Pediatric Risk Factors for Candidemia Secondary to *Candida glabrata* and *Candida krusei* Species

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This 13-year retrospective study investigated risk factors for candidemia secondary to *Candida* species with increased likelihood of fluconazole resistance. Of 344 candidemia cases, 23 were caused by *C glabrata* or *C krusei* (CGCK). Age >2 years, recent fluconazole exposure, and recent surgery were independent risk factors for CGCK.

Key words. Candidemia; fluconazole resistance; pediatrics; risk factors

Candida species are the third most common organism implicated in pediatric healthcare-associated bloodstream infections in the United States, with a resultant case fatality rate of 13% and an attributable mortality of 10% [1, 2]. While *Candida albicans* still remains the most common cause of candidemia, prior literature suggests an increase in the frequency of non-*albicans Candida* species [3], and more specifically species with an increased likelihood for resistance to fluconazole, such as *C glabrata* and *C krusei* (CGCK) [4].

Published literature including adult subjects suggests that infection from CGCK may be associated with fluconazole prophylaxis and severe illness [5, 6]. Although the increased incidence of CGCK has been documented at some U.S. pediatric centers, little has been published regarding factors that predispose pediatric patients to infection from these species. Therefore, we investigated potential risk factors associated with CGCK infection among inpatient pediatric patients with candidemia. We hypothesized that previous exposure to fluconazole would be associated with CGCK infection.

METHODS

We conducted a retrospective cohort study of patients >28 days and <19 years of age admitted to the Children's Hospital of Philadelphia (CHOP) between January 1, 1997 and December 31, 2009 who had a blood culture positive for *Candida* spp. Due to substantial differences surrounding the epidemiology of candidemia in neonates versus older children, patients ≤28 days of age were excluded from the analysis.

Our primary outcome was candidemia secondary to CGCK, as these species are known to have increased resistance to fluconazole [7, 8]. Patients with CGCK candidemia were compared to patients with candidemia secondary to other *Candida* spp. All subjects were identified through CHOP's Clinical Microbiology Laboratory records. *Candida* was speciated using the VITEK®2 YST ID Card (bioMeriux, Durham, NC). Minimum inhibitory concentrations (MIC) to amphotericin B, caspofungin, fluconazole, and voriconazole were available for all isolates obtained after 2007. Susceptibility testing was performed using the YeastOne microtiter system (TREK Diagnostic Systems, Cleveland, OH). In the event of multiple episodes of candidemia, only the first episode was included.

Clinical and laboratory data were collected from the inpatient medical record using a structured data collection instrument. Data obtained included demographics and in-hospital mortality within 30 days of candidemia onset. The underlying reason for hospitalization, length

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of stay prior to and following infection onset, and admission to the intensive care unit (ICU) was also captured.

Specific comorbid conditions present at the time of candidemia diagnosis were also documented, including malignancy, renal insufficiency, human immunodeficiency virus infection, primary immunodeficiency, and prior organ transplantation. Pertinent laboratory values, including neutropenia (absolute neutrophil count of $<500\ mm^3$) and duration of neutropenia, as well as medication exposures, including antibiotics, antifungal agents, and immunosuppressive agents, were collected in the 15 days prior to candidemia onset. Surgical interventions and trauma in the 15 days prior to infection were also documented. Finally, presence of a central venous catheter (CVC), urinary catheter, arterial catheter, and administration of hyperalimentation (TPN) were recorded in the week prior to infection, while mechanical ventilation within 2 days of candidemia onset was also documented.

Univariate *P*-values were obtained using rank sum or χ^2 tests and all factors with a *P*-value of <.05 were considered for inclusion in the multivariate logistic model to identify independent risk factors for CGCK infection as compared to infection with other *Candida* spp. Odds ratios that excluded 1 were considered statistically significant. All analyses were conducted using Stata 12 (College Station, TX).

