream infection.[9] Recurrent candidaemia is defined as the occurrence of two or more episodes of candidaemia at least 4 weeks apart, with apparent clinical and microbiological resolution in between episodes, regardless of whether the same *Candida* species is isolated.[10] Positive blood cultures with candidaemia obtained 2 weeks after at least two negative cultures were considered a new episode. Death which ensues within 30 days of the onset of candidaemia with no apparent alternative cause is recognised as a candidaemia-attributable mortality. Absolute neutropaenia is defined as the presence of a neutrophil count of $<0.5 \times 10^9$ l^{-1}, whereas thrombocytopaenia is defined as a thrombocyte count of $<150 \times 10^9$ l^{-1}. Hypoalbuminaemia is defined as the presence of a serum albumin concentration of <2.5 g dl^{-1} in infants younger than 7 months of age and <3.4 g dl^{-1} in older children. Patients with a serum phosphate level of <2.5 mg dl^{-1} are considered to have hypophosphataemia.

Microbiological methods

BACTEC Blood Culture System (Becton Dickinson Diagnostic Instrument Systems, Towson, MD, USA) was used in our hospital in routine practice during the study period. Blood specimens cultured in BACTEC media (Becton, Dickinson & Company, Clare, Ireland) were incubated in the automated system for 7 days. In presence of a growth signal in the cultivated bottle, Gram stained samples were promptly prepared for

microscopic examination and concomitant subcultures were performed onto blood, chocolate and EMB agar plates according to the standard procedures. When a yeast growth is detected on cultivated media, the isolate was identified to the species level by standard mycological methods, including colony morphology, microscopic appearance on cornmeal tween 80 agar, and assimilation profile determined by ID 32C (Bio Merieux SA, Marcy-L'Etoile, France).[11] Blind subcultures were also performed from the cultivated bottles in case of no growth signal on day 7.

Statistical analyses

All statistical analyses were performed using the SPSS package program for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Values for numerical variables were provided as mean ± standard deviation or median [minimum–maximum] depending on normality of distribution. Categorical variables were provided as absolute values or percentages, the comparisons of which were made using the chi-square test. Two-way comparisons for numerical variables were made using the Mann–Whitney *U* test, whereas the Kruskal–Wallis test was used for comparison involving more than two groups. Factors associated with an increased mortality risk were identified using logistic regression analysis. A *P*-value of <0.05 was considered indicative of statistical significance.

Results

A total of 236 patients (58.8% male) were identified to have developed 248 episodes of candidaemia during the 9-year study period. The median age at diagnosis was 13.9 months (range: 3 days–222 months). A review of age distribution during episodes of candidaemia revealed that 26 patients (10.4%) were <1 month of age, 25 patients (10.1%) were aged between 1 and 3 months, 64 patients (25.8%) were 3 and 12 months old and 133 patients (46.4%) were older than 1 year of age. All patients had at least one recognised potential risk factor for developing candidaemia. The most commonly encountered underlying conditions and potential risk factors were summarised in Table 1.

The median length of hospital stay before a blood culture identified candidaemia was 21.5 (1–217) days, while the median duration of total hospital stay was 51 (3–298) days. Furthermore, neutropaenia was present in 33 episodes (13.3%), thrombocytopaenia in 117 episodes (47.1%), hypoalbuminaemia in 30 episodes (12.1%) and hypophosphataemia in 30 episodes (12.1%). Echocardiographic examination for endovascular candidiasis, which was performed during 93 episodes (37.5%) of candidaemia revealed the presence of a vegetation in 12 instances (12.9%). Findings on ophthalmological evaluation performed during three episodes (1.2%) of candidaemia were unremarkable.

In 153 episodes of candidaemia (61.7%), *Candida* species were isolated in blood cultures obtained both peripherally and central catheter, while in the remaining 95 episodes (38.3%) only peripheral blood cultures yielded growth. A positive blood culture prompted removal of a CVC in 120 episodes (55.1%), but not in 98 episodes (44.9%). *C. albicans* was isolated in 132 episodes (53.2%), while in 116 episodes (46.8%) a non-albicans strain was identified. The distribution of isolated Candida strain according to age group is depicted in Table 2.

