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RISK FACTORS FOR CANDIDEMIA IN CRITICALLY ILL INFANTS:

A MATCHED CASE-CONTROL STUDY

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Abstract

Objective—To determine risk factors for late-onset candidemia among infants in the neonatal intensive care unit (NICU).

Study design—We performed a matched case-control study from March 2001 to January 2003 in 2 level III-IV NICUs. Case subjects had candidemia diagnosed more than 48 hours after hospitalization. Control subjects (3 per case) were matched by study site, birth weight, study year, and date of enrollment. Potential risk factors included medical devices, medications, gastrointestinal (GI) pathology (congenital anomalies or necrotizing enterocolitis) and previous bacterial bloodstream infections (BSIs).

Results—Forty-five cases of candidemia occurred during the study period and accounted for 15% of BSIs. *C. albicans* caused 62% of infections (28/45); *C. parapsilosis*, 31% (14/45). Multivariate analysis revealed that catheter use (odds ratio [OR] = 1.06 per day of use; 95% confidence interval [CI] = 1.02 to 1.10), previous bacterial BSIs (OR = 8.02; 95% CI = 2.76 to 23.30) and GI pathology (OR = 4.57; 95% CI = 1.62 to 12.92) were significantly associated with candidemia. In all, 26/45 cases (58%) of candidemia occurred in infants who would not have qualified for fluconazole prophylaxis according to the Kaufman criteria.

Conclusions—We confirmed previous risk factors (catheter-days) and identified novel risk factors (previous BSI and GI pathology) for candidemia in critically ill infants that could guide future targeted antifungal prophylaxis strategies.

During the past 2 decades, *Candida* species have become an increasingly important cause of late-onset sepsis in critically ill infants, especially in very low birth weight (VLBW) infants hospitalized in the neonatal intensive care unit (NICU).[1] According to published data, 0.004% to 1.5%[1-5] of all patients in the NICU, 2.6% to 3.1%[1,6-8] of VLBW infants (birth weight < 1500 g), and 5.5% to 10%[1,9] of extremely low birth weight (ELBW) infants (birth weight < 1000 g) develop candidemia. Risk factors consistently cited by multiple studies include VLBW, use of central venous catheters, total parenteral nutrition, and prolonged antimicrobial therapy.[1,2,3,5,10] The importance of other risk factors, such as administration of histamine-2 (H2) blocking agents, corticosteroids, specific classes of antibiotics, and concomitant gastrointestinal (GI) pathology are less well studied in pediatric populations.

Despite the fact that low birth weight is a well-known risk factor, few studies have matched study subjects by birth weight in an effort to examine additional risk factors.[3,10] Furthermore, risk factors may have changed in recent years because of infections caused by increasingly

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resistant bacterial pathogens requiring treatment with broad-spectrum antibiotics.[11] In efforts to reduce the morbidity and mortality associated with *Candida* infections in ELBW infants, fluconazole prophylaxis was evaluated prospectively in a single-center, randomized, placebo-controlled trial.[12] Although efficacy was demonstrated in this subset of hospitalized neonates, other subsets of infants in the NICU are also at risk for candidemia. Therefore, in view of increasing rates of candidemia noted at our institution,[1] potentially changing risk factors, and increasing interest in antifungal prophylaxis, we performed a matched case-control study to determine risk factors that could aid in further targeting antifungal prophylaxis strategies for NICU patients.

METHODS

Study Design

We performed a matched case-control study with a 1:3 ratio of case to control subjects. This substudy was part of a larger clinical trial examining the effects of hand hygiene practices on hospital-associated infections in critically ill neonates conducted from March 1, 2001 to January 31, 2003.[13] A cross-over month occurred in February 2002 in which hand hygiene products (2% chlorhexidine vs alcohol-based hand rub) were exchanged and no data were collected.

Study Sites

The study was performed in 2 geographically distinct level III-IV NICUs. NICU 1 (43 beds) and NICU 2 (50 beds) are both part of the New York Presbyterian Hospital in New York City and do not share personnel. The Institutional Review Boards of both institutions approved the clinical trial, and a waiver of informed consent for collection of neonatal data was granted.

Surveillance for Candidemia

Surveillance for hospital-acquired infections, as defined by the National Nosocomial Infections Surveillance system and adapted for neonates, was performed prospectively by a trained surveillance officer.[14] Sources of data included laboratory, radiology and pharmacy records, patient medical records, information from physician and nursing staff, and direct observations of neonates. Blood cultures were obtained by the NICU staff as clinically indicated. Systematic antifungal prophylaxis (ie, the use of fluconazole in infants without signs or symptoms of disease) was not used by either NICU during the study.

