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Incidence and Predictors of Invasive Candidiasis Associated with Candidemia in Children

Ara Festekjian, M.D.[1] and **Michael Neely, M.D.**[1,2,*]

[1]Childrens Hospital Los Angeles, CA, USA

[2]University of Southern California, Los Angeles, CA, USA

Abstract

Background—Risk factors for invasive candidiasis in children with candidemia are poorly defined.

Methods—We performed a retrospective cohort study of all children with candidemia at our tertiary children's hospital from 2000 to 2006. Invasive candidiasis was diagnosed by review of the medical record and standardized EORTC/MSG criteria. A variety of risk factors for invasive candidiasis were explored.

Results—Of 194 episodes of candidemia in the microbiology laboratory database, 180 clinical records were available. Evaluation for invasive candidiasis consisted of 174 (97%) echocardiograms; 167 (93%) dilated ophthalmologic examinations, 136 (76%) chest CT scans, and 108 (60%) abdominal ultrasounds (complete, hepatosplenic or renal). Of the 180, 15 (8%) patients were identified with invasive candidiasis (4 proven, 1 probable, 10 possible). Prematurity <32 weeks ($P<0.01$), an underlying immunocompromising disorder ($P<0.01$), and ≥2 days of candidemia ($P=0.05$) were significantly associated with invasive candidiasis.

Conclusions—Invasive candidiasis, especially proven or probable, in the setting of candidemia was not common in our hospital, but premature infants and immunocompromised children were at significantly higher risk. Based on our findings, extensive imaging and examination by an ophthalmologist was particularly low-yield for invasive candidiasis in immunocompetent children beyond infancy.

Keywords

Pediatric; Candidemia; Invasive; Risk Factors

Background

For over a decade, *Candida* species have been cited as the fourth most common nosocomial bloodstream infection in the United States and many other countries, with a proportion of all bloodstream infections that has risen over the past two decades 5- to 10-fold, to approximately 9% (1;2). While the majority of data are collected from adults, available evidence indicates that *Candida* species cause a similar or even higher proportion of bloodstream infections among children, especially in neonates (3–8). Although *Candida*-associated mortality in children is generally lower than that in adults, it nonetheless ranges from 10% to 54% (3;9;10) and by one estimate adds an average of 3 weeks of hospitalization at nearly $100,000 in cost (3).

*Corresponding author, 1640 Marengo St., #300, Los Angeles, CA 90033, tel: (323) 226-2330, fax: (323) 226-2505, mneely@usc.edu.

Risk factors for the development of candidemia, or recovery of *Candida* species from the blood, have been well described and include use of central venous catheters (9;11), extremely low birth weight (<1500gm) (12;13), and recent broad-spectrum antibiotic use, such as with third-generation cephalosporins (14–16). Candidemia may be associated with invasive candidiasis, defined as infection of at least one normally sterile extravascular site such as the eye, central nervous system, heart, lung, kidney, liver, or spleen. Invasive candidiasis is associated with significant morbidity and mortality, ranging from 20% to 70% (9;17). Therefore, upon identification of candidemia, evaluations for evidence of organ invasion are often made, which may include radiography or ultrasonography, dilated ophthalmologic examination, and possibly cerebrospinal fluid examination. The most recent Infectious Disease Society of America (IDSA) guidelines for the management of candidiasis, which are largely based on data from adults, endorse the ophthalmologic exam in all patients with candidemia as well as abdominal imaging when sterile fluid is "persistently positive" in neonates (18).

In contrast to the development of candidemia, risk factors for associated focal or multi-focal invasive candidiasis in a patient with identified candidemia have not been thoroughly defined in adults, let alone children. Consequently, there are few data to inform the decision of which additional investigations should be made in the setting of candidemia, in whom, and when. To our knowledge only one pediatric study has specifically addressed this issue, and it demonstrated that immunosuppression and more than three days of candidemia with a central venous catheter in place were separate, independent risk factors for invasive candidiasis in children with candidemia (19).