Patients were divided into two groups (Group 1, <3 months of age, $n = 51$; Group 2, ≥3 months, $n = 197$) to identify any potential difference between the neonatal-early infantile periods and late infantile-childhood periods in terms of risk factors and distribution of *Candida* spp. In both groups, comparison of demographic and laboratory findings revealed *C. albicans* to be associated with preponderance of males (Group 1, $P = 0.029$; Group 2, $P = 0.015$), higher white cell count (Group 1, $P = 0.035$; Group 2 $P = 0.007$) and higher absolute neutrophil count (Group 1, $P = 0.034$; Group 2, $P = 0.001$) when compared to non-albicans strains.

Risk factors and mortality rates were compared in both groups based on *Candida* species. In Group 1, patients with non-albicans Candida infections had statistically longer durations of CVC insertion ($P = 0.049$), while a history of surgery and admission to surgical ward were also observed more frequently ($P = 0.005$ and <0.001, respectively). In the same group, a history of admission to the ICU patients was observed more frequently in patients with *C. albicans* infection ($P = 0.001$). In Group 2, a history of immunosuppressive treatment was observed more frequently ($P = 0.002$) in patients with non-albicans infections, also had significantly longer durations of mechanical ventilation ($P = 0.034$).

In terms of antifungal treatment, fluconazole was used in 120 candidaemia episodes (48.4%), followed by amphotericin B (deoxycholate or lipid formulation) in 44 episodes (17.7%) and caspofungin in 16 episodes (6.5%). In 59 episodes (23.7%), sequential antifungal treatment was administered. Nine cases (3.6%) with

Table 1 Underlying conditions and potential risk factors in children with candidaemia

	<3 months (n = 51)	≥3 months (n = 197)	Total (n = 248, %)
Underlying conditions			
Gastrointestinal system disorders	21	44	65 (26.2)
Solid tumours	2	55	57 (22.9)
Haematological disorders	–	20	20 (8)
Congenital heart disorders	4	15	19 (7.6)
Neurometabolic disorders	3	14	17 (7.2)
Prematurity	12	–	12 (4.8)
Syndromic disorders	3	9	12 (4.8)
Congenital immune deficiencies	–	10	10 (4)
Burns	–	5	5 (2)
Other varying conditions	6	25	31 (12.5)
Potential risk factors			
Use of broad-spectrum antibiotics	51	193	244 (98.4)
Presence of a CVC	48	170	218 (87.9)
History of prior hospitalisation	17	178	195 (78.6)
History of MV	36	75	111 (44.8)
History of TPN	42	43	85 (34.3)
History of admission for ICU	30	53	83 (33.5)
Receiving immunosuppressive treatment	1	78	79 (31.9)
Concomitant bacteraemia	17	58	75 (30.2)
History of surgery	21	52	73 (29.4)
Prematurity	12	–	12 (4.8)

CVC, central venous catheter; MV, mechanical ventilation; TPN, total parenteral nutrition; ICU, intensive care unit.

Table 2 Distribution of isolated *Candida* strains according to age group.

Isolated strain	<1 months (n = 26)	1–3 months (n = 25)	3–12 months (n = 64)	>12 months (n = 133)	Total (n = 248)
C. albicans, *n* (%)	16 (61.5)	13 (52)	36 (56.2)	67 (50.4)	132 (53.2)
Non-albicans *Candida*, *n* (%)	10 (38.5)	12 (48)	28 (43.8)	66 (49.6)	116 (46.8)
C. parapsilosis	6 (23.1)	6 (24)	19 (29.7)	34 (25.6)	65 (26.2)
C. tropicalis	2 (7.7)	4 (16)	2 (3.1)	12 (9)	20 (8.1)
C. sake	1 (3.8)	1 (4)	3 (4.7)	6 (4.5)	11 (4.4)
C. famata	–	–	–	7 (5.3)	7 (2.8)
C. kefyr	1 (3.8)	–	2 (3.1)	2 (1.5)	5 (2)
C. lusitaniae	–	–	1 (1.6)	2 (1.5)	3 (1.2)
C. glabrata	–	–	–	1 (0.8)	1 (0.4)
C. guilermendii	–	–	–	1 (0.8)	1 (0.4)
C. lipolytica	–	1 (4)	–	–	1 (0.4)
C. pelliculosa	–	–	–	1 (0.8)	1 (0.4)
Unidentified	–	–	1 (1.6)	–	1 (0.4)