Case and Control Subject Definitions

In this substudy, a case subject was defined as an infant with hospital-acquired candidemia occurring more than 48 hours after hospitalization in 1 of the 2 study sites. For each case subject, 3 control subjects were selected and matched to their respective case by several characteristics. These characteristics included study site (NICU 1 or NICU 2); 250-g birth weight groups (group 1, < 500 g; group 2, 500 to 750 g; group 3, 751 to 1000 g; group 4, 1001 to 1250 g; group 5, 1251 to 1500 g; group 6, 1501 to 1750 g; group 7, 1751 to 2000 g; group 8, 2001 to 2250 g; group 9, 2251 to 2500 g; or group 10, > 2500 g); study year (year 1, March 2001 to January 2002; year 2, March 2002 to January 2003); and enrollment date within 60 days of the date of case enrollment in the study.

When more than 3 eligible control subjects were matched to a given case subject, those with an enrollment date closest to the enrollment date of the respective case subject were selected. Only 1 infant from a multiple gestation could serve as a control subject, and a sibling could not serve as a control for a sibling case. The enrollment date was defined as the date of admission to the study NICUs except for infants admitted before March 1, 2001 (the date the

study began) or during February 2002 (the cross-over month), for whom the enrollment date was defined as March 1, 2001 or March 1, 2002, respectively.

Assessment of Risk Factors

Patient characteristics and exposure to potential risk factors for candidemia were evaluated prospectively among all case subjects from their date of enrollment until the day before the onset of candidemia (ie, the "candidemia risk period"). To assess comparable "risk periods" for matched control subjects, exposure to potential risk factors for each control subject was assessed prospectively from their enrollment date through the same number of hospital-days as the "candidemia risk period" of the respective case subject. If a control subject's hospitalization was shorter than the "risk period" of the matched case, then exposure to risk factors was determined from enrollment date until the date of discharge. Risk factors examined included central catheter-days, ventilator-days, and nasal cannula continuous positive airway pressure (NC-CPAP)-days; prior conjunctivitis, pneumonia, or bacterial bloodstream infections (BSIs); receipt of parenteral nutrition, intralipids, medications (eg, corticosteroids, H2 blocking agents/proton pump inhibitors, antifungal agents, different classes of antibiotics); and GI pathology. GI pathology was defined as congenital anomalies (eg, tracheoesophageal fistula, gastroschisis, omphalocele, Hirschprung disease, intestinal atresias) or episodes of necrotizing enterocolitis (NEC). NEC was defined as a combination of 1 or more clinical signs (eg, bilious gastric aspirate/emesis, abdominal distention or occult/gross blood in stool) and 1 or more radiographic findings (eg, pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum) or evidence of bowel perforation/necrosis during surgery. Exposure to risk factors occurring outside of the study sites could not be assessed; thus both case and control subjects may have had incomplete risk factor data if they had been discharged and readmitted to the study sites, were admitted to the study NICU at > 3 days of life or were admitted to the study sites before March 1, 2001 or during February 2002.

Microbiology Methods

Blood cultures were collected in Bactec Peds Plus bottles (Becton, Dickinson and Company, Sparks, MD) in accordance with usual clinical practice; positive cultures were subcultured onto Sabouraud dextrose agar (Becton Dickinson, Cockeysville, MD) and BBL chromagar (Becton Dickinson), which were then incubated for 48 hours. The Microscan 4-Hour Rapid Yeast Identification Panel (Dade Behring, West Sacramento, Calif) and corn meal agar with polysorbate 80 (Becton Dickinson) were used for identification of *Candida* species. Biomerieux API (Biomerieux, Durham, NC) was used to confirm identification if needed. Antifungal susceptibility testing was not performed routinely.

Statistical Analysis

Each potential risk factor was entered into a univariate conditional logistic regression model matching for birth weight, site, year of study, and admission date. All risk factors found to be significantly associated ($P < .05$) with candidemia by univariate analysis were entered into a multivariate conditional logistic regression model using a stepwise selection procedure (P for entry and retention <.05). Potential interactions were also assessed. Analysis was conducted using SAS 8.02 (SAS Institute, Cary, NC).

