A 7-year study of the distribution of nosocomial candidemia in children with cancer

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Candidemia is an important cause of morbidity and mortality in cancer patients. The incidence of candidemia has been reported to have shifted toward non-albicans species. The aim of this study was to determine the distribution of *Candida* species resulting in bloodstream infections or catheter-related blood stream infections (CRBSIs) in pediatric hematology-oncology (PHO) patients over a 7-year-period. Medical and computerized microbiology laboratory records of all positive blood fungal cultures during the study period were analyzed retrospectively. The ratio of non-albicans *Candida* species (81.4%) was nearly four times higher than that of *C. albicans* candidemia (18.5%). Overall, *C. parapsilosis* caused the majority (61.4%) of candidemia episodes, followed by *C. tropicalis* (14.8%), *C. famata* (2.9%), *C. ciferrii* (1.4%) and *C. glabrata* (0.7%). The rate of CRBSIs was significantly higher in *C. parapsilosis* candidemia. The overall rate of 30-day mortality in 135 candidemia episodes was 4.44%. Nearly half of the *C. parapsilosis* candidemia was associated with CRBSIs, suggesting its importance in PHO, in which several types of central venous catheters have been used.

Key words: candidemia, bloodstream infection, children.

Invasive fungal infections (IFIs) are important causes of morbidity and mortality in cancer patients with prolonged neutropenia as a result of high-dose intensive chemotherapy or hematopoietic stem cell transplantation (HSTC)[1]. The incidence of candidemia in pediatric patients mimics the pattern of increase found in adults, but it is accelerating more quickly[2]. *Candida* species are among the leading causes of nosocomial bloodstream infections (BSIs), being the fourth most common such pathogen in the United States and the sixth most common in Europe[3-6], as well as the most commonly isolated fungus species[4]. Moreover, the distribution of *Candida* species has changed during the last decade. Non-albicans *Candida* species have increased in incidence as the causative agents of IFI[7-10]. This trend has also been observed in hematology-oncology patients, with the epidemiology reported to have shifted toward non-albicans species[11], most probably due to the widespread use of fluconazole prophylaxis[12].

The main mechanisms for the increase of fungal infections in patients with cancer are impaired integrity of host defense mechanisms and potential exposure to pathogenic microorganisms in the host's environment[13]. Impaired mucosal barriers due to chemotherapeutic drugs, such as in the case of the buccal mucosa, have been reported to be associated with *Candida* BSIs[14]. In addition to these factors, the use of wide-spectrum antibiotics, treatment with corticosteroids and cytostatic substances, and invasive surgical procedures often predispose children to development of fungal infections[15]. One of the additional risk factors for candidemia, especially for *C. parapsilosis*, has been reported to be central venous catheterization (CVC), which has been widely used in pediatric cancer

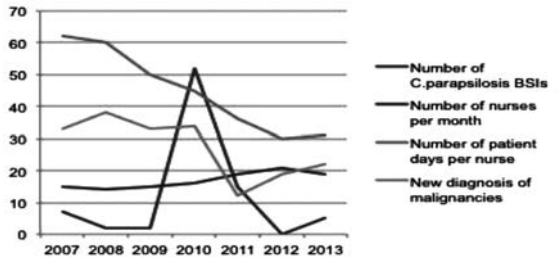

Fig. 1. Number of patient days per nurse, number of nurses per month, new diagnosis of malignancies and number of *C. parapsilosis* BSIs, 2007–2013.

patients[16-18].

The aim of this study was to determine the distribution of *Candida* species among pathogens resulting in BSIs and catheter-related bloodstream infections (CRBSIs) in pediatric hematology-oncology (PHO) patients over a 7-year period. The current study represents one of the largest cohorts of PHO patients from a single institution with *Candida* infections.

Material and Methods

A retrospective–cohort study design was used to evaluate the presence of candidemia and the distribution of *Candida* species in febrile neutropenic patients who were hospitalized at the PHO and infectious disease units of Dr. Behçet Uz Children's Hospital (İzmir) for treatment of malignancies from December 2007 to December 2013. Computerized microbiology laboratory records of all positive fungal cultures during the study period were cross-matched with medical records for PHO patients to distinguish infection from colonization. In accordance with our infection control procedures, blood cultures, one from the peripheral veins and one through the ports, were taken in each patient with fever. If multiple consecutive positive cultures with the same *Candida* species were obtained, it was considered to be an isolation, and a new attack occurring 14 days after negative blood cultures were taken from the CVC and peripheral veins was considered to be a new isolation.