positive cultures did not receive antifungal treatment since culture results were only obtained after their death. Median duration of antifungal treatment was 18 days (1–100), and duration of antifungal therapy was shorter in patients who died and this difference was statistically significant (16.22 ± 14.67 vs. 20.89 ± 11.18, $P = 0.001$). In 35 episodes (14.1%) patients had a history of prior fluconazole use before positive culture. In *C. albicans* group the history of fluconazole use was 10.9% (13/119) and in non-albicans group the history of fluconazole use was 23.4% (22/94), this difference was statistically insignificant ($P = 0.061$) and have no correlation. Mortality rate was determined higher in patients who were used fluconazole empirically (42.9% vs. 26.3%, $P = 0.045$).

Antifungal susceptibility was evaluated in almost all patients (98.7%); fluconazole susceptibility in 245 episodes (98.7%), voriconazole susceptibility in 170 episodes (68.5%), caspofungin susceptibility in 40

episodes (16.1%) and amphotericin B susceptibility in 5 episodes (2%). Fluconazole resistance was detected in 14 episodes, followed by voriconazole resistance in four episodes and caspofungin resistance in two episodes. None of the isolated strains tested for amphotericin B susceptibility were resistant to the antifungal. A summary of susceptibility testing and antifungal resistant Candida strains is provided in Table 3.

Overall, 71 patients (28.6%) who developed candidaemia died within 30 days from the detection of *Candida* species. The mortality rate for *C. albicans* was 34.1% compared to a rate of 22.4% with non-albicans species, a statistically significant difference ($P = 0.042$). Break down of mortality rates based on *Candida* species is as follows: *C. albicans* 34.1%, *C. parapsilosis* 23%, *C. tropicalis* 40%, *C. sake* 10% and other *Candida* species 10%. Comparison of demographic and laboratory characteristics of patients who died and those who survived showed patients in Group 1 who died to have lower thrombocyte counts ($P = 0.022$) and shorter durations of antifungal treatment ($P = 0.037$). In Group 2, patients who died were older ($P = 0.010$), with a higher preponderance of males ($P = 0.016$). Neutropaenia and thrombocytopaenia were also observed more frequently in those who died ($P = 0.001$), with significantly lower thrombocyte counts ($P = 0.02$). Patients who died also had more significant hypoalbuminaemia and hypophosphataemia ($P = 0.003$ and $P = 0.023$, respectively).

Risk factors of patients who died and those who survived were compared in each group. In Group 1, history of mechanical ventilation and admission to the ICU was observed more frequently in patients who died ($P = 0.003$ and 0.047, respectively), whereas those who survived had CVC inserted for longer periods ($P = 0.002$). Rate of CVC removal was higher in patients who survived ($P < 0.001$). On the other hand, patients who died in Group 2 had a more frequent history of hospital admission, mechanical ventilation and admission to the ICU ($P = 0.022$, <0.001 and <0.001, respectively). Number of antibiotics used and duration of stay prior to growth on culture were both significantly higher in patients who died ($P < 0.001$ and equal to 0.004, respectively), whereas the rate of CVC removal after a positive culture was higher in those who survived ($P < 0.001$). Culture positivity according to peripheral and/or CVC, distribution of Candida isolates and survival rates was showed in Fig. 1.