RESULTS

Case Ascertainment and Incidence of Candidemia

During the 2-year study, 2829 infants were enrolled, of whom 1655 (58%) were hospitalized in NICU 1 and 1174 (42%) were hospitalized in NICU 2. In all, 298 episodes of BSI occurred, of which 159 (53%) were caused by gram-positive pathogens, 56 (19%) by gram-negative

pathogens, 38 (13%) by *Candida* spp. and 45 (15%) by more than 1 pathogen, including 7 polymicrobial infections with *Candida* spp. Thus, 45 cases of candidemia occurred, 37 (82%) in NICU 1 and 8 (18%) in NICU 2. *C. albicans* caused 28 of 45 (62%) episodes of candidemia, *C. parapsilosis* caused 14 episodes (31%), and *C. glabrata, C. stellatoidea* and *C. lusitaniae* caused 1 episode (2%) each. The median and mean age at the onset of candidemia was 21 and 24 days, respectively.

The incidence of candidemia during the study was 1.6% of all admissions, or 2.5 cases per 1000 catheter-days, or 15.9 cases per 1000 admissions. The distribution of birth weight was comparable in the 2 NICUs, except that NICU 1 had a significantly higher ($P = .007$) proportion of infants (12.1%) weighing ≤1000 g compared with NICU 2 (8.4%). The incidence of candidemia was inversely proportional to birth weight; 9.4% (17/180), 8.0% (24/300), 5.2% (32/610), and 2.5% (37/1457) of infants weighing ≤800, ≤1000, ≤1500, and ≤2500 g (inclusive groups), respectively, were diagnosed with candidemia. Of the 22 infants with birth weight < 1000 g who developed candidemia, 19 had central vascular catheters or endotracheal tubes during the first 5 days of life.

Characteristics of Case and Control Subjects

Demographic characteristics generally were similar among case and control subjects, as shown in Table I. However, length of hospital stay and length of "risk period" were different among case and control subjects. The risk period for case and control subjects with birth weight ≤1500 g was 22.1 days and 15.7 days, respectively ($P = .03$) and that for case and control subjects with birth weight > 1500 g was 24.9 days and 7.1 days, respectively ($P = .005$). There was no difference in the proportion of case subjects (n = 6; 13%) and control subjects (n = 10; 7%) admitted before the start of the study or during the cross-over month of February 2002 ($P = .24$). The crude mortality rate was 22% (10/45) for cases and 10% (14/135) for controls ($P = .043$); deaths occurred in 25% (7/28), 14% (2/14), and 33% (1/3) of infants infected with *C. albicans*, *C. parapsilosis*, and other *Candida* species, respectively. The mortality rate did not significantly differ between infants infected with *C. albicans* and those infected with *C. parapsilosis* (Fisher's exact test; $P = .693$).

Univariate Analysis

Potential risk factors for candidemia found to be significant by univariate analysis are given in Table II.Of the 22 case subjects with previous bacterial BSIs, 14 cases (64%) were due to gram-positive organisms, 5 cases (23%) were due to gram-negative organisms, and 3 cases (13%) were polymicrobial. Bacterial BSI rates among case and control subjects were 21.3 and 4.5 per 1000 patient-days, respectively ($z = 6.67$; $P < .01$). Of the 15 case subjects with GI pathology, 7 had NEC and 8 had congenital anomalies. As expected, NEC occurred more often in preterm infants (mean birth weight, 1277 g; range, 600 to 3060 g), and congenital anomalies occurred more often in term infants (mean birth weight, 2497 g; range, 782 to 3720 g). Only 7 of 15 (47%) case subjects with GI pathology had undergone surgery before their episode of candidemia. Three case subjects had candidemia without a central venous catheter in place.

Multivariate Analysis

The final multivariate model is given in Table III. Only central venous catheter use, GI pathology, and previous bacterial BSIs were significant predictors of candidemia. Interactions between these variables were not significant. To address differential exposure time between case and control subjects, central venous catheter-days were used in the model rather than risk period-days. This avoided the impact of collinearity in the model ($r = .869$ for catheter-days and risk period-days). Furthermore, the variable catheter-days was selected because of its importance as a risk factor for candidemia in previous studies and because of the superior explanatory power demonstrated in the univariate analysis (catheter-days, OR = 1.09 per day,

$P < .0001$, compared with risk period-days, OR = 1.05 per day, $P = .0003$). To assess the effect of missing risk factor data resulting from time spent away from the participating NICUs, the multivariate analysis was repeated excluding 12 case subjects, their 36 matched control subjects, and 17 additional control subjects with missing data. This analysis demonstrated that catheter-days (OR = 1.07 per day; 95% CI = 1.01 to 1.14; $P = .02$), previous BSI (OR = 11.83; 95% CI = 2.73 to 51.32; $P = .001$), and GI tract pathology (OR = 4.03; 95% CI = 1.15 to 14.17; $P = .03$) remained significant predictors of candidemia.