Episodes of candidemia were detected using standard aerobic and anaerobic blood culture media in automated blood culture systems (BacT/Alert, bioMérieux, France). Yeast isolates that were detected by routine Gram staining of positive blood culture bottles were subcultured on Saburoud dextrose agar and potato dextrose agar plates. Isolates from subcultures were identified by germ tube formation testing, corn meal agar evaluation and a commercial carbohydrate assimilation test (API 20 C AUX, bioMérieux, France).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA), version 16.0. Data are presented as numbers (percentages), mean ± standard deviation (SD), or median (range), as appropriate. Categorical variables were compared using a chi-square test or Fisher's exact test.

Results

Distribution of etiologic agents

Candidemia was observed as 135 episodes in 114 patients during the study period of 2007 to 2013. The ratio of non-albicans *Candida* species (81.4%) was nearly four times higher than that of *C. albicans* candidemia (18.5%). Overall, *C. parapsilosis* caused the majority (61.4%) of candidemia episodes, followed by *C. tropicalis* (14.8%), *C. famata* (2.9%), *C. ciferrii* (1.4%) and *C. glabrata* (0.7%) (Table I).

There was a marked increase in *C. parapsilosis* candidemia cases in 2010; this number decreased after 2011. The number of patient

Table I. Distribution of *Candida* Species in Nosocomial BSIs in Pediatric Cancer Patients

	2007	2008	2009	2010	2011	2012	2013	Number (percentage)
C. albicans	1	1	5	7	10	1	-	25 (18.5%)
C. parapsilosis	7	2	2	52	15	-	5	83 (61.4%)
C.tropicalis	-	5	-	-	10	5	-	20 (14.8%)
C. famata	2	1	1	-	-	-	-	4 (2.9%)
C. glabrata	-	-	-	-	-	1	-	1 (0.7%)
C. ciferrii	1	-	-	-	-	-	1	2 (1.4%)
Total	11	9	8	59	35	7	6	135

days per nurse displayed a significant decrease and the number of nurses per month a significant increase from 2007 to 2013, giving an indirect indication of better nurse staffing at the hospital over time (Fig. 1). In the PHO department, Taurolidine-citrate lock solution (TauroLock) had been used during the 2007 to 2009 period, but could not be used in 2010 due to a shortage in the hospital. TauroLock was again obtained after the year 2011 and used from then on.

Vascular catheter-related bloodstream infections

Among the 135 candidemia episodes, CRBSIs were observed in 54 febrile episodes with candidemia (40%). Among the CRBSIs, the most commonly isolated *Candida* species was *C. parapsilosis* (n=41, 78.8%), followed by *C. tropicalis* (n=8, 14.8%), *C. albicans* (n=4, 7.4%) and *C. glabrata* (n=1, 1.8%).

The rate of CRBSI was significantly higher in *C. parapsilosis* candidemia than in *C. albicans* (p=0.003) or the other *Candida* species as a group (p=0.006); however, no significant difference was observed between other individual *Candida* species (p>0.05) (Table II).

Mortality rates associated with* Candida *species

The overall 30-day mortality rate in candidemia episodes was 4.44%. Six patients died during the 30-day period due to *Candida* species-related BSIs, distributed among species as follows: *C. parapsilosis*, 2; *C. tropicalis*, 2; *C. ciferrii*, 1; and *C. glabrata*, 1.

Discussion

At our cancer center, the leading pathogen of nosocomial BSIs in pediatric malignancies was *Candida* spp.; *C. parapsilosis* was the most common microorganism not only among *Candida* species but among all microbes as well. Previous studies clearly demonstrated that *Candida* spp. had become the third most common microbial cause of BSIs overall[4]. For the last two decades, not only have BSIs associated with *Candida* species increased; the distribution of the individual species has also changed. The prevalence of *C. albicans*, which was once the most prominent *Candida* species, has been decreasing dramatically[7-10], it having been replaced in this respect by non-albicans species, especially *C. parapsilosis*, as indicated by reports from European[3], Asian[19,20], and South American[21] hospitals.

