MAJOR ARTICLE

Risk Factors and Predictors for Candidemia in Pediatric Intensive Care Unit Patients: Implications for Prevention

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Background. *Candida* species are the leading cause of invasive fungal infections in hospitalized children and are the third most common isolates recovered from patients with healthcare-associated bloodstream infection in the United States. Few data exist on risk factors for candidemia in pediatric intensive care unit (PICU) patients.

Methods. We conducted a population-based case-control study of PICU patients at Children's Hospital of Philadelphia during the period from 1997 through 2004. Case patients were identified using laboratory records, and control patients were selected from PICU rosters. Control patients were matched to case patients by incidence density sampling, adjusting for time at risk. Following conditional multivariate analysis, we performed weighted multivariate analysis to determine predicted probabilities for candidemia given certain risk factor combinations.

Results. We identified 101 case patients with candidemia (incidence, 3.5 cases per 1000 PICU admissions). Factors independently associated with candidemia included presence of a central venous catheter (odds ratio [OR], 30.4; 95% confidence interval [CI], 7.7–119.5), malignancy (OR, 4.0; 95% CI, 1.23–13.1), use of vancomycin for >3 days in the prior 2 weeks (OR, 6.2; 95% CI, 2.4–16), and receipt of agents with activity against anaerobic organisms for >3 days in the prior 2 weeks (OR, 3.5; 95% CI, 1.5–8.4). Predicted probability of having various combinations of the aforementioned factors ranged from 10.7% to 46%. The 30-day mortality rate was 44% among case patients and 14% among control patients (OR, 4.22; 95% CI, 2.35–7.60).

Conclusions. To our knowledge, this is the first study to evaluate independent risk factors and to determine a population of children in PICUs at high risk for developing candidemia. Future efforts should focus on validation of these risk factors identified in a different PICU population and development of interventions for prevention of candidemia in critically ill children.

Candida species are the leading cause of invasive fungal infections in hospitalized children and are the third most common isolates recovered from pediatric cases of healthcare-associated bloodstream infection in the United States [1]. Candidemia is frequently associated with signs and symptoms of sepsis syndrome [2]. The annual number of cases of sepsis caused by fungal organisms increased by 207% from 1979 to 2000 [3]. Fungal infections possess the second highest case fatality rate (13%) among all causes of sepsis in children [4].

The attributable mortality of candidemia in children has been reported to be 10%. In children, candidemia is associated with prolonged hospital length of stay (median, 21 days) and increased hospital charges (median, $39,331.00) [5]. Pediatric intensive care unit (PICU) patients are at highest risk for death to due candidemia [6, 7]; however, few data exist on the risk factors for candidemia in PICU patients. Understanding these risk factors may provide an epidemiologically based rationale for development of preventative strategies. Antifungal prophylaxis has been an effective preventative strategy in other pediatric populations at high risk for candidemia, including neonates and oncology patients [8, 9]. If the rate of candidemia is sufficiently high, then

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demonstrating the value of a preventative strategy is straightforward. However, the potential benefit of instituting preventative or prophylactic strategies in a large group of patients with a lower event (candidemia) rate is also weighed against the potential risks (eg, antifungal drug resistance or toxicity). Previous investigators have suggested that preventative strategies in intensive care should be targeted to populations with a baseline rate of candidemia of ⩾10% [10]. Further refining the risk factors helps to identify the subpopulations that may benefit most from antifungal prophylaxis and other preventive measures. Therefore, we conducted a population-based case-control study to determine the risk factors and predictors for candidemia in the PICU.

METHODS

Study Population

We conducted a population-based case-control study of all patients ⩽18 years of age admitted to the PICU at The Children's Hospital of Philadelphia (CHOP) during the period from 1997 through 2004. CHOP is an academic tertiary care center with 418 beds and ~24,000 hospital admissions per year. The PICU at CHOP consists of a 45-bed critical care unit that has ~3000 admissions per year and a 24-bed cardiac intensive care unit that has ~3600 admissions per year. All patients admitted to the PICU were identified using both hospital and unit-specific databases.