RESULTS

CGCK species accounted for 23 (15 *C glabrata*, 8 *C krusei)* (6.7%) of 344 candidemia episodes in pediatric inpatients >28 days of age. *C albicans* was most commonly isolated, accounting for 47% of candidemia episodes.

Demographic and clinical characteristics of patients with candidemia are shown in Table 1. In unadjusted analyses, patients with CGCK infections were more frequently >2 years of age ($P = .006$), and more likely to have an underlying malignancy ($P = .037$) compared to those patients infected with other species. Patients with CGCK were also more likely to have had a surgical procedure ($P = .043$) or to have received TPN ($P = .049$) during the 15 days or week prior to infection, respectively. Those with CGCK infection more often received at least one dose of any antifungal agent ($P = .008$) and more specifically at least one dose of fluconazole in the 15 days prior to infection ($P = .003$). A total of 40 patients (12%) died within 30 days of infection. Case fatality rates were similar between those with CGCK versus all other *Candida* spp. (12% vs 13%, $P = .74$).

After controlling for malignancy and receipt of TPN, receipt of at least one dose of fluconazole in the 15 days preceding infection (odds ratio [OR], 3.03; 95% confidence interval [CI], 1.08, 8.48), age >2 years (OR, 4.63; 95% CI, 1.01, 21.19) and receipt of a surgical procedure in the 15 days preceding infection (OR, 2.73; 95% CI, 1.08, 6.88) remained significant independent risk factors for CGCK infection.

Resistance data for 36 *Candida* isolates was available, including one *C glabrata* isolate and one *C. krusei* isolate, both of which were resistant to fluconazole. One isolate of *C albicans* was found to be highly resistant to fluconazole (minimum inhibitory concentration [MIC] $\geq$ 256 g/mL) and to voriconazole (MIC $\geq$ 16 g/mL), while one *C guilliermondii* isolate was resistant to caspofungin.

DISCUSSION

Our adjusted analysis identified recent fluconazole exposure as an independent risk factor for CGCK candidemia. The association of recent fluconazole exposure with subsequent fluconazole nonsusceptible candidemia has previously been documented in published studies including adults but not in pediatric patients [6]. This association is plausible, as recent fluconazole exposure may increase the potential for colonization and subsequent infection from fluconazole-resistant *Candida*. This finding has potential implications regarding the benefits and risks of utilizing fluconazole as a prophylactic agent. Studies have shown that the rate of CGCK infection has remained stable in adult populations [9] as well as in the neonatal intensive care unit [10, 11] but may be increasing in pediatric patients [12]. Continuous local surveillance of the rate of and impact from breakthrough infections is warranted to help inform the decision to continue with fluconazole prophylaxis or to consider an alternative approach such as no prophylaxis or prophylaxis with a different antifungal agent. It should be noted that during the study period, our institution was not routinely recommending fluconazole prophylaxis among all high-risk oncologic populations (ie, acute myelogenous leukemia); however, more recently fluconazole prophylaxis has been employed in this patient population. Continued surveillance for fluconazole-resistant *Candida* isolates following implementation of fluconazole prophylaxis is necessary.

Additionally, we found that age >2 years was an independent risk factor for CGCK candidemia. It is possible that older children are more frequently colonized with CGCK species; however, we are not aware of data

Table 1. Unadjusted Analysis of the Association of Various Demographic and Clinical Factors Relative to Acquisition of *Candida krusei* and *C glabrata*