The objective of this study was to add to the definition of risk factors for invasive candidiasis in children with candidemia. In particular, we suspect that routine specialty examination and imaging is excessive and that a more targeted approach may be feasible.

Patients and Methods

Study design and setting

This study was approved by the institutional IRB with a waiver of informed consent for anonymous data collection. We conducted a retrospective cohort study by reviewing the medical records of children who were admitted to Children's Hospital Los Angeles, a tertiary care, stand-alone, 324-bed pediatric referral hospital.

Inclusion criteria

Eligible children were identified by searching the microbiology laboratory database for blood cultures which grew any *Candida* species from January 1, 2000 through February 28, 2006, inclusive.

Data abstraction

In addition to the dates and species of all blood cultures positive for *Candida*, the following data were abstracted as available from the paper and electronic medical records of identified patients: age and if under one year gestational age at birth, with severe or extreme prematurity defined as less than 32 weeks gestation (20); concurrent medical diagnoses; medications received two weeks prior to the onset of candidemia through the resolution of candidemia; peripheral white blood cell (WBC) count at the onset of candidemia; presence or absence of a central venous catheter (CVC) and if present, insertion date, removal date; duration of candidemia; and results of diagnostic studies including computed tomography scans, ultrasounds, cultures of normally sterile fluid (including cerebrospinal fluid), direct tissue biopsies, and ophthalmology examination.

The duration of candidemia in days was calculated beginning with the date of the first positive blood culture and continuing until the date of the last positive culture. Days between positive cultures were counted as positive. Intermittent negative cultures followed by positive cultures within 30 days were ignored. At least one final negative culture with no subsequent positive cultures was obtained from all surviving patients. If a patient died without a negative culture, the date of death was used to calculate the days of candidemia. Blood cultures positive for the same *Candida* species in the same patient fewer than 30 days apart were considered as the same candidemia event.

Classification of invasive candidiasis and statistical analysis

Patients were diagnosed with invasive candidiasis by review of the medical record, and were classified as proven, probable, or possible according to standard criteria defined (21) and revised (22) by the Invasive Fungal Infections Cooperative Group (IFICG) of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycology Study Group (MSG). Although the revised case definitions downplay the least-evidence-based category of “possible” as unsuitable for research use, we began the study prior to this revision, and had decided *a priori* to include these cases in anticipation of low numbers of children with invasive candidiasis. Further, we wished to capture a range of risk factors associated with invasive candidiasis, or what is treated as such in clinical practice. Data analysis was performed using SPSS 12.0 (SPSS, Inc., Chicago, IL) and R 2.9.0 (R Foundation, Vienna, Austria). Categorical variables were compared with the Chi-Square or Fisher’s Exact tests. Continuous variables were compared using Student’s t-test for variables with normal or log-normal distributions.

Results

Candidemia

Within the study window of 74 months, 194 patients with candidemia were identified from microbiology laboratory records, for an average of 2.6 patients/month. Two patients had mixed infections for a total of 196 blood isolates of *Candida* species: *C. parapsilosis* and *C. albicans* in one patient and *C. albicans* and *C. glabrata* in the other. *C. albicans* comprised 109 (56%) of the 196 isolates. Of the 87 non-*albicans* isolates, there were 49 (56%) *C. parapsilosis*, 20 (23%) *C. glabrata*, six (7%) *C. lusitaneae*, six (7%) *C. tropicalis*, five (6%) *C. krusei*, and one (1%) *C. rugosa*. The incidence of infections increased by an average of 1.9 episodes per year (P=0.13). The percentage of infections caused by *C. albicans* decreased by an average of 4% per year (P=0.30).