Logistic regression analysis was performed for risk factors that showed a statistically significant difference between the groups (Table 4). In Group 1, failure of CVC removal was found to be associated with a 20.5-fold increase in mortality [95% CI (3.9, 106.5); $P < 0.001$], compared to a 5.9-fold increased risk with hypoalbuminaemia [95% CI (1.03, 34.1); $P = 0.046$]. For Group 2, the increased risk was 23-fold for failure of CVC removal [95% CI (7.48, 70.77); $P < 0.001$], 7.4-fold for mechanical ventilation [95% CI (2.64, 21.08); $P < 0.001$], 4.4-fold for hypoalbuminaemia [95% CI (1.56, 12.56); $P = 0.005$], 3.1-fold for neutropaenia [95% CI (1.31, 7.69); $P = 0.010$] and

Table 3 Susceptibility patterns of isolated resistant Candida strains to four antifungal drugs.

Isolated strain	Fluconazole	Voriconazole	Caspofungin	Amphotericin B
C. albicans	R	R	–	–
C. albicans	R	–	–	–
C. tropicalis[1]	R	S	–	–
C. tropicalis[1]	R	S	–	–
C. tropicalis[1]	R	S	S	–
C. tropicalis	R	S	–	–
C. tropicalis	R	S	S	–
C. parapsilosis[1]	R	–	S	–
C. parapsilosis	S	–	R	–
C. parapsilosis	S	S	R	–
C. famata[1]	R	–	–	–
C. famata	R	–	–	–
C. sake[1]	–	R	–	–
C. sake	R	R	–	–
C. glabrata	R	R	–	–
C. kefyr[1]	R	S	S	S
C. lipolytica[1]	R	S	S	–

R, resistant; S, sensitive.

[1]History of fluconazole use prior to growth.

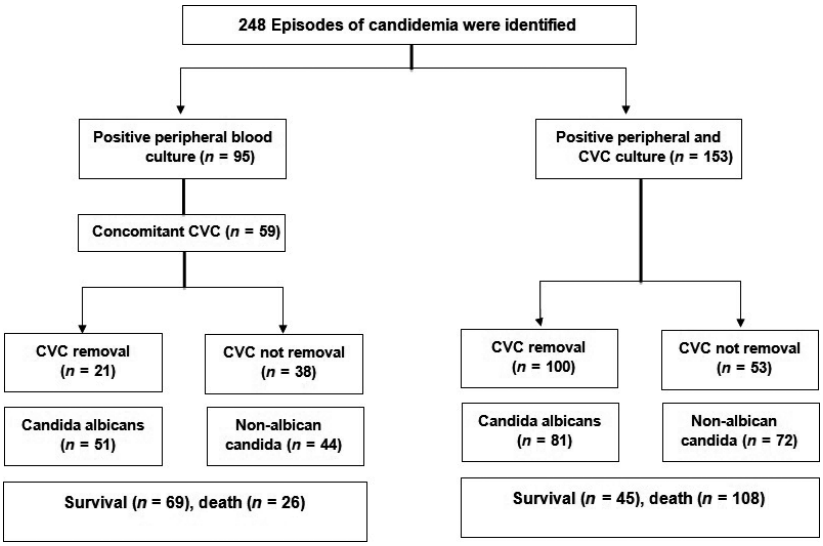

Figure 1 Culture positivity according to peripheral and/or central venous catheter, distribution of Candida isolates and survival rates.

2.2-fold for male gender [95% CI (1.02, 4.71); $P = 0.043$].

Discussion

This study was an analysis of the demographic and clinical characteristics of a cohort of patients presenting to a single institution where an ongoing blood culture surveillance program identified 248 episodes of candidaemia over a period of 9 years (2004–2012). The distribution of Candida strains isolated in this study was consistent with previous studies on paediatric and adult populations,[12,13] *C. albicans* being the most commonly identified species. While previously reported frequencies of *C. albicans* ranged from 50% to 70%,[3,8,14] the detection rate in our study was 53.2%. *C. parapsilosis* was the most frequently isolated non-albicans Candida strain in children, compared to *C. glabrata* in adult patients.[15,16] In several studies from different countries, *C. parapsilosis* was the second most frequently isolated strain in adults; reported frequencies are 15.5% from North America, 16.3% from Europe, 17% from the Asia-Pacific region, 18.8% from Australia and 23.4% from Latin America, the latter showing an increase from 14% in the last decade.[17–19] With a frequency of 26.2%, *C. parapsilosis* was the second most commonly encountered non-albicans strain in our study as well, followed in decreasing frequency by *C. tropicalis* (8.1%), *C. sake* (4.4%) and *C. famata* (2.8%). *C. glabrata* was isolated in only one patient (0.8%) who was in the >12 month old group. *C. glabrata* is known to occur more frequently in adults and older children, whereas infections involving children have rarely been reported.[5,15,16]

