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Epidemiology, Risk Factors and Outcome of *Candida parapsilosis* Bloodstream Infection in Children

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Abstract

Background—*Candida parapsilosis* constitutes a common *Candida* spp. isolated in children with candidemia. Few data exist on risk factors and outcome of candidemia caused by *C. parapsilosis* in pediatric patients.

Methods—We conducted a retrospective analysis of demographic data, clinical features, therapeutic procedures and outcomes associated with *Candida* bloodstream infections (BSIs) that occurred at the Children's Hospital of Philadelphia between 1997–2009.

Results—Among 406 *Candida* BSIs, *Candida albicans* accounted for 198 (49%), *C. parapsilosis* for 99 (24%) and all other species for 109 (27%) episodes. There was no consistent change in proportion of *C. parapsilosis* BSIs during the study. *C. parapsilosis* BSI was more frequent than non-*parapsilosis Candida* spp. at age ≥ 2 years as compared with older patients [62% vs. 50%; OR=1.24, 95% CI=1.03–1.51, $p=0.038$]. Patients with *C. parapsilosis* were more likely to be mechanically ventilated within 48 hours of BSI (OR=1.38, 95% CI=1.01–1.85, $p=0.047$). Presence of a urinary catheter a week before infection was a protective factor for developing candidemia due to *C. parapsilosis* spp. ($p=0.003$). No significant differences were found between the two groups in presence of central intravascular catheters, co-morbidities and clinical or surgical procedures, previous administration of immunosuppressive or antifungal agents and mortality.

Conclusions—*C. parapsilosis* is the second most frequent cause of candidemia after *C. albicans*. While it is more frequent at the age of ≥ 2 years and is more likely associated with mechanical ventilation than other *Candida* spp., mortality does not significantly differ between those with and without *C. parapsilosis* candidemia.

Keywords

Candida parapsilosis; candidemia; children; risk factors

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INTRODUCTION

Invasive candidiasis is an important cause of morbidity and mortality in children. Historically, *Candida albicans* has been the most common isolate from fungal bloodstream infections (BSIs).¹ Recently, there has been a reported increase in the incidence of non-*albicans Candida* spp., especially of *Candida parapsilosis*.^{2–7} Indeed, *C. parapsilosis* is often the second most commonly isolated *Candida* spp. from blood cultures and even outranks *C. albicans* in some cases, causing common-source outbreaks and clusters.^{8–11} These studies, however, were frequently small in size and covered a short period of time.

This increasing trend of *C. parapsilosis* has been attributed to several factors including the organism's growth capacity, its affinity for intravascular devices and prosthetic materials, gastrointestinal colonization and transmission from the colonized hands of healthcare workers.^{7,12–14} Adhesion and biofilm formation are very important characteristics of *C. parapsilosis*, as indwelling devices appear to be the predominant route of infection.¹² The majority of patients with *C. parapsilosis* BSIs reported, have suffered from an underlying disease that requires use of indwelling catheters and parenteral nutrition. The increasing use of antifungal agents as prophylaxis for fungal infections in high-risk patients, might have caused changes in the frequency of isolation of *C. parapsilosis*.^{13,14} In neonatal age, very low-birth-weight infants are the population at greatest risk for nosocomial infection caused by *C. parapsilosis*, especially when they present signs of gastrointestinal tract disease, compromised skin integrity, or long term endotracheal intubation.^{2,9} Few data, however, exist on risk factors and outcome of candidemia caused by *C. parapsilosis* in pediatric patients.

Challenged by reports on the changing pattern of epidemiology of candidemia we conducted this large cohort study. The aim of it was to determine risk factors for and outcomes of *C. parapsilosis* BSIs compared with those due to other species of *Candida* in children hospitalized at a large United States children's hospital.

PATIENTS AND METHODS

Study setting and population

This retrospective cohort study was conducted at the Children's Hospital of Philadelphia (CHOP), a 418-bed urban tertiary care medical center with approximately 24,000 hospital admissions per year. Study subjects were identified through records of the CHOP Clinical Microbiology Laboratory, which processes and cultures all clinical specimens for the hospital. All patients 18 years with a positive blood culture for *Candida* spp. from January 1, 1997 to December 31, 2009 were eligible for inclusion. The study protocol was reviewed and approved by the Committee for the Protection of Human Subjects at CHOP.

