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Candidemia in Children Caused by Uncommon Species of *Candida*

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Abstract

Background: The aspects of the epidemiology of bloodstream *Candida* infections including clinical features, the causal agents, underlying conditions, and risk factors have not been well-defined in Iranian pediatric patients. The aim of this observational study was to identify uncommon *Candida* species isolated from blood and other normally sterile specimens of the neonates and children admitted to intensive care units at Children's medical center, Tehran, Iran.
Methods: The study was carried out prospectively on patients < 16 years, who were hospitalized in Children's medical center, Tehran, Iran, during 25 months, from June 2014 to July 2016. Blood and other normally sterile specimens were collected from 6,075 pediatric patients and only pure growth of yeasts were included the study. The yeast isolates were subjected to DNA extraction, PCR of ITS-region, and sequencing followed by Blast analysis to accurately identify the species.
Results: A total of 16 out of 136 isolates were recognized as uncommon or rare *Candida* species. According to the sequence analysis, these isolates were identified as *C. orthopsilosis* (N = 5, 3.7%), *C. glabrate* (n = 4, 2.5%), *C. dubliniensis* (n = 2, 1.5%), *C. lusitaniae* (n = 2, 1.5%), *C. kefyr* (n = 2, 1.5%), and *C. intermedia* (n = 1, 0.75%)
Conclusions: *Candida* species, which were once considered harmless, have now been recognized as causative agents of candidemia. It is essential to consider, manage, and control the conditions that lead to the development of these unusual but severe cases of candidemia.

Keywords: Pediatrics, Candidemia, Uncommon *Candida* Species

1. Background

Invasive candidiasis is defined as candidemia. *Candida* infection involving normally sterile body sites is the most common cause of fungal disease worldwide (1). *Candida* may be the only genus for which the outcome of nosocomial blood stream infections depends on species (1). Although about 95% of all invasive *Candida* infections are caused by *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei* (2), several factors have led to the involvement of other *Candida* species in candidemia. These factors include an increase in the population at risk as a result of advances in medical and surgical interventions and infection management, increased use of antifungals prophylaxis, and improvements in diagnostic methods such as introduction of molecular assays in the routine diagnosis of candidemia (3). Little is known about the epidemiology of candidemia in Iran, particularly in pediatric patients, the purpose of this study was to evaluate the frequency, distribution, risk factors, and outcomes associated with uncommon *Candida* species, in Children's medical center's ICUs in Tehran, Iran. Since differences in *Candida* species are associated with varying degrees of disease severity and diversity in antifungal susceptibility patterns, understanding the mentioned tips is clinically important. All patients in this study were exposed to major risk factors such as a prolonged stay in the ICU for at least 7 days and receiving broad-spectrum antibiotics during admittance to ICU.

2. Methods

Samples were obtained from June 2014 and July 2016 in the main Children's Medical Center affiliated to Tehran University of Medical Sciences, Tehran, Iran from pediatric patients < 16 years old, who were hospitalized in the neonatal and pediatric intensive care unit (NICU and

PICU) and for whom fungal infection was suspected. Blood samples and other normally sterile specimens were examined by inoculation into aerobic culture medium bottles (BACTEC Peds Plus/F Culture Vials, Ireland) followed by incubation for a period of 5 days in the automated blood culture system BACTEC 9120 (Becton Dickinson, Spark, MD, USA). Each case of invasive candidiasis was defined as having more than 1 positive culture specimen. In addition, each episode of infection was considered as a new case if at least $\geq$ 1 month would have been passed from a previously treated occurrence. All positive cultures were subcultured on blood agar, chocolate agar, and MacConkey agar (all from Merck, Darmstadt, Germany) at 35°C and checked each day for up to 5 days for any yeast growth.

Positive cultures were subcultured on CHROMagar (CHROMagar Paris, France) to obtain pure colonies and preliminary species identification. Final identification of *Candida* species was based on amplification of the ITS1-5.8SrDNA-ITS2 region of DNA extracted from each isolate followed by the analysis of species-specific electrophoretic patterns of PCR products digested with the restriction enzyme *MspI* (4). Doubtful species that had unspecific enzyme similar patterns (*C. lusitaniae*, *C. intermedia*, and *C. rugosa*), or that had no restriction site (*C. parapsilosis*, *C. orthopsilosis*, *C. metapsilosis*, *C. kefyr*, and *C. famata*) were subjected to sequencing of the entire ITS region using the forward ITS1 primer (5, 6). Sequences were then subjected to nucleotide BLAST search (http://blast.ncbi.nlm.nih.gov/Blast.cgi) and the species were defined by comparison of the sequences with the sequences deposited in the GenBank. For differentiation of *C. albicans* and *C. dubliniensis*, all isolates identified as *C. albicans* were subjected to a specific duplex-PCR as already described (7).