Table 4 Causes of increased mortality risk according to age.

Risk factor	OR	95% CI	*P*-value
<3 months			
Hypoalbuminaemia	5.93	1.03–34.1	0.046
Removal of CVC	20.57	3.9–106.5	<0.001
>3 months			
Male gender	2.2	1.02–4.71	0.043
Neutropaenia	3.1	1.31–7.69	0.010
Hypoalbuminaemia	4.43	1.56–12.56	0.005
History of MV	7.4	2.64–21.08	<0.001
Removal of CVC	23	7.48–70.77	<0.001

CVC, central venous catheter; MV, mechanical ventilation; OR, odds ratio; CI, confidence interval.

Identifying the *Candida* strain that is responsible for any particular invasive Candida infection is of great importance in terms of guiding treatment, since antifungal susceptibility may be predicted based on isolated strain. Varying rates of fluconazole resistance have been described for *C. albicans*. While no resistance has been described from some centers,[20] in a study from Northern India,[21] a resistance rate of 18.2% was reported compared to rate of 1.2% in another study from the USA.[22] The rate of fluconazole resistance observed with *C. albicans* in our study was 1.5%, with none of the patients having a history of previous use of fluconazole.

Although reported fluconazole resistance rates for *C. parapsilosis* vary slightly from centre to centre, described

rates are generally within the region of 4%.[20,23] *C. parapsilosis* has been shown to exhibit high Minimum inhibitory concentration (MIC) values with the echinocandins, which is reflected in a recent report on decreased clinical echinocandin susceptibility.[24] Of the 65 isolated strains of *C. parapsilosis*, three showed resistance to antifungals; one strain exhibited resistance to fluconazole (1.5%), while the two other isolates demonstrated echinocandin resistance (3%). Interestingly, the fluconazole resistance rate observed in our study for *C. tropicalis* was 25%, a finding that is inconsistent with other studies. Previously reported resistance rates for this particular non-albicans *Candida* strain are between 2.2% and 4.9%, which leads to the belief that the high rate observed in our study could be linked to previous fluconazole use.[20,23] *C. glabrata* isolates show decreased susceptibility to azole group antifungals which has been reported to be associated with prior fluconazole use.[24] A *C. glabrata* strain which was resistant to the azoles was isolated in only one episode of candidaemia in our study from a patient who did not have a history of previous fluconazole use.

Comparison of demographics, laboratory findings and risk factors of albicans and non-albicans Candida species yielded mixed results. In a study by Dutta *et al.* [25] comparing albicans and non-albicans infections on paediatric patients, no significant difference was observed in terms of demographics, underlying disorders, clinical features and risk factors. In another study from Turkey, *C. albicans* infections were reported to occur in younger patients while also being associated with presence of a urinary catheter, longer durations of hospital stay prior to candidaemia episode as well as longer overall durations of hospital stay. On the other hand, neutropaenia and longer durations of hospital stay were observed more frequently in patients with non-albicans infections. Investigators also reported on a higher mortality rate and incidence of disseminated candidiasis in association with *C. albicans*.[26]

Taking into consideration the potential differences between patients of different ages in terms of Candida strain and associated risk factors, participants in the current study were divided into two groups; early infancy (<3 months) and older children (≥3 months). Comparison of demographics and laboratory findings with regard to *Candida* species (albicans and non-albicans) revealed *C. albicans* infections to occur more frequently in males (<3 months, $P = 0.029$; ≥3 months, $P = 0.015$), with affected patients having significantly higher total white blood cell counts (<3 months, $P = 0.035$; ≥3 months, $P = 0.007$) and absolute neutrophil counts (<3 months, $P = 0.034$; ≥3 months, $P = 0.001$) compared to those with infections due to non-albicans *Candida* species.