Of the 194 episodes of candidemia, 14 (7 %) medical records were missing, precluding further assessment. The remaining 180 episodes of candidemia occurred in 155 unique patients: 136 patients had only one episode of candidemia; 14 had two episodes separated by at least 30 days; four had three episodes; and one had four episodes. The median time between episodes was 9.7 months, with a range of 1.6 to 52.1 months. Because of the temporal separation of episodes in the same patient, each was considered independently for analysis of associated risk factors and outcomes. The number of blood cultures obtained per patient ranged from two to 36, with a median of four. All surviving patients had a final negative culture. In 144 (80%) of the 180 episodes, the last positive culture was followed by a negative culture or death the next day, leading to an accurate calculation of the duration of candidemia. In an additional 20 (11%) the final positive culture was two days before a documented negative culture. In the remaining 16 (9%), the final positive and first negative cultures were separated by 3–6 days. Candidemia persisted a median of three days and ranged from one to 29 days.

The age at the time of candidemia ranged from six days to 22 years, with a median of 2.3 years and interquartile range of 10 months to 8.3 years. Of the 55 (30%) episodes that occurred when the patient was under a year of age, 14 (25%) were also in a patient with a history of extreme or severe premature birth prior to 32 weeks gestation. In addition to prematurity, the majority of evaluable cases of candidemia occurred in patients with underlying chronic medical conditions, including gastrointestinal disorders (26%), neoplasms (19%), cardiac anomalies (13%), non-oncologic hematologic disorders (e.g. sickle cell disease, chronic granulomatous disease, 7%), cystic fibrosis (4%), and solid organ or bone marrow transplantation (2%). However, 19% did not have an underlying chronic condition and developed candidemia during treatment for acute or subacute conditions such as osteomyelitis or traumatic injury.

Central venous catheter (CVC) use was common: 160 (89%) of the 180 episodes had a CVC in place at the time of first positive blood culture for *Candida*, with 150 (94%) of these in place for more than 2 weeks prior. Although it is the standard recommendation at our institution to remove infected catheters, in practice it is often delayed due to limited vascular access and the need for multiple infusions: 63 (39%) CVCs were never removed despite the candidemia; only 11% were removed within one day of obtaining the first positive blood culture (when results may not have been known), 17% after two to five days when results would have been first reported to the clinicians, and 33% more than five days after the first positive culture. The geometric mean duration of candidemia in patients with a CVC was one day longer than in those without a CVC, regardless of when it was removed, if ever (3.3 vs. 2.3 days, P=0.05, Student's T-Test). Line removal did not affect the geometric mean duration of candidemia: 3.3 days in both groups (P=0.89, Student's T-Test).

Of the 180 candidemia episodes, 66 (37%) were associated with admission to an intensive care unit in the week prior or after first positive blood culture. Use of medications which could potentially affect the risk of invasive candidiasis was also relatively common, with 39 (22%) having ever received anti-neoplastic chemotherapy, 16 (9%) with chemotherapy, systemic steroids or other immunosuppressive agents given within 30 days of first positive blood culture, and 147 (82%) and 56 (31%) with systemic broad-spectrum antibiotics or antifungals, respectively, within one week prior to onset of candidemia. Crude mortality in this cohort was relatively high with 19 (11%) deaths.

Invasive candidiasis: diagnosis

Invasive candidiasis was diagnosed in 15 (8%) of the 180 episodes of candidemia. All 15 cases were in unique patients, and of these, 13 (87%) were suspected to have invasive disease on the basis of routine physical examination or laboratory data, prior to diagnostic imaging or ophthalmologic examination. By EORTC criteria, ten cases were possible, one was probable, and four were proven.

Among all 180 episodes of candidemia, at least one imaging study was performed to evaluate for invasive candidiasis. Echocardiograms were performed in 174 (97%); dilated ophthalmologic examination in 167 (93%), chest CT in 136 (76%), and abdominal ultrasound (complete, hepatosplenic, and/or renal ultrasound) in 108 (60%). Complete abdominal ultrasound was performed in 85 of these patients, while more limited hepatosplenic ultrasound (without renal imaging) was done in a single patient, and renal ultrasound alone in the remaining 22 patients. In 173 (97%) of the 180 episodes, more than one of these studies was obtained over time. Cerebrospinal fluid was only obtained in 21 (12%) episodes; 8 (50%) of the premature infants vs. only 13 (8%) of older children had cerebrospinal fluid samples (P<0.001, Fisher's Exact Test). There was no significant difference between those with and without invasive candidiasis with respect to the number of diagnostic studies obtained (P=0.56, Fisher's Exact Test). However, not surprisingly,

there was a bias towards more extensive workup in those who had a longer duration of candidemia: 101 (91%) of 111 with at least 2 days of candidemia had more than two diagnostic evaluations, vs. 51 (74%) of 69 with fewer than two days of candidemia (P=0.003, Fisher's Exact Test).