Definitions

All cases of nosocomial candidemia were identified using the Centers for Disease Control and Prevention (CDC) criteria.¹⁵ A case of candidemia was defined as the isolation of *Candida* spp. from at least one blood culture drawn from either an intravascular catheter or a peripheral vein/artery. To capture nosocomial candidemia, only blood cultures that were drawn at least 48 hours after the patient's admission to the hospital were considered. If multiple episodes of candidemia occurred in the same patient during the study period, the patient was included as a study participant using only the first episode of candidemia. Death in the 30 days following infection was captured.

Data collection

Data were collected with the use of a structured data abstraction form by review of the electronic hospital medical records and reports from the CHOP Clinical Microbiology Laboratory. Demographic and clinical data such as prior hospitalization, presence of a medical device, prior use of medications and co-morbidities/clinical procedures were collected. Co-morbidities and clinical procedures included prior transplantation, malignancy, peritoneal dialysis or hemodialysis and graft versus host disease (GvHD).

Statistical analysis

Categorical variables were compared with the use of Fisher's exact test. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of selected associations. Continuous variables were compared using the Wilcoxon rank sum test. A 2-tailed p value of <0.05 was considered significant. Multivariate analysis using logistic regression was performed to identify associations between variables and risk factors for developing candidemia due to *C. parapsilosis* compared to other species of *Candida*. All variables with a univariate p -value <0.20 were considered for inclusion in the multivariate model.

RESULTS

During the 13-year study period 1997–2009, 406 children developed BSIs due to *Candida* spp. at CHOP. The incidence of candidemia in this period was 10.5 cases per 1,000 patient admissions/year. Specifically, the incidence of *C. parapsilosis* fungemia was 2.5 cases per 1,000 patient admissions/year.

The demographic characteristics of children with candidemia are shown in online Table 1. Among them, 198 (49%) episodes were caused by *C. albicans*, 99 (24%) by *C. parapsilosis* and 109 (27%) by other non-*albicans* and non-*parapsilosis Candida* spp. (online Table 2). The total number of non-*albicans Candida* episodes was 136 (51%), equivalent to that of *C. albicans*. The proportion of candidemia attributed to *C. parapsilosis* did not show a consistent trend through the years 1999–2009 (online Figure 1).

By univariate analysis there was a significant difference between patients with *C. parapsilosis* and patients infected with other *Candida* spp. with regards to age at time of infection. Specifically, infection with *C. parapsilosis* was more common among patients 2 years of age (62% vs. 50%, OR=1.24, 95% CI=1.03 to 1.51, $p=0.038$) as compared to children between 3 and 18 years of age (38% vs. 51%, OR=0.76, 95% CI=0.58 to 0.99, $p=0.038$). When compared to patients infected with non-*parapsilosis Candida* spp., patients infected with *C. parapsilosis* were more likely to be mechanically ventilated in the 48 hours prior to candidemia (40% vs. 29%, OR=1.38, 95% CI=1.01 to 1.85, $p=0.047$).

No significant differences were found between patients with candidemia due to *C. parapsilosis* and patients with candidemia due to all other *Candida* spp., regarding sex, length of hospital stay, time to candidemia, being in intensive care unit at diagnosis, co-morbidities and clinical procedures (Table 1), presence of central intravascular catheters, surgical procedures and previous administration of immunosuppressive or antifungal agents (Table 2). In addition, there was no difference in 30-day mortality (12% vs. 14%, $p=0.738$).

Multivariate analysis showed that the only independent risk factor for developing candidemia due to *C. parapsilosis* was mechanical ventilation 48 hours prior to infection [adjusted OR (95% CI) 2.44 (1.44 to 4.14), $p = 0.001$]. On the opposite, presence of a urinary catheter one week prior to infection was found to reduce the risk for the

development of candidemia due to *C. parapsilosis* as compared to all other *Candida* spp. [adjusted OR (95% CI) 0.37 (0.19 to 0.72), $p = 0.003$] (Table 3).

A number of different antifungal agents/classes were used to treat BSIs due to *C. parapsilosis* and *non-parapsilosis Candida* spp. (Table 4). More cases caused by *C. parapsilosis* were treated with polyenes ($p = 0.006$), whereas fewer cases caused by the same species were treated with polyenes and fluconazole. Due to the small number of cases caused by individual species, it was not possible to correlate antifungals used and outcome of the patients.