Characteristic	Non-CGCK *Candida* Species (n = 321)	CGCK (n = 23)	*P* Value*
Patient characteristics			
Age in years	3.48 (1.11, 11.93)	9.27 (4.32, 13.80)	.017
Age > 2 years	206 (64%)	21 (91%)	.006
Male	8 (35%)	182 (57%)	.051
Length of hospital stay in days	34 (16, 69)	25 (15, 44)	.327
Time to infection	13 (4, 25)	12 (0, 27)	.487
Length of stay following infection	18 (9, 38)	15 (6, 25)	.219
Admitted to the ICU at diagnosis	132 (41%)	6 (26%)	.189
Comorbidities and clinical procedures			
Receipt of a prior bone marrow or solid organ transplantation	30 (9%)	5 (22%)	.071
Malignancy	97 (30%)	12 (52%)	.037
Dialysis (peritoneal/hemodialysis)	11 (3%)	1 (4%)	.570
Clinical features 48 hours prior to a positive blood culture for *Candida*			
Mechanical ventilation	85 (26%)	6 (26%)	>.999
Clinical features within 1 week prior to a positive blood culture for *Candida*			
Presence of a central venous catheter	293 (91%)	21 (91%)	>.999
Presence of an arterial catheter	77 (24%)	5 (22%)	>.999
Presence of a urinary catheter	78 (24%)	6 (26%)	.805
Receipt of total parenteral nutrition	182 (57%)	18 (78%)	.049
Clinical features within 15 days of study entry			
Receipt of a surgical procedure	75 (23%)	10 (43%)	.043
Neutropenia	53 (17%)	7 (30%)	.149
Non-candidal bloodstream infection	114 (36%)	7 (30%)	.822
Medication use within 15 days of study entry			
Receipt of antibiotics	290 (90%)	21 (91%)	>.999
Receipt of immunosuppressive agents	113 (35%)	7 (30%)	.821
Receipt of fluconazole	33 (10%)	8 (35%)	.003
Receipt of antifungal agents other than fluconazole	35 (11%)	3 (13%)	.730

**P* values obtained using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.
CGCK, *C glabrata* or *C krusei*; ICU, intensive care unit.

supporting this hypothesis. We also found that a recent surgical intervention was associated with CGCK candidemia. A previous pediatric analysis associated prior gastrointestinal surgery with CGCK infection [12]. Due to sample size limitations, we were unable to analyze risk of infection by type of procedure. Finally, TPN exposure did approach significance (OR, 2.49; 95% CI, 0.85, 7.30) for association with CGCK infection. Our sample size may have limited an ability to find a true association with TPN and thus future investigation in larger cohorts should consider this as a risk factor.

Prior publications have suggested a difference in important clinical outcomes among individuals who experience candidemia caused by fluconazole nonsusceptible species [5]. However, in our study we did not observe differences in mortality or hospital length of stay after candidemia onset between those with CGCK and those with other *Candida* spp. Given our small sample size of CGCK, we may have been underpowered to detect these differences. Additionally, we did not explore differences in other important clinical outcomes (eg, need for intensive care unit stay, organ failure).

In addition to a small sample size, other limitations exist. First, this was a single center study at a large pediatric hospital and thus the results may not be generalizable to all pediatric institutions. Second, we used CGCK status as a proxy for fluconazole resistance. While *C krusei* is often considered intrinsically resistant to fluconazole, *C glabrata* is frequently fluconazole sensitive [7, 8]. It would have been ideal to dichotomize the outcome as fluconazole resistance versus fluconazole-sensitive *Candida* spp.; however, MIC data were only available for a small subset of our isolates. Finally, our risk factors were somewhat arbitrarily defined by creating time windows ranging from 2 days to 15 days prior to infection, and for some risk factors these ranges may have been too small. Furthermore, in retrospect, for some of the covariates (mechanical ventilation and presence of CVC) we may have identified interventions that were needed as a result of candidemia rather contributing to the onset of candidemia.

We determined that recent fluconazole exposure, recent surgical intervention, and age >2 years were each independently associated with a risk for developing CGCK infection as compared to infection with other *Candida* species. Future multicenter studies should focus on confirming these factors as increasing the risk for candidemia secondary to microbiologically defined fluconazole-resistant species. Ultimately, establishing a

clinical prediction rule that can accurately predict fluconazole-resistant candidemia may help improve initial antifungal therapeutic choices and thus improve clinical outcomes.

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