The most commonly diagnosed site of invasion was the lungs in 10 (67%) of the patients, although 8 of these were only possible cases, based on host factors, respiratory symptoms, and chest CT scans, in addition to the positive blood cultures. The remaining two were proven by biopsy. Renal mycetomas were detected in four (27%) patients: one probable, and three proven to be invasive candidiasis. *Candida* endophthalmitis/retinitis was diagnosed in two patients: one proven, and one possible. The spleen and liver were involved in one patient each, as probable and proven cases, respectively. Proven meningitis due to *Candida* was found in one patient, a premature infant. None of the echocardiograms were consistent with invasive candidiasis, i.e. endocarditis or endovasculitis.

Characteristics associated with invasive candidiasis

C. albicans was identified in the majority of episodes of candidemia with and without invasive candidiasis (67% vs. 52%, respectively, P=0.42, Chi-Square). *C. parapsilosis* was isolated in 29% of those without invasive candidiasis and 7% of those with invasive candidiasis; conversely, *C. krusei* was isolated in only 2% with no invasive candidiasis and 13% with invasive candidiasis. However, there was no overall significant association between species and a diagnosis of invasive candidiasis (P=0.12, Fisher's Exact Test), nor between *albicans* vs. non-*albicans* and invasive candidiasis (P=0.57, Chi-Square).

Table 1 summarizes univariate associations between risk factors and invasive candidiasis. While age itself was not significantly associated with invasive candidiasis, among children less than a year old at the time of candidemia, those with a history of premature birth prior to 32 weeks gestation were much more likely to have invasive candidiasis than those who were term infants at birth (OR 10.2, 95% CI 1.41 – 123.52, P=0.004, Fisher's Exact Test). All of these premature infants developed their invasive candidiasis before 6 months of age.

Excluding prematurity, there was a significantly different distribution of the type of underlying diagnosis among those with and without invasive candidiasis (P=0.01, Fisher's Exact Test). Although the low number of patients with invasive candidiasis did not permit identification of one or more specific disease groups significantly at risk compared to the others, children with disorders characterized by endogenous or exogenous immunocompromise (cystic fibrosis, neoplastic, hematologic, or transplantion-related) were more likely to have invasive candidiasis than children with underlying competent immune systems (P<0.001, Fisher's Exact Test).

At least two days of positive blood cultures for *Candida* species was significantly associated with invasive candidiasis (OR 4.41, 95% CI 0.95 – 41.59, P=0.05, Fisher's Exact Test). All of the episodes with uncertain duration of candidemia were at least two days, so extending the calculated duration of candidemia in these patients by including the interval between the last positive and first subsequent negative culture did not change the association with invasive candidiasis. Although duration of candidemia may be more relevant to the risk of invasive candidiasis when considered after removal of CVCs, the high rate of CVC retention in this population precluded such analysis.

Other factors related to presence, absence, or duration of central venous catheters, WBC count, use of immunosuppressant drugs, broad-spectrum antibiotics or antifungals, or admission to an intensive care unit were not significantly associated with invasive candidiasis in this dataset. The odds of death was 3.6-fold higher (95% CI 0.74 – 14.14,

P=0.06, Fisher's Exact Test) in those with invasive candidiasis compared to those without, and for every day of candidemia, the odds of death increased by 1.09-fold (95% CI 0.99 – 1.20, P=0.07, Logistic Regression).