Definition of Case Patients

Candidemia was defined by use of a blood culture that yielded *Candida* species in a patient hospitalized in the CHOP PICU. Case patients were identified through the records of the clinical microbiology laboratory at CHOP. If multiple episodes of candidemia occurred in the same patient during the study period, then the patient was included as a study participant using only the first episode of candidemia.

Selection of Control Patients: Incidence Density Sampling

Study control patients were selected by use of unit-specific patient admission databases. To increase statistical efficiency, incidence density sampling was used to match control patients to case patients with respect to time at risk for developing infection. Time at risk is an important confounding variable because it represents the opportunity for both exposures (eg, antibiotics) and development of candidemia. For example, a patient who develops candidemia on day 10 of his or her PICU stay becomes a case patient, and the potential control patients are patients who have been in the PICU for at least 10 days and have not developed candidemia by day 10 of their stay. As such, a patient who ultimately develops candidemia is eligible to be selected as a control patient for the exposure period prior to his infection. In addition, time at risk is likely to be associated with severity of illness, which is another important confounding variable.

Control patients were selected for case patients using the following mechanism: we determined the length of PICU stay prior to infection for a given case patient, restricted the roster of PICU patients to those who had lengths of stay at least as long as the case patient's time to infection, and then randomly selected 2 control patients per case patient. For purposes of the conditional regression analysis, each subject was assigned an index date, which was the day of infection for the case patients and the corresponding day in the PICU for the matched control patients.

Data Collection

Research assistants used a structured data collection instrument to retrieve clinical and laboratory data from the inpatient medical record. Data obtained included age, sex, race, type of ICU, duration of hospitalization prior to infection, date of infection, and reason for admission.

All data on antimicrobial therapy in the 2 weeks prior to the index date were recorded. Data regarding the specific antimicrobial agent, duration of use, as well as the class of antibiotics to which it belongs (eg, cephalosporin) were also collected. Antimicrobial therapy was further classified as to whether it had activity against anaerobic bacteria in the gastrointestinal tract. Antimicrobials with antianaerobic activity (metronidazole, clindamycin, piperacillin-tazobactam, ticarcillin-clavulanic acid, ceftriaxone, ampicillin-sulbactam, amoxicillin-clavulanic acid, oral vancomycin, and the carbapenems) were of particular interest because they eliminate normal flora and thereby promote the growth of *Candida* species [11, 12]. Vancomycin was included because it has potent in vitro activity against gram-positive anaerobes and because oral administration results in broader activity against gram-negative species such as *Bacteroides* [13]. Similarly, ceftriaxone was included because it markedly decreases the levels of anaerobic gastrointestinal flora in humans [14, 15].

Comorbid conditions at the time of study entry were considered as potential confounders. These conditions included malignancy (specifying the type of malignancy), renal insufficiency (including requirement of hemodialysis or peritoneal dialysis), human immunodeficiency virus infection, primary immunodeficiency, neutropenia (absolute neutrophil count, $<500\ mm^3$) and duration of neutropenia, prior organ transplant (specifying the date and type of transplant), use of immunosuppressive agents (specifying which agents) in the preceding 2 weeks, and surgical procedure or trauma in the 2 weeks preceding the index date.

Information was collected regarding devices that were in place prior to the index date. Data on the presence of a central venous catheter (CVC) (including type and anatomic location), a urinary catheter, or a arterial catheter, receipt of mechani-

cal ventilation, and administration of enteral nutrition and/or hyperalimentation (ie, total parenteral nutrition) were also recorded.

Statistical Analysis

Following data collection, continuous variables were summarized using the median and interquartile range (IQR), whereas categorical variables were summarized using frequencies and percents. Univariate *P* values were obtained, adjusting for the matched analysis. All analysis was performed using Stata, version 10.1 (StataCorp). After univariate statistics were generated, we analyzed the data using 2 paradigms, conditional logistic regression and weighted logistic regression.