3. Results

A total of 134 episodes of candidemia were identified in 129 patients, all admitted to the ICU. The proportion of males was similar to that of females (50.7% vs 493%). The age range was $\leq$ 28 days to 16 years. A total of 29 (22.4%) patients were $\leq$ 28 days as neonates, and 105 (77.6%) were $\geq$ 28 days or more, up to 16 years. The mean duration of hospitalization before onset of candidemia was 25.1 days (range 7 - 60 days). Patients had received antibiotic therapy in a wide range, including β-lactamase inhibitors such as the 3rd and 4th generation of cephalosporins, glycopeptides including vancomycin, aminoglucosides, carbapenems, and anti-anaerobic bacterial agents. There was no evidence of antifungal prophylaxis based on the treatment protocol and medical records.

A total of 136 *Candida* strains were recovered from 134 episodes of candidemia. Of all cases of infection proven by culture in the study period, a total of 16 episodes of invasive candidiasis were caused by uncommon species of *Candida*. Uncommon *Candida* species were responsible for approximately 12% of all cases of candidemia. These species were identified as *C. orthopsilosis* (n = 5, 31.3%), *C. glabrata* (n = 4, 25%), *C. lusitaniae* (n = 2, 12.5%), *C. kefyr* (n = 2, 12.5%), *C. dubliniensis* (n = 2, 12.5%), and *C. intermedia* (n = 1, 6.2%). One patient had 2 episodes of infection with *C. orthopsilosis*. *C. albicans* was the most commonly isolated *Candida* species (n = 72, 53.7%). The overall mortality rate was estimated to be 42.5% among patients with candidemia, (47.6%, 50.0%, and 26.9% for neonates, infants, and children, respectively). Patient demographics, underlying diseases, risk factors, infecting *Candida* species, and outcomes of infection are summarized in Table 1.

4. Discussion

The number of uncommon or rarely reported species of *Candida* isolated from clinical specimens is growing, and invasive candidiasis caused by uncommon species may paradoxically be a result of advances in medical care (2). Since resistance to antifungal agents such as fluconazole and echinocandins has been shown to be more common in non-albicans *Candida* species that in turn may affect the outcome of the disease, identification of *Candida* species is necessary for targeted management. Species emerging in clinical settings such as *C. lusitaniae*, *C. kefyr*, *C. guilliermondii*, and *C. dubliniensis* may be associated with specific susceptibility patterns (8).

There are some special risk factors for candidemia in children. The main groups of pediatrics at risk of candidemia are premature neonates, patients admitted to the NICU and PICU, and immunocompromised children due to treatment of neoplastic disease, transplants, and autoimmune conditions (9). In this study, a variety of underlying conditions were observed, including anatomical and metabolic disorders, immunodeficiency, and malignancy. Prematurity, presence of CVC, and parenteral nutrition, were the main risk factors of candidemia and common in all neonates and most children, as well as, surgery, tracheal intubation, and steroid therapy. All of the neonates with candidemia caused by uncommon *Candida* species in our study were premature, which is associated with up to 40% mortality and increased risk of neurodevelopmental impairments among survivors complicated with invasive candidiasis (10).

In contrast to the situation for adults, *C. glabrata* is a rare cause of invasive candidiasis in NICU and PICU

Table 1. Characteristics of Patients with Candidemia Caused by Uncommon *Candida* Species