There have been limited studies of specific candidemia rates in PHO patients. In one study from the United States, the authors suggested a trend toward increase in non-albicans *Candida* species and *Aspergillus* species, although the evidence did not reach the level of statistical significance. In a study from Brazil documenting a relatively small series of candidemia episodes, *C. parapsilosis* and *C. guillermondii* were present in 9 pediatric cancer patients, followed by *C. albicans* in 7 and *C. tropicalis* in 2[22]. Another study reported that non-albicans *Candida* was the most common cause of candidemia in pediatric cancer patients, supporting our findings[23]. In the same study, the distribution of specific *Candida* species displayed a high incidence of *C. albicans* (29%), *C. tropicalis* (26%) and *C. parapsilosis* (24%)[23]. In our center, however, *C. parapsilosis* was the predominant and *C. albicans* the second most common *Candida* spp. found to be causing candidemia.

Table II. Association of CRBSIs with Specific *Candida* Species

	C. parapsilosis	Other *Candida* species	*p*-values
CRBSIs	41 (49.4%)	13 (25.5%)	p=0.006
Candidemia	42 (50.6%)	38 (74.5%)	
	C. parapsilosis	C. albicans	
CRBSIs	41 (49.4%)	4 (16.0%)	p=0.003
Candidemia	42 (50.6%)	38 (84.0%)	
	C. parapsilosis	C. tropicalis	
CRBSIs	41 (49.4%)	4 (40.0%)	p=0.450
Candidemia	42 (50.6%)	12 (80.0%)	
	C. albicans	C. tropicalis	
CRBSIs	4 (16.0%)	4 (40.0%)	p=0.198
Candidemia	38 (84.0%)	12 (80.0%)	

This trend may be due to the widespread use of fluconazole prophylaxis[12]. Since there has been limited study in pediatric cancer patients, our findings may serve as a source for further studies and possible strategies for prophylaxis.

In our study, catheter involvement was more commonly seen in *C. parapsilosis* candidemia than in candidemia related to the rest of the *Candida* species found in our study, including *C. albicans*. *Candida parapsilosis*, in particular, been found in association with CRBSIs[24,25]. Cancer patients who require prolonged use of CVCs and indwelling devices are at risk for infection with *C. parapsilosis*[26]. The increased association of CRBSIs with *C. parapsilosis* may be attributed to several factors, including the organism's growth capacity, affinity for intravascular devices and prosthetic materials, biofilm production, association with gastrointestinal colonization, and common transmission from the colonized hands of healthcare workers[26,27]. The high incidence of *C. parapsilosis* compared to other *Candida* species in pediatric malignancy patients poses an important threat for this group of patients due to its tendency to cause CRBSIs and the difficulty in treating *C. parapsilosis* catheter infections without removing the catheters. A recent study from Turkey reporting that catheter removal was unavoidable in long-term catheter infections with *C. parapsilosis* independent of the choice of antifungal systemic therapy[18] highlighted the impact of this pathogen, in that *C. parapsilosis* infections can delay the therapy of primary disease at pediatric cancer patients.

Data on the outcome and mortality rates of IFIs, especially those of candidemia in children with cancer, are limited. The few studies that have been conducted have generally focused on patients with leukemia or HSCT, in which invasive *Aspergillus* species are the predominant IFIs. The mortality rates of IFIs have been reported as ranging from 5% to 59%[28,29]. Castagnola et al.[30] reported an overall mortality rate of 28% for IFIs from all causes; however, when only fungemia cases, most of which were candidemia cases, were evaluated, the mortality rate was reported to be low as 5%. Mor et al.[31] reported a mortality rate of 21.7% in a population of 1047 children with hematologic or oncologic disease or HSCT; however, only 15 candidemia episodes (of which 60% were associated with non-albicans *Candida*) were included in that study. In our study, the mortality rate for all candidemia cases was found to be only 4.44%. This lower rate could be due to the early initiation of antifungal drug therapy and the nature of the patients.

Candida parapsilosis has become of greater importance, due not only to its increasing prevalence among *Candida* species as a cause of candidemia, but also to its affinity for CVCs and the increasing mortality consequent to nosocomial *Candida* infections. To the best of our knowledge, our study is one of the few large-scale studies focusing on candidemia in pediatric malignancy patients.

In conclusion, *Candida* species have become the most common pathogens of nosocomial BSIs in pediatric patients with cancer. Moreover, non-albicans *Candida* species, in particular *C. parapsilosis*, have overtaken *C. albicans* as a cause of candidemia. In our study, nearly half of the *C. parapsilosis* candidemia was associated with CRBSIs, suggesting that candidemia caused by this organism will in future be more significant in pediatric oncology patients, in whom several types of central venous catheters are used.

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