Conditional logistic regression. All factors with a univariate *P* value of <.20 were considered for inclusion in the multivariate model. Conditional logistic regression was used to identify independent risk factors for development of candidemia as we matched case patients to control patients on the basis of time at risk.

Weighted multivariate logistic regression. Because the case-control design with incidence density sampling was matched on time, we could not estimate the association between candidemia and time. To this end, we reconstructed with the use of weights the entire cohort by estimating the probability of the selection of each case patient and each control patient under incidence density sampling. The inverse of this selection probability was the sampling weight, and the sum of these sampling weights over the sampled subjects equaled the number of children in the cohort. The case patients plus the weighted control patients represent the entire group of children. Then using a weighted logistic regression, we examined the association between time and other risk factors with candidemia, just as a logistic regression could be applied to the entire cohort. In addition, we compared the results of these analyses with those of conditional logistic regression that are detailed above. Each variable included in the regression model was first cross-classified with each other variable to identify zero cells that would prohibit their simultaneous inclusion in a regression model. Factors that were prespecified as clinically important were forced into a multivariable model. Owing to the small number of case patients, we took care to avoid both overfitting (inclusion of too many variables) and confounding (omission of a factor related to both outcome and exposure).

Predicted probabilities. Using the weighted multivariate model, we derived predicted probabilities and 95% confidence intervals (CIs) for combinations of factors that were independently associated with the acquisition of candidemia. All combinations with predicted probability point estimates of $\geqslant$.10 were considered for our predictive model.

RESULTS

During the study period, we identified a total of 101 case patients with candidemia. The incidence of candidemia was 3.5 cases per 1000 PICU admissions. The most commonly isolated *Candida* species was *C. albicans* (46% of isolates), followed by *C. parapsilosis* (30%). Other *Candida* species accounted for 15% of the isolates (6% *C. tropicalis*, 3% *C. glabrata*, 3% *C. krusei*, and 3% *C. lusitaniae*). The remaining 9% of organisms isolated were multiple or unknown *Candida* species. A total of 184 control patients were selected; 18 case patients were matched to only 1 control patient.

Demographic and Clinical Characteristics

The demographic and clinical characteristics of patients with candidemia and control patients are shown in Table 1. Case patients were more likely than control patients to have a malignancy (17% vs 7%; $P = .008$) and neutropenia (6% vs 1%; $P = .036$) prior to study entry. In addition, case patients were more likely than control patients to have a CVC in place (92% vs 57%; $P < .001$) and to have received total parenteral nutrition (68% vs 33%; $P < .001$).

Multivariate Analysis

Table 2 displays the results from the weighted multivariate regression. The following factors remained independently associated with candidemia: the presence of a CVC (odds ratio [OR], 30.4; 95% CI, 7.7–119.5), malignancy (OR, 4.0; 95% CI, 1.23–13.1), the use of vancomycin for >3 days in the 2 weeks preceding study entry (OR, 6.2; 95% CI, 2.4–16), and the receipt of antimicrobial agents with activity against anaerobic organisms for >3 days in the 2 weeks preceding study entry (OR 3.5; 95% CI, 1.5–8.4).

Predictive Model for Candidemia

Figure 1 displays the predicted probability of developing candidemia in children who have various combinations of the risk factors significantly associated (>10% risk) with candidemia in weighted multivariate logistic regression analysis. On the basis of our data, the predicted probability of developing candidemia varied from 10.7% to 46%. Children with malignancy, a CVC in place, and who received vancomycin for >3 days are at 10.7% risk of candidemia (95% CI, 2.8%–32.9%). Children with malignancy who received >3 days of vancomycin and >3 days of antimicrobial agents covering anaerobic organisms, who have a CVC, and received total parenteral nutrition are at 46% risk of candidemia (95% CI, 19.0%–75.5%). Table 3 includes point estimates of predicted probabilities for children who have various combinations of risk factors significantly associated with candidemia.