DISCUSSION

To our knowledge, this is the largest single-center cohort of pediatric patients with candidemia caused by *C. parapsilosis* reported in the English literature. The main findings of this study are: a) *C. parapsilosis* represents the second most common isolated *Candida* species after *C. albicans*, which is a relatively unchanged trend during the last decade. b) *C. parapsilosis* is the cause of candidemia at age 2 years more frequently than in older patients with candidemia. c) Patients with candidemia due to *C. parapsilosis* are significantly more likely to be mechanically ventilated at the time of candidemia than those with other *Candida* spp. d) No independent risk factors for mortality or differences in mortality between candidemia due to *C. parapsilosis* and all other *Candida* spp. were found.

The *Candida* species distribution identified in our study is consistent with previously published smaller studies in children and adults.^{2–6} In general, *C. albicans* is the species most commonly isolated from patients with candidemia. However, *C. parapsilosis* isolation has been reported as the second most common *Candida* species recovered from BSIs in North America (15.5%), Europe (16.3%), Asia-Pacific region (17%), Australia (18.8%); it has been reported that the frequency of *C. parapsilosis* has increased from 14% to 23.4% in Latin America during the last decade.^{16–19} In recent studies, the overall incidence of *C. parapsilosis* BSIs reported has been between 7% and 24%.^{5,19} In our large study, the proportion of candidemia attributable to *C. parapsilosis* ranged between approximately 14% to 34%, but it did not show any consistent trend of change through a relatively long period.

In this study we found that among patients with candidemia, those with age 2 years were at increased risk for developing candidemia due to *C. parapsilosis*. This finding is supported by previous reports, in which *C. parapsilosis* was most prevalent in patients less than 1 year of age, especially neonates, as compared to adults. Specifically, the distribution of *C. parapsilosis* in neonates has been found to range from 15.5% to 65.1% as compared to 5–15% in adults.^{2,5,13,18–20} In the largest reported study including 128 NICUs, among a total of 130,523 patients, *C. parapsilosis* accounted for 33.7% of candidemia cases higher than that of adults and our finding in all the children (24%).²¹ Taken these data together, the population at greatest risk for nosocomial infections with *C. parapsilosis* appears to be that of very low- and extremely low-birth-weight neonates.

Although the exact reasons for this relatively high incidence of *C. parapsilosis* are not well known, indwelling devices, and parenteral nutrition have been recognized as potential risk factors.^{7,14,22} This high incidence may reflect the aggressive use of intravascular devices to treat neonates.²³ Adhesion and biofilm formation are especially important for *C. parapsilosis* fungemia as suggested by infections related to central venous and peritoneal dialysis catheters.^{12–14} Parenteral nutrition and high glucose environment seem to play a determinant role by promoting the development of biofilm production, indicating a strong relation between *C. parapsilosis* fungemia and the administration of parenteral nutrition.^{13,24} However, in our study, the central venous, arterial or urinary catheters and total parenteral

nutrition were not found to be significant risk factors of *C. parapsilosis* BSIs. Notably, presence of a urinary catheter one week prior to infection was found to be an independent factor for developing candidemia due to *Candida* spp other than *C. parapsilosis*. This finding is a paradox difficult to be explained; however, one could guess that the existence of urinary tract catheter can be related with infections due to other than *C. parapsilosis* *Candida* species, especially *C. albicans*. Differences observed in previous studies can be explained by the small number of patients included, their focus on specific age, ie adults and neonates, or other methodological limitations, which have led to conclusions that have not proved in our large analysis.

C. parapsilosis fungemia has been associated with gastrointestinal colonization and transmission from the hands of healthcare workers contributing to its higher frequency in young patients found in our study.¹⁴ Colonization of the gastrointestinal tract with *C. parapsilosis* occurs at a higher rate in neonates, further increasing their risk of *C. parapsilosis* fungemia. Transmission of *C. parapsilosis* from the hands of healthcare workers as a source to neonates and children has been suggested as a contributing factor, because the organism is commonly carried on the hands of healthcare personnel or other healthy hosts.^{8,14,22}

Retrospective cohort studies involving patients with candidemia and different underlying diseases have revealed an excess attributable mortality rate of 10–49%.^{4,7} Survival appears to be improved by earlier diagnosis of candidemia and pre-emptive or empirical treatment with new, effective and well-tolerated antifungal agents. Specifically, recent studies have found lower mortality rates among children with *C. parapsilosis* than those with all other *Candida* spp. ranging from 4% to 45%.^{13,14} Lower mortality rates were explained in part by the relatively lower virulence of *C. parapsilosis* when compared with other *Candida* spp. in experimental models.²⁵ In addition, a higher inoculum size of *C. parapsilosis* was required as compared with *C. albicans* for a lethal infection to occur.²⁵ In our study, the mortality rate of 12% for *C. parapsilosis* fungemia was not significantly lower than 14% for all other *Candida* spp. fungemia, perhaps due to the role of underlying disease. Another hypothesis is that some of the *C. parapsilosis* isolates were biofilm-forming, which have been associated with significantly higher mortality rates compared to *Candida* isolates of same or other species, incapable of forming biofilm.¹³ Due to the retrospective nature of our study, the biofilm-forming capacity of *C. parapsilosis* isolates was not measured.