No	Gender	Age	Ward	Clinical Specimen	Underlying Disease	Risk Factors	*Candida* Species	Antifungal	Outcome
1	F	18 D	NICU	Blood	Prematurity; Respiratory disorders	Abdominal surgery; CVC; TPN; TI	*C. orthopsilosis*	AmB + Fluconazole	Died
2	M	28 D	NICU	Blood	Prematurity; Neurological and respiratory disorder	Surgery; CVC; TPN; TI	*C. orthopsilosis*	AmB + Fluconazole	Alive
3	F	24 D	NICU	BAL	Prematurity; Respiratory disorder	Surgery; CVC; TI; TPN	*C. kefyr*	AmB	Alive
4	M	25 D	NICU	Blood; Urine	Prematurity; Multiorgan disorders	CVC; TPN; TI	*C. glabrate*; + *C. albicans*	AmB + Fluconazole	Died
5	F	3 M	PICU	Blood	Metabolic disease	CVC; TPN	*C. lusitaniae*	AmB + Fluconazole	Died
6	F	9 M	PICU	Blood	Metabolic disease	CVC; TPN	*C. lusitaniae*	AMB + Fluconazole	Died
7	M	1 Y	PICU	Blood; Dialysis fluid	Acute renal disorders	Abdominal surgery; Dialysis catheter; CVC; TPN	*C. dubliniensis*	AmB	Died
8	M	1 Y	CICU	Blood	Congenital Heart Disease	Surgery; CVC; TPN; TI	*C. kefyr*	AmB	Alive
9	F	2 Y	PICU	Biopsy	Bladder exstrophy	Surgery; Urine catheter	*C. glabrate*	AmB + Fluconazole	Alive
10	F	3 Y	PICU	Blood	Cerebral palsy; Respiratory disorders	Surgery; CVC; TPN; TI	*C. intermedia*	AmB	Alive
11	F	3 Y	PICU	Blood	Gastrointestinal disorders	Abdominal surgeries; CVC; TPN; Steroid therapy	*C. glabrate*	AmB + Fluconazole	Died
12	F	3 Y	PICU	Blood	B cell leukemia	CVC; TI; Steroid therapy	*C. orthopsilosis*	AmB	Alive
13	F	6 Y	PICU	Blood; Urine	Hyper IgM Syndrome	Surgery; Urine catheter; CVC	*C. dubliniensis*	AmB + Fluconazole	Alive
14	M	8 Y	PICU	Blood	Hyper IgM Syndrome	Surgery; CVC; Steroid therapy; TI	*C. glabrate*	AmB	Alive
15	F	12 Y	PICU	Blood	Metabolic andGastrointestinal disorders	CVC; TPN; TI; Catheter	*C. orthopsilosis*	AmB	Died

Abbreviations: AmB, amphotericin B, BAL, Bronchoalveolar lavage; CVC, central venous catheter, TI, Tracheal intubation; TPN, Total parenteral nutrition.

(3). It has presumably emerged predominantly among patients with hematological malignancies possibly due to increased use of azole prophylaxis (11); however, in the present study, none of the patients with *C. glabrata* candidemia had any type of malignancy. In a study carried out on neonatal sepsis, prior exposure to antibiotics, low birth weight, and prematurity have been identified as specific risk factors for all cases of *C. glabrata* candidemia in neonates (12). Some studies have noted that *C. glabrate* may be more prevalent associated with increase in medically complex pediatric patients such as gastrointestinal disorders (13). Emergence of fluconazole resistance in this species results from drug pressure due to frequent use of fluconazole as prophylaxis (14). Resistance to the echinocandins is emerging in *C. glabrata*, and along with *C. albicans*, this species is the most frequent *Candida* species at a risk of developing echinocandin resistance (3, 15). Generally, *C. glabrata* candidemia is difficult to manage, and high mortality is seen (3). Nevertheless, since that is very infrequent in the pediatric setting, fluconazole is a logical choice for candidemia treatment before species identification, except in children with prior azole exposure (16).