Table 1. Unadjusted Risk Factors for Candidemia in the Pediatric Intensive Care Unit

Characteristic	Control patients (n = 184)	Case patients (n = 101)	Unadjusted OR (95% CI)
Median age (IQR), years	1.94 (0.3–11.2)	3.4 (0.7–11.1)	1.02 (0.98–1.06)
Male sex	85 (46)	43 (43)	0.86 (0.52–1.42)
Transferred from another healthcare institution	95 (52)	58 (57)	1.31 (0.79–2.17)
Comorbidities and clinical procedures			
Receipt of a prior transplantation	13 (7)	13 (13)	1.91 (0.82–4.46)
Malignancy	12 (7)	17 (17)	3.22 (1.36–7.60)
Dialysis (peritoneal or hemodialysis)	8 (4)	9 (9)	2.0 (0.72–5.57)
Graft vs host disease	1 (1)	2 (2)	3.24 (0.29–36.63)
Mechanical ventilation	110 (60)	71 (70)	1.68 (0.99–2.86)
Clinical features within 1 week of study entry			
Presence of a CVC	104 (57)	93 (92)	13.4 (4.80–37.42)
Presence of an arterial catheter	81 (44)	56 (55)	1.77 (1.02–3.06)
Presence of a urinary catheter	77 (42)	49 (49)	1.30 (0.78–2.17)
Receipt of total parenteral nutrition	61 (33)	69 (68)	5.30 (2.80–10.05)
Receipt of enteral nutrition	124 (68)	62 (61)	0.75 (0.44–1.27)
Clinical features within 15 days of study entry			
Receipt of a surgical procedure	61 (33)	41 (41)	1.05 (0.95–1.17)
Neutropenia	2 (1)	6 (6)	5.58 (1.12–27.79)
Noncandidal BSI	26 (14)	29 (29)	2.47 (1.35–4.52)
Medication use within 15 days of study entry			
Receipt of immunosuppressive agents	74 (41)	35 (35)	0.78 (0.47–1.32)
Receipt of antifungal agents	23 (13)	29 (29)	2.86 (1.44–5.66)
Receipt of antibiotics	146 (80)	93 (92)	5.44 (1.87–15.77)
Receipt of antibiotics, by class			
Parenteral or oral vancomycin			
0 days	123 (67)	42 (42)	Ref
1–3 days	24 (13)	21 (21)	2.56 (1.27–5.16)
⩾4 days	37 (20)	38 (38)	3.17 (1.73–5.82)
Extended-spectrum cephalosporins			
0 days	128 (70)	54 (53)	Ref
1–3 days	23 (13)	16 (16)	1.64 (0.79–3.39)
⩾4 days	33 (18)	31 (31)	2.31 (1.26–4.22)
Carbapenems			
0 days	176 (96)	90 (89)	Ref
1–3 days	3 (2)	2 (2)	1.44 (0.19–11.12)
⩾4 days	5 (3)	9 (9)	3.29 (1.10–9.89)
Aminoglycosides			
0 days	104 (57)	43 (43)	Ref
1–3 days	24 (13)	15 (15)	1.73 (0.80–3.76)
⩾4 days	56 (30)	43 (43)	2.09 (1.17–3.74)
Receipt of antibiotics, by spectrum of action			
Agents covering anaerobic organisms[a]			
0 days	122 (66)	52 (52)	Ref
1–3 days	12 (7)	6 (6)	1.34 (0.47–3.81)
⩾4 days	50 (27)	43 (43)	2.30 (1.29–4.11)

NOTE. Data are no. (%) of patients, unless otherwise indicated. All data are derived from the conditional matched analysis. BSI, bloodstream infection; CI, confidence interval; CVC, central venous catheter; IQR, interquartile range; OR, odds ratio; Ref, reference.

[a] Including ampicillin-sulbactam, clindamycin, imipenem, meropenem, metronidazole, and ticarcillin-clavulanate.