This study has two limitations. First, its retrospective nature limits the ability of drawing specific conclusions, which is minimized as a problem by the very large number of patients studied. Second, the potential of clustering of *C. parapsilosis* in the hospital may have been a problem; however, it does not seem possible due to the very long period of study.

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Table 1

Risk factors including patient characteristics, co-morbidities and clinical procedures for candidemia due to *Candida parapsilosis* and to all other *Candida* spp.

Characteristics	<i>Candida parapsilosis</i> (n=99)	All other <i>Candida</i> spp. (n=307)	p-value
Patient Characteristics			
Length of hospital stay *	38 (16–72)	34.5 (18–70)	0.819
Time to BSI *	15 (2–29)	12 (3–25)	0.230
^I ICU at diagnosis	46 (46%)	118 (38%)	0.160
Death	12 (12%)	44 (14%)	0.738
Co-morbidities and Clinical Procedures			
Prior transplantation	6 (6%)	29 (9%)	0.410
Malignancy	21 (21%)	88 (27%)	0.154
Peritoneal dialysis / Hemodialysis	5 (5%)	8 (3%)	0.321
Graft versus Host Disease	1 (1%)	5 (2%)	1.000

^IICU = Intensive Care Unit

* In parenthesis, range between

Table 2

Risk factors including clinical features and medications for BSIs due to *Candida parapsilosis* and to all other *Candida* spp.

Characteristics	<i>Candida parapsilosis</i> (n=99)	All other <i>Candida</i> spp. (n=307)	p-value
Clinical Features within 48 Hours prior to Study Entry			
Mechanical ventilation	40 (40%)	90 (29%)	0.047
Clinical Features within one Week prior to Study Entry			
Central venous catheter	88 (89%)	272 (89%)	1.000
Arterial catheter	22 (22%)	87 (28%)	0.244
Urinary catheter	16 (16%)	77 (25%)	0.074
Total parenteral nutrition	63 (64%)	189 (62%)	0.812
Enteral nutrition	48 (48%)	145 (47%)	0.908
Clinical Features within 15 Days prior to Study Entry			
Receipt of a surgical procedure	23 (23%)	83 (27%)	0.512
Neutropenia	13 (13%)	48 (16%)	0.629
Non-candidal BSI	34 (34%)	109 (36%)	0.904
Medication Use within 15 Days prior to Study Entry			
Receipt of immunosuppressive agents	31 (31%)	106 (35%)	0.625
Receipt of antifungal agents	26 (26%)	74 (24%)	0.688
Receipt of antibacterial agents	89 (90%)	277 (90%)	1.000

Table 3

Independent risk factors for developing candidemia due to *Candida parapsilosis* as compared to all other *Candida* spp. (multivariate analysis)

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-values
Mechanical ventilation 48 hours prior to BSI	1.71 (1.07 to 2.75)	2.44 (1.44 to 4.14)	0.001
Presence of a urinary catheter one week prior to infection	0.58 (0.32 to 1.04)	0.37 (0.19 to 0.72)	0.003

Table 4

Antifungal agents/classes administered for the treatment of cases caused by *Candida parapsilosis* and all other *Candida* spp.

Treatment combination	<i>C. parapsilosis</i> (n=99)	Other <i>Candida</i> spp. (n=306)
Polyene	50 (51%) *	106 (35%)
Echinocandin	1 (1%)	3 (1%)
Fluconazole	4 (4%)	17 (6%)
Polyene plus echinocandin	3 (3%)	7 (2%)
Polyene plus fluconazole	27 (27%) **	136 (44%)
Echinocandin plus fluconazole	1 (1%)	9 (3%)
Polyene plus echinocandin plus fluconazole	2 (2%)	8 (3%)
Other antifungal combinations	3 (3%)	1 (<1%)
None	8 (8%)	19 (6%)

* Difference from polyene treatment for other *Candida* spp., p = 0.006

** Difference from polyene plus fluconazole treatment for other *Candida* spp., p = 0.003