With regard to risk factors in the early infancy group (<3 months), *C. albicans i*nfections were found to be significantly associated with a history of admission to the ICU ($P = 0.001$), whereas in patients with non-albicans Candida infections a positive history of surgery ($P = 0.005$) or admission to a surgical ward ($P < 0.001$) was observed more frequently with patients also having significantly longer durations of follow-up with CVC ($P = 0.049$). In the older group (≥3 months) patients with non-albicans infections were found to have significantly longer durations on mechanical ventilation ($P = 0.034$) and on immunosuppressive treatment ($P = 0.002$). Candidaemia-related mortality rates in children range between 13% and 40%, with higher rates reported in infants (43%–54%) and adults (60%).[3–5] Mortality rates due to Candida infections may vary with patient age and the species responsible. Previous studies have shown invasive Candida infections to have higher mortality rates in newborns compared to older infants, while also proving *C. albicans* to be more aggressive than *C. parapsilosis*.[4,27]

The *C. albicans*-related mortality in our study was 34.1% compared to a mortality rate of 23% for *C. parapsilosis*. These findings differ from those of a study by Dutta *et al.* [25] on children, where no significant difference was observed between strains in terms of 30-day mortality. Overall mortality rate in our study was 28.6%, which is consistent with the pertinent literature. Comparison of mortality rates based on *Candida* species revealed that *C. albicans* to be associated with significantly higher mortality than non-albicans species ($P = 0.042$).

To date, several studies have addressed risk factors associated with Candida-related mortality. In one study, admission to a paediatric ICU and the presence of an arterial catheter during an episode of invasive candidiasis were found to be linked with increased mortality.[27] In another prospective study involving newborns, children and adults, spanning 3 years (August 2001–July 2004), multivariate analysis on older paediatric participants revealed mechanical ventilation on day 1 and admission to an ICU to be independent risk factors for mortality.[19] In the same study, no independent predictors of mortality were identified for newborns. In our study, failure to remove an indwelling CVC during an episode of candidaemia was established as an important risk factor for mortality in both groups. The increased risk was 20.5-fold in the

<3 months group and 23-fold in the ≥3 months group. The current guideline of the Infectious Diseases Society of America recommends removal of a CVC in a patient with established candidaemia.[28] In contrast, early CVC removal was not found to be of any clinical benefit in a study on 842 adult patients with candidaemia.[29] Based on our study findings, we endorse early removal of CVC in children. Among the other factors evaluated, hypoalbuminaemia was also established as an important risk factor for mortality (5.9 fold in <3 months group and 4.4-fold in ≥3 months group). Zhang *et al.* [30] observed a 2.4-fold increased mortality risk in patients with hypoproteinaemia.

This study included an evaluation of risk factors, causative *Candida* species and their antifungal susceptibilities, and clinical outcome of candidaemia episodes in children occurring between 2004 and 2012. This study has two limitations. First, its retrospective nature limits the ability of drawing specific conclusions and second antifungal susceptibility test was not available for all Candida isolates.

Conclusions

In our study, catheter-related candidaemia was observed in 61.7% of patients, and this high rate of catheter-related infections highlights the importance of catheter care and early catheter removal. The mortality rate in children with candidaemia was 28.6%; failure of catheter removal, male gender, neutropaenia, hypoalbuminaemia and history of mechanical ventilation are risk factors associated with increased mortality. Candida infection should be considered in the differential diagnosis in a patient with known risk factors who develops signs of sepsis, with early initiation of empirical antifungal treatment.

Acknowledgement

We thank Sevilay Karahan, PhD (Department of Biostatistics, Hacettepe University) for her help in the statistical analysis.

Conflicts of interest

We have no conflicts of interest related to this study.

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