Table 2. Multivariate Model for Candidemia in the Pediatric Intensive Care Unit

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Receipt of vancomycin		
0 days	Ref	Ref
1–3 days	2.56 (1.27–5.16)	3.04 (0.98–9.46)
⩾4 days	3.17 (1.73–5.82)	6.19 (2.40–15.99)
Receipt of agents covering anaerobic organisms		
0 days	Ref	Ref
1–3 days	1.34 (0.47–3.81)	0.86 (0.17–4.37)
⩾4 days	2.30 (1.29–4.11)	3.51 (1.47–8.38)
Receipt of total parenteral nutrition	5.30 (2.80–10.05)	2.03 (0.80–5.12)
Presence of a CVC	13.4 (4.80–37.42)	30.45 (7.76–119.49)
Malignancy	3.22 (1.36–7.60)	4.02 (1.23–13.11)

NOTE. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are derived from the weighted regression analysis (for details, see Methods). Other factors were considered and ruled out as potential confounders. CVC, central venous catheter; Ref, reference.

Outcomes

The 30-day mortality rate was 44% for children with candidemia, compared with 14% for control patients (OR, 4.22; 95% CI, 2.35–7.60). The median length of PICU stay was 35 days (IQR, 17–69 days) for children with candidemia and 27 days (IQR, 14–67 days) for control patients (OR, 1.0; 95% CI, 0.99–1.01). The hospital length of stay was 46 days (IQR, 24–79 days) for children with candidemia and 36 days (IQR, 17–77 days) for control patients (OR, 1.0; 95% CI, 0.99–1.01). There was no statistical difference between case patients and control patients with respect to time between study entry and ICU discharge ($P = .509$).