Discussion

From 2000 through early 2006, candidemia in children at our hospital occurred at an average rate of nearly 3 new cases/month, similar to rates reported by others (14;16;19;23). Approximately 40% of the cases were caused by non-*albicans* species, also reflective of national trends (3;4;24–27). Invasive candidiasis, however, was diagnosed in fewer than 10% of these cases, and two thirds of the diagnoses were made with minimal certainty. This overall rate of pediatric invasive candidiasis is slightly lower than the rate of 17% reported by Zaoutis et al. (19), possibly due to reduced use of prophylactic/empiric antifungal agents (6.5%) in their population vs. the 29% use prior to the onset of candidemia in our population.

Two distinct groups at risk for invasive candidiasis in the setting of candidemia emerged from this analysis: premature infants in the first year of life and immunocompromised children. Invasive candidiasis was diagnosed in 36% of episodes of candidemia in premature infants, which was higher than the prevalence of 22% reported by Noyola et al in their 10-year neonatal study (28), possibly related to different diagnostic criteria. There is a large body of evidence documenting the relatively high frequencies of candidemia (12;13;16;29;30) and invasive candidiasis (28;31–33) in premature infants, who also have the least specific signs of a focal, invasive infection. Among this group of patients in our cohort, there was little clinical evidence to separate those infants who had candidemia with invasive candidiasis from those without invasive candidiasis, indicating that imaging and ophthalmologic work up for invasive candidiasis is appropriate in infants who have candidemia, particularly those with a history of prematurity. This is in agreement with IDSA guidelines (18).

Although recent use of immunosuppressive agents was not a significant predictor of invasive candidiasis, an underlying disorder associated with immunosuppression (endogenous or exogenous, i.e. iatrogenic) did significantly predict the odds of invasive candidiasis in agreement with previous findings (19). The overall prevalence of invasive candidiasis among immunocompromised children with candidemia was 15%, and they comprised 90% of the cases among children who were not premature infants. Only one case of invasive candidiasis was diagnosed in the 71 episodes of candidemia that occurred in immunocompetent children who were beyond infancy. In contrast to the premature infants, 8 (89%) of the 9 older patients with invasive candidiasis had localizing signs on routine physical exam that suggested a deep focal infection. The only child with no routine clinical evidence of invasive candidiasis was a patient with sickle cell disease who was found to have ultrasonographic lesions "consistent with fungus" in the kidney, but no *Candida* isolated from the urine, resulting in an EORTC/MSG "possible" diagnosis of invasive candidiasis. These data show that beyond infancy, the physical exam is an important indicator of the likelihood of invasive candidiasis.

Thirteen (87%) of the 15 cases of invasive candidiasis had more than one positive blood culture for *Candida*. One of the two cases of invasive candidiasis with a single positive blood culture was a premature infant, and the other was the patient with sickle cell anemia discussed above. This cutoff of two days is similar to the cutoff of at least three days found in the pediatric population studied by Zaoutis et al (19). It is clear that prolonged candidemia, at least in populations with other underlying risk factors, is associated with an increased risk of invasive candidiasis. What is less clear is whether prolonged candidemia

causes or results from invasive candidiasis. Furthermore, the high prevalence of retained CVCs in our population renders this relationship difficult to interpret,

Not surprisingly, invasive candidiasis tended to be associated with a greater crude mortality in this cohort compared to candidemia with no identified invasive candidiasis; this agrees with previous reports (9;17). Individual treatment strategies including choice of antifungal, combination, or sequential therapies did not significantly impact outcome, but this study was never designed to answer the question of which therapy is best for invasive candidiasis.

There are clearly limitations to our study, inherent in the design, which need to be taken into consideration. The retrospective nature means that not all patients had the same workup for invasive candidiasis and some may have been misclassified. Nonetheless, our study population was fairly consistently evaluated, particularly with respect to echocardiography and ophthalmologic exams. Imaging of the chest and/or abdomen was more sporadic, but still performed in well over half the children. We attempted to control for misclassification and charting bias by using MSG/EORTC criteria, although it must be stated that these guidelines are intended for adults, and none exist for children.