In some regions, *C. orthopsilosis* is reported as the 5th species more frequently isolated from blood (17). We found 5 episodes of candidemia by *C. orthopsilosis* in 4 patients. The patient with 2 episodes of *C. orthopsilosis* candidemia was a 3-year-old girl with pre B-cell leukemia receiving corticosteroid therapy. This cryptic species belonging to the *C. parapsilosis* complex (6) is less virulent than *C. parapsilosis sensu stricto*; however, it is increasingly observed as a cause of candidemia in pediatric patients, presumably as a direct consequence of the rapidly growing population prone to this infection (18, 19). A previous study indicated that parenteral nutrition increased the risk of developing candidemia caused by *C. orthopsilosis* (19); however, 2 particular features of members of the *C. parapsilosis* group include I) having the capacity of adhering to and colonizing plastic materials such as catheters and II) transmission via the hands of healthcare workers; both contribute to the development of the infection (17). *C. orthopsilosis* is known to produce higher levels of phospholipases and hemolysins than *C. metapsilosis* and *C. parapsilosis*, as well as it has as the same ability as *C. parapsilosis* to adhere to epithelial cells and cause damage tissue. In addition, its culture supernatants produce more levels of lactate dehydrogenase and tumor necrosis factor-α in comparison with *C. metapsilosis* (20). *C. parapsilosis* has been observed to be less susceptible to echinocandins at hospitals that use this class of antifungal (17, 19). Lockhart et al. reported that for *C. orthopsilosis*, the minimal inhibitory concentrations (MICs) of amphotericin B and caspofungin are lower than those exhibited by *C. parapsilosis*; in comparison, the MIC of fluconazole is slightly higher (19). A 12-year-old female patient in our study died despite treatment with amphotericin B. This appeared to be due to the severe underlying disease rather than the severity of infection caused by *C. orthopsilosis*, due to the fact that *C. parapsilosis* is generally less virulent than other *Candida* species and associated with the lowest crude mortality rate, despite its high frequency in younger patients (3, 21).

Pfaller et al. ranked *C. dubliniensis* as the 6th most common of non-albicans *Candida* species (3). They found that 21.1% of patients infected with *C. dubliniensis* had been receiving surgery; there was no case of infection in NICU patients (3). Both of our patients with *C. dubliniensis* were hospitalized in the PICU and shared similar risk factors such as surgery, presence of CVC, and other catheters. Pfaller et al. also found that in patients less than one year of age, *C. lusitaniae* was responsible for 14.6% of all infections caused by non-albicans *Candida* species (3). The importance of this species is reflected in the development of acquired resistance to amphotericin B during therapy, even in strains that are originally susceptible to this antifungal agent (22). In our study, 2 infected infants with *C. lusitaniae* died despite treatment with amphotericin B and fluconazole; however, Diekema et al. believed that, *C. lusitaniae* remains quite susceptible to both triazoles and echinocandins (23).

Candida kefyr was responsible for 2/16 cases. No sign of neutropenia was seen in these 2 cases, although Sendid et al. reported a particularly high prevalence of *C. kefyr* colonization in patients with onco-hematological disease, isolating it twice as often from this group of patients than from patients with other underlying conditions (24). *C. kefyr* inhabits the gastrointestinal tracts and is associated with consumption of dairy products harboring this species (25). According to a large study carried out by Pfaller et al. *C. kefyr* is usually susceptible to all antifungal drugs, especially to echinocandins (26), although Fekkar et al. reported on rapid emergence of resistance to echinocandins in *C. kefyr* during the 1st day of treatment (27).

C. intermedia, a member of the microbiota of the human oropharyngeal cavity and rarely pathogenic, was isolated from a 3-year-old child with cerebral palsy and respiratory disorder. In addition, the child had risk factors such as surgery and presence of CVC, which was in agreement with the study by Ruan et al. who reported 2 cases of fungemia by *C. intermedia*, both associated with a presence of intravenous catheter (28).

In general, nosocomial *Candida* infections by uncommon *Candida* species are associated with selective pressure of some antifungal agents or hospital procedures such as previous antibacterial therapy, intravascular catheters, parenteral nutrition, and mechanical ventilation, as well as flaws in infection control procedures (3). The distribution of uncommon *Candida* species identified in invasive candidiasis varies by geographic region, patient population, and antifungal treatment practices. However, some researchers concluded that there is no difference between *Candida* species in terms of demographics, underlying diagnosis, risk factors, clinical features, and outcomes (29, 30, 31). Still, reliable and accurate identification of emerging *Candida* species that cause blood stream infections such as *C. lusitaniae* and *C. intermedia* is essential for selecting the most effective therapeutic strategies in the management of invasive candidiasis caused by these species.

4.1. Conclusions

This is the first study of blood stream infections in children caused by uncommon *Candida* species in Iran. Since *Candida* species, which were once considered to be harmless, have now been identified as causes of candidemia, the underlying conditions and risk factors in ICU patients must be considered seriously. Given the severity of the disease and risk of mortality, epidemiological data can serve as a template for the careful management.

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Footnotes

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