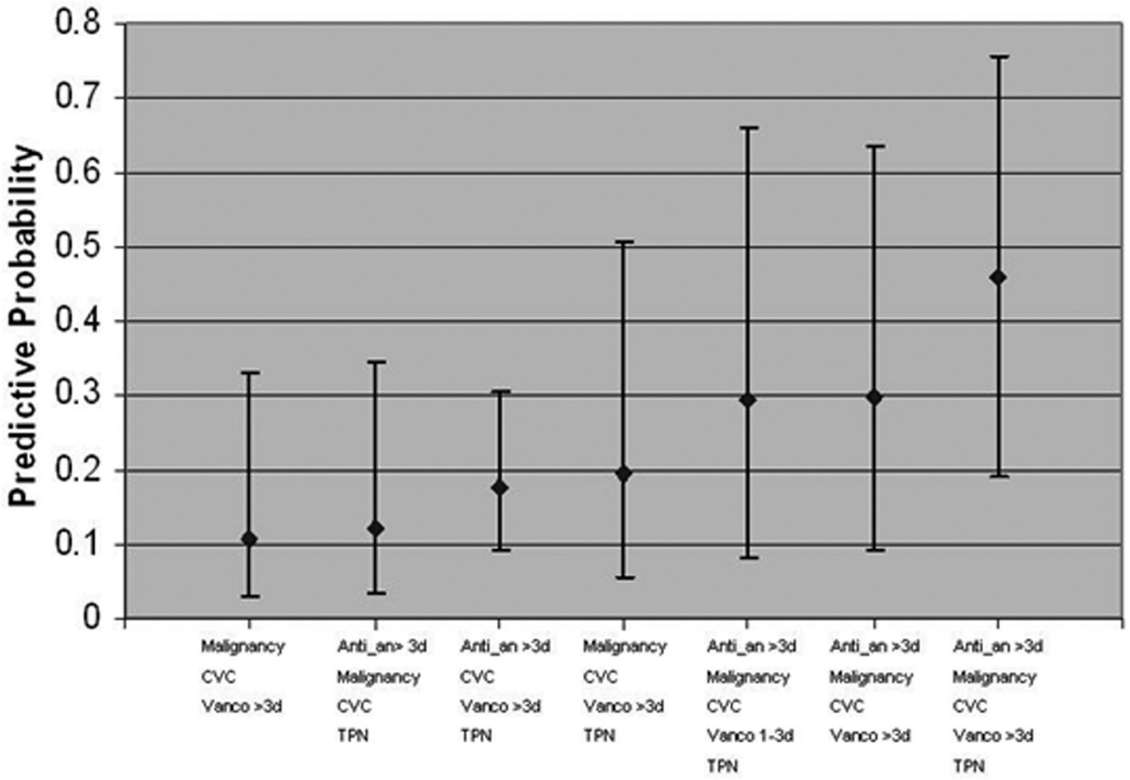

Figure 1. Predicted probabilities and 95% confidence intervals for candidemia in children in the intensive care unit, by risk factor combinations. Anti_an >3d, receipt of antimicrobials with antianaerobic activity for >3 days in the 2 weeks prior to study entry; CVC, central venous catheter; Malignancy, malignancy as a comorbid condition; TPN, total parenteral nutrition in the week prior to study entry; ; Vanco 1-3d, receipt of vancomycin for 1–3 days in the 2 weeks prior to study entry; Vanco >3d, receipt of vancomycin for >3 days in the 2 weeks prior to study entry.

Table 3. Predicted Probabilities of All Risk Factor Combinations with >10% Risk of Candidemia

Risk factors					
Anti-an	Malignancy	CVC	Vanco	TPN	Predicted probability (95% CI)
None	Yes	Yes	>3 days	No	0.106903 (0.028384–0.329068)
>3 days	Yes	Yes	None	Yes	0.120818 (0.034794–0.343777)
>3 days	No	Yes	>3 days	Yes	0.174846 (0.09297–0.304614)
None	Yes	Yes	>3 days	Yes	0.195158 (0.054084–0.506984)
>3 days	Yes	Yes	1–3 days	Yes	0.29465 (0.082548–0.659801)
>3 days	Yes	Yes	>3 days	No	0.295844 (0.09158–0.63649)
>3 days	Yes	Yes	>3 days	Yes	0.459778 (0.190498–0.754787)

NOTE. Anti_an, receipt of antimicrobials with antianaerobic activity in the 2 weeks prior to study entry; CI, confidence interval; CVC, central venous catheter; Malignancy, malignancy as a comorbid condition; TPN, total parenteral nutrition in the 1 week prior to study entry; Vanco, receipt of vancomycin in the 2 weeks prior to study entry.

DISCUSSION

To our knowledge, the present study is the first to evaluate independent risk factors and to determine a population of children in the PICU at high risk for developing candidemia. We found that the presence of a CVC, a diagnosis of malignancy, and receipt of either vancomycin or antimicrobials with activity against anaerobic organisms for >3 days were independently associated with the development of candidemia in the PICU. Children in the PICU with ⩾3 of these risk factors in different combinations had between 10% and 46% predicted probability of developing candidemia.

Previous studies have described risk factors for candidemia in neonatal intensive care unit (NICU) patients with an emphasis on premature neonates, a population of children with unique characteristics that may not be relevant to other pediatric patients [16, 17]. There is a paucity of data on risk factors outside the NICU. Several studies have reported the general characteristics of children outside the neonatal period who have developed candidemia [18–22]; however, data from studies using multivariate analysis to adjust for confounding are limited. In one of the previously conducted controlled pediatric studies of 24 cases of candidemia, investigators identified hyperalimentation as an independent risk factor for candidemia in children [20]. Although, hyperalimentation was not independently associated with candidemia in our study, it did contribute significantly to predicting candidemia, in addition to the other variables.