There was a significant bias towards more extensive workup in patients with prolonged candidemia; however, there was no significant difference in the number of diagnostic evaluations in those who were actually diagnosed with invasive candidiasis compared to the other children. Nonetheless, the diagnosis of invasive candidiasis would more likely have been missed in children with shorter periods of candidemia. This bias is of uncertain clinical significance since shorter duration of candidemia also improved survival.

The small number of patients with invasive candidiasis in this population, while strengthening our argument that extensive workup in every child with candidemia is excessive, limits our ability to detect the rarest of factors which might be significantly associated with invasive candidiasis. Furthermore, the diagnostic certainty of the majority of the cases of invasive candidiasis was only “possible”, which reflects the great difficulty clinicians and researchers can experience when trying to diagnose invasive fungal infections.

Conclusion

In conclusion, invasive candidiasis in our hospital, especially proven or even probable cases, was rare among children with candidemia, occurring less than 10% of the time. Two-thirds of the cases were diagnosed with minimal certainty, based solely on imaging and host factors. Infants with a history of premature birth less than 32 weeks gestation and children with underlying immunocompromise were at significantly higher risk of invasion. Based on our findings, an extensive workup consisting of imaging and examination by an ophthalmologist was particularly low-yield for invasive candidiasis in immunocompetent children beyond infancy, These findings should be further studied prospectively.

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Table 1

Characteristics of invasive candidiasis (IC). Percentages are columnar; odds ratios greater than one indicate that the odds of IC are higher for a given variable.

Variable	IC *(n=15)*	No IC *(n=165)*	Odds Ratio	95% CI	P-Value
Age <12 months	7 (47%)	48 (29%)	2.12	0.62 – 7.12	0.24
+ Prematurity <32 weeks	5 (33%)	9 (5%)	10.20	1.41 – 123.52	**<0.01**
Central venous catheter (CVC) present[a]	15 (100%)	145 (88%)	-	-	0.38
CVC removed	12 (80%)	85 (52%)	0.36	0.06 – 1.40	0.16
Candidemia ≥ 2 days	13 (87%)	98 (57%)	4.41	0.95 – 41.59	**0.05**
Recent broad spectrum antibiotics[b]	14 (93%)	133 (81%)	3.03	0.43 – 133.40	0.47
Recent systemic antifungals[b]	7 (47%)	49 (30%)	2.01	0.59 – 6.74	0.25
Intensive Care Unit Admission[c]	8 (53%)	58 (35%)	2.10	0.63 – 7.18	0.17
Total WBC (10^3 cells/mm^3)					
≤5	3 (20%)	30 (18%)	Ref	-	
5 – 15	10 (67%)	94 (57%)	1.06	0.30 – 4.97	0.93
>15	2 (13%)	41 (25%)	0.48	0.06 – 3.12	0.45
Absolute neutrophil count					
<500	1 (7%)	13 (8%)	Ref	-	-
500–1000	1 (7%)	10 (6%)	1.30	0.05 – 35.67	0.86
>1000	13 (87%)	137 (83%)	1.23	0.22 – 23.29	0.85
Pharmacologic immunosuppression					
Chemotherapy (ever)[d]	5 (33%)	34 (21%)	1.87	0.47 – 6.52	0.33
Recent immunosuppression[e]	1 (7%)	14 (8%)	0.70	0.02 – 5.28	1.00

Variable	IC *(n=15)*	No IC *(n=165)*	Odds Ratio	95% CI	P-Value
Underlying immunocompromise (excluding prematurity)					
Any[f]	9 (60%)	49 (30%)	18.78	2.48 – 841.38	**<0.01**
Oncologic	5 (33%)	30 (18%)	2.24	0.56 – 7.84	0.17
Crude mortality	4 (27%)	15 (9%)	3.57	0.74 – 14.14	0.06

[a] At time of first blood culture positive for *Candida* species

[b] Within one week of first positive blood culture

[c] Any admission from one week before to one week after onset of candidemia

[d] Chemotherapy, immunosuppressives or systemic steroids

[e] Within 30 days of first positive blood culture

[f] Cystic fibrosis, chronic granulomatous disease, sickle cell disease, neoplasm, or post-transplatation (bone marrow or solid organ)