DISCUSSION

To our knowledge, this is the largest case-control study to date examining risk factors for candidemia among NICU patients.[3,10,15] Previous case-control studies, performed in the 1980s and 1990s, assessed only 8 to 21 cases of candidemia,[3,10,15] infrequently used controls matched for birth weight, or rarely used multivariate analysis.[15] Previous studies demonstrated that birth weight and use of catheters, parenteral nutrition, antibiotics, H2 blocking agents, and ventilatory support were risk factors for candidemia.[1,2,3,8,10] Although our univariate analysis suggested that ventilatory support, parenteral nutrition, and administration of certain antibiotics were associated with candidemia, these associations were not statistically significant in the multivariate model. In this study, we controlled for the most important risk factor (ie, birth weight) and identified that previous bacterial BSIs and GI pathology were risk factors for candidemia. These factors are consistent with our current understanding of the pathogenesis of candidemia.

Central venous catheters are well-described risk factors for candidemia in critically ill infants.[1,3,10] We found an increased risk (OR = 1.06 per day; 95% CI = 1.02 to 1.10) of candidemia associated with each day of central catheter use. This finding is not surprising, because *Candida* can adhere to platelets and fibrinogen on the surface of catheters and form biofilms that may protect the organisms from the immune response and antifungal agents.[16]

We identified that bacterial BSIs before the onset of candidemia were associated with an increased risk (OR = 8.02; 95% CI = 2.76 to 23.30) of candidemia. Michalopoulus et al[17] also identified previous bacterial BSIs as an independent predictor for candidemia in adults cared for in a cardiothoracic intensive care unit. We examined whether BSIs were a surrogate for antibiotic use, but there was no significant correlation between BSIs and different antibiotic classes ($r = .23$ to $.41$), nor did antibiotic use become significant in a multivariate model that eliminated previous BSIs. We speculate that these analyses highlight the substantial use of antibiotics empirically in this population, and that a previous BSI may be a surrogate for more prolonged antimicrobial use. Alternatively, both bacterial and fungal infections may be markers of impaired host immune function. Finally, the actual treatment of bacterial BSIs may be associated with interventions that are themselves risk factors for candidemia, such as the use of central venous catheters for antibiotic delivery or parenteral nutrition due to the inability to tolerate enteral feeding.

GI pathology, including congenital anomalies and NEC, was an independent predictor for candidemia (OR = 4.57; 95% CI = 1.62 to 12.92). Factors that affect the integrity of the bowel mucosa, such as abdominal surgery, may promote translocation of *Candida* strains colonizing the GI tract.[1,18,19] Although NEC occurred largely in preterm infants and congenital GI anomalies occurred largely in term infants, we hypothesize that both conditions have similar pathogenic characteristics.

Our study has some limitations. Several infants were admitted before starting the study or during the cross-over month; this occurred with similar frequency among case and control subjects. However, risk factor data for these time periods could not be assessed. Further, some

infants had more than 1 admission to the study sites or were admitted to the study sites at > 3 days of life; thus, data are lacking from hospitalizations outside the study NICUs. Transfer notes for control subjects transferred from an outside hospital were reviewed for previous candidemia, but we could not review the blood culture results from the outside hospitals. Nevertheless, the same risk factors for candidemia (at similar magnitudes of effect) were demonstrated by multivariate analysis with and without infants with missing risk factor data. Further, the age at enrollment of the case subjects and control subjects differed within some matched groups despite controlling for birth weight. Finally, despite random selection of controls and attempts to assess the same "risk period" for both control and case subjects, control subjects had a significantly shorter "risk period" than case subjects, due largely to the earlier discharges of the former.