Both the presence of a CVC and malignancy have been previously identified as risk factors for candidemia [23, 24]; however, we were surprised by the magnitude of the effect CVCs had in PICU patients, suggesting that CVCs may be a significant source of candidemia in this patient population. Patients with malignancy are clearly at increased risk for candidemia because of their underlying immunocompromised state. That *Candida parapsilosis* comprised 30% of all isolates causing candidemia is consistent with the role of vascular catheters as a potential portal of entry. However, the source of *Candida* in patients with neoplastic diseases more likely derives from the gastrointestinal tract [24]. Mucosal disruption caused by cytotoxic chemotherapy and abrogation of normal gastrointestinal flora by antimicrobial therapy create a permissive environment that allows *Candida* to invade the mesenteric circulation.

There have been several studies that have investigated the relationship between antibiotic use and candidemia [25–32], but little is known about the relationships between the spectrum of antimicrobial activity or the duration of antibiotic use and candidemia. Numerous studies in animals have shown that the normal anaerobic gastrointestinal flora provide an important defense mechanism against infection by inhibiting the growth of potentially pathogenic organisms, a concept known as colonization resistance [33–35]. Colonization resistance is the limiting action of the normal flora that prevents overcolonization by endogenous organisms such as *Candida* species [34, 36, 37]. It has been clearly established that the presence of anaerobic bacteria in the gut inhibits the overgrowth of *Candida* species [34, 36, 37]. Therefore, we hypothesized that the use of antimicrobials with activity against the anaerobic gastrointestinal flora would be associated with the development of candidemia, an independent association that was found in our analysis. Although we did not include parenteral vancomycin in the group of antimicrobials with activity against anaerobic organisms, it is not surprising that parenteral vancomycin use was an independent risk factor for candidemia, because it does have significant activity against many anaerobic bacteria found in the gastrointestinal tract.

In the absence of a clinical prediction rule that could be used to identify patients who will benefit most from antifungal prophylaxis, other strategies to decrease rates of candidemia could be considered. Anecdotally, NICUs have observed decreasing rates of candidemia by improving infection control practices and antimicrobial stewardship strategies. In addition, because of the significant risk CVCs posed for developing candidemia

in our study, reeducation of healthcare providers who are involved in the day-to-day care of critically ill patients on best practices surrounding CVC maintenance may yield decreased rates of the illness.

There were several potential limitations to our study. Selection bias is normally of concern in a case-control study, but the nested case-control study design applied to our analysis allows selection of case patients and control patients from the same distinct source cohort (ICU admission), thus minimizing the likelihood of selection bias. Misclassification bias is likewise of concern in case-control studies. Case patients and control patients were drawn from the same hospitalized patient population and were identified solely on whether *Candida* species was isolated from blood culture. Because these cultures were performed for clinical care, without previous knowledge of the patient's status regarding possible exposures of interest, there was unlikely to be any differential misclassification. Missing data can be an issue in studies involving retrospective review of medical records; however, past studies utilizing the same database of inpatient medical records used in our study found 97% of records complete and available for review. Any missing data would result in a nondifferential bias and bias toward the null; yet, our results show strong associations between the hypothesized risk factors and candidemia.

Although the population from which the case patients and control patients were drawn was large, the number of observations is necessarily limited by the incidence of candidemia. Consequently, the confidence bounds around the ORs (Table 2) and predicted probabilities (Figure 1 and Table 3) are wide. Despite this limitation, our results suggest that combinations of risk factors are strongly associated with a higher probability of developing candidemia. Our institution is one of the largest children's hospitals in the United States, but our findings may not be generalizable to other institutions; therefore, further work to validate our results will require multicenter collaboration.

We identified several combinations of predictors that identified a group of children in the PICU with a >10% risk of developing candidemia who may potentially benefit from prophylaxis. Clinical prediction rules for candidemia are currently being evaluated in adult ICU patients [38, 39]. Currently, no such scores exist for PICU patients. A predictive model could be of great clinical value to intensivists who care for children in the PICU (patients who are at high risk for candidemia because of their underlying severity of illness). A predictive model would also facilitate the evaluation of preventative strategies. Future efforts should focus on validation of the risk factors identified in our study in a different PICU population and development of interventions for prevention of candidemia in critically ill children.

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