Our study findings have implications for assessing potential strategies for antifungal prophylaxis in high-risk neonates. A previous study demonstrated that prophylactic fluconazole during the first 6 weeks of life in ELBW infants (birth weight < 1000 g) with central vascular catheters or intubation decreased fungal colonization (eg, skin, stool, and nasopharynx) and invasive disease (*Candida* in the urine, blood, or cerebrospinal fluid); 0/50 (0%) fluconazole participants versus 10/50 (20%) placebo participants developed candidemia, candiduria, or fungal meningitis.[12] However, this was a single-center study with high rates of candidemia relative to previous studies,[1,9] and it is difficult to assess whether this prophylactic strategy is generalizable to other NICU populations. During our study period, this prophylactic strategy would not have been provided to most of the case subjects (n = 26; 58%), because we demonstrated that infants with birth weight < 1000 g without central venous catheters or intubation (n = 3) and infants with birth weight ≥1000 g (n = 23) with risk factors such as GI pathology or previous BSIs developed candidemia. The widespread use of fluconazole prophylaxis in other patient populations has led to increasing rates of azole resistance,[20] and, although this phenomenon has not yet been observed among NICU patients,[12] with increased use of fluconazole prophylaxis, the risk remains. Therefore, efforts to identify risk factors that can better predict candidemia could improve the future development of targeted prophylactic strategies. We support the need for a multicenter study examining targeted prophylactic fluconazole in critically ill infants.

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Abbreviations

BSI, Bloodstream infection; ELBW, Extremely low birth weight; GI, Gastrointestinal; H2, Histamine-2; NC-CPAP, Nasal cannula continuous positive airway pressure; NEC, Necrotizing enterocolitis; NICU, Neonatal intensive care unit; VLBW, Very low birth weight.

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Table I

Demographic characteristics of matched case and control subjects

Characteristics	Case subjects (n = 45)	Control subjects (n = 135)	*P* value
Study site, n (%)			
1	37 (82%)	111 (82%)	-
2	8 (18%)	24 (18%)	-
Gender (males), n (%)	23 (51%)	77 (57%)	.49
Birth weight (g), mean (±SD)	1397 (±914)	1440 (±971)	.76
Gestational age (weeks), mean (±SD)	30 (±5)	30 (±5)	.62
Mean age at enrollment (days), mean (±SD)	7 (±24)	10 (±26)	.49
Median age (days)	0	0	-
Length of total hospital stay (days), mean (±SD)	75 (±56)	32 (±37)	<.0001
“Risk period” (days), mean (±SD)	23 (±16)	13 (±13)	<.01

Case and control subjects (1:3) were matched on birth weight, site, year of study, and date of enrollment.

SD, standard deviation.

Table II

Significant risk factors for candidemia in univariate analysis

Characteristics	Parameter estimate [±SE]	Case subjects (n = 45)	Control subjects (n = 135)	Odds ratio [95% Confidence interval]	*P* value
		Mean [± SD]			
Catheter-days	0.09 [±0.02]	21.76 [±16.22]	7.58 [±9.49]	1.09 [1.06, 1.13]	<.0001
NC-CPAP-days	0.03 [±0.01]	12.42 [±12.53]	7.54 [±10.61]	1.04 [1.01, 1.07]	.01
Ventilator-days	0.09 [±0.02]	12.29 [±13.35]	3.82 [±7.05]	1.09 [1.05, 1.14]	<.0001
		N (%)			
Previous BSIs	2.55 [±0.46]	22 (49%)	8 (6%)	12.81 [5.18, 31.68]	<.0001
GI pathology	1.71 [±0.44]	15 (33%)	11 (8%)	5.52 [2.31, 13.19]	.0001
Antifungal agents	1.38 [±0.63]	6 (13%)[a]	5 (4%)	3.96 [1.15, 13.62]	.03
Aminoglycoside agents	1.03 [±0.51]	40 (89%)	100 (74%)	2.79 [1.02, 7.60]	.046
Carbapenems	1.67 [±0.58]	9 (20%)	6 (4%)	5.31 [1.78, 15.84]	<.01
Third generation cephalosporins	1.40 [±0.46]	12 (27%)	11 (8%)	4.06 [1.65, 9.98]	<.01
Vancomycin	1.56 [±0.37]	29 (64%)	37 (27%)	4.75 [2.32, 9.72]	<.0001
Parenteral nutrition	2.01 [±0.75]	43 (96%)	101 (74%)	7.47 [1.72, 32.40]	<.01
Intralipids	2.65 [±0.74]	43 (96%)	81 (60%)	14.18 [3.30, 69.91]	<.01

SE, standard error.

[a]Four of 6 received amphotericin for 2 to 11 days, 1 to 17 days before candidemia. Two of 6 received fluconazole for 4 to 7 days, 1 to >30 days before candidemia.

Table III

Final multivariate model

Variable	Parameter estimate	Odds ratio [95% Confidence interval]	*P* value
Catheter-days	0.06	1.06 [1.02, 1.10]	<.01
Prior bacterial BSIs	2.08	8.02 [2.76, 23.30]	.0001
GI tract pathology	1.52	4.57 [1.62, 12.92]	<.01