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Major Article

Risk factors and clinical analysis of candidemia in very-low-birth-weight neonates

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Key Words:
Risk factors
Case-control study

Background: Candidemia is the third leading cause of morbidity and mortality in preterm or very-low-birth-weight infants. The incidence and risk factors of candidemia in this population are poorly known in western China.

Methods: A case-control retrospective study of candidemia was conducted from January 2012-November 2015 in the Liuzhou Maternity and Child Healthcare Hospital. Data were analyzed by univariate analysis and multivariate logistic regression.

Results: Forty-eight confirmed cases of candidemia were identified during the study period, indicating an incidence of 106.9 per 1,000 admissions of very-low-birth-weight infants. *Candida albicans* was the most common pathogen and was isolated in 39.6% of infants with candidemia. The mortality rate of the case group was 10.4% versus 2.1% in the control group ($P = .128$). The multivariable logistic regression model identified that carbapenem use (odds ratio [OR], 11.39; 95% confidence interval [CI], 3.28-39.54), total parenteral nutrition (OR, 10.16; 95% CI, 2.25-45.94), and prolonged hospitalization (OR, 1.04; 95% CI, 1.01-1.07) were all associated with the risk of developing neonatal candidemia.

Conclusion: Very-low-birth-weight infants are at a significantly high risk of developing candidemia. The local neonatal intensive care unit management teams should effectively focus on decreasing the overall use of carbapenems, improving catheter care, removing catheters early, and shortening hospitalizations to reduce the incidence of candidemia.

Candidemia represents a leading cause of late-onset sepsis in very-low-birth-weight (VLBW) infants (birth weight < 1,500 g) and is associated with significant morbidity and mortality.[1] It is reported that invasive candidiasis develops in 2%-5% of VLBW infants.[2] The most commonly documented causative pathogen of invasive candidiasis is *Candida albicans*; however, the emergence of non-*C albicans* candida species such *parapsilosis*, *glabrata,* and *tropicalis* with resistance to azole[3] is of concern, highlighting the need to actively monitor the epidemiology of candidemia in VLBW populations. Predisposing factors associated with candidemia include prematurity, VLBW, vascular catheters, parenteral nutrition, administration of broad-spectrum antibiotics, abdominal surgery, prolonged hospitalization, and artificial ventilation.[4,5]

There have been only a limited number of epidemiologic studies of candidemia in neonates in China, and an evaluation of the morbidity and mortality of VLBW infants in western China is lacking. It is important to obtain local candidemia data in neonatal units to conduct infection control and to identify high-risk patients for prevention efforts.

METHODS

Study design

A retrospective, single-center, matched, case-control study among VLBW neonates was conducted in the Liuzhou Maternity and Child Healthcare Hospital. The VLBW neonates (< 1,500 g at birth) who were eligible for inclusion in this study were born between January 1, 2012, and November 30, 2015, survived for more than 3 days, and were subsequently screened for candidemia based on laboratory and 1 or more clinical variables of sepsis: fever (>38.2°C), increased neutrophil percentage (>50%), thrombocytopenia (< 150×10^9 cells/L), or increased C-reactive protein (> 1.4 mg/dL).[6]

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The electronic records of candidemia were screened, and the data were extracted as follows: birth weight, gestational age, admission date, admission age, gender, necrotizing enterocolitis, neurodevelopmental impairment, maternal underlying diseases (eg, preeclampsia, gestational diabetes, pregnancy-induced hypertension, cholestasis, hyperthyroidism, and hypothyroidism), respiratory distress, vaginal birth, fetal membrane rupture, neonatal congenital diseases (eg, congenital heart disease, glucose-6-phosphate dehydrogenase deficiency, and thalassemia), abdominal surgery, mechanical ventilation, central venous catheter, intubation, pulmonary surface active substance use, steroid use, rescue history, antacid use, total parenteral nutrition, hospitalization duration, third-generation cephalosporin use, carbapenem use, vancomycin use, piperacillin tazobactam use, multiple antibiotic (≥ 3 types) use, antibiotic therapy duration, prophylaxis antifungal therapy, antifungal therapeutic duration, and outcome of candidemia. For each case, 1 control (negative blood culture) was matched on 6 factors: gestational age, birth weight, admission date (within 3 months), admission age, gender, and ward. The medical records were also extracted for the variables listed above.

Definition

An episode of candidemia was defined if an infant had a positive blood culture for candidemia without bacteria and with signs and symptoms compatible with neonatal sepsis.[7] Episodes separated by clinical and microbiologic resolution (defined as candidemia observed 2 weeks after at least 2 negative cultures in a single patient) were considered recurrent candidemia.[8] Cases with radiologic signs of fungal balls and isolation of fungi in 1 or more sites (eg, ear canal swab or urine, skin, stool, nasopharyngeal, or endotracheal secretions) but with a negative blood culture were excluded.[7] The duration of intubation was defined as the days of ventilation. The duration of central venous catheter was defined as the days between central venous catheter insertion and removal. The duration of parenteral nutrition was defined as the total days between parenteral nutrition insertion and removal. The Bayley Scales of Infant Development II[9] and a neurologic examination were used to determine the vision and hearing status. The mental developmental index and psychomotor developmental index from the Bayley Scales were used determine neurodevelopmental impairment. Neurodevelopmental impairment was defined as mental developmental index score < 70, psychomotor developmental index score < 70, bilateral blindness, or bilateral hearing impairment.[10] Overall mortality was defined as all deaths occurring within 30 days of the onset of candidemia; when no other pathogen was isolated from the blood; and when there was no apparent alternative cause, these deaths were determined as candidemia-attributable mortality.[11]

Microbiologic methods

The BacT/ALERT 3D rapid culture and monitoring system (bioMerieux, Marcy-l'Étoile, France) was used for routine blood cultures. Candida isolates were cultured in ChromoAgar medium (bioMerieux), and identification was confirmed using API 20C AUX (bioMerieux).

Statistical analysis

The statistical analysis was performed using SPSS version 20.0 (IBM-SPSS Inc, Armonk, NY). The potential risk factors associated with increased development of candidemia were identified using univariate analysis. Variables with a 2-tailed $P < .05$ in the univariate analysis were included in the multivariate logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of any association.

Ethical considerations

The study was approved by the local ethics committee.

RESULTS

Incidence and pathogen

During the 4-year study, there were 449 VLBW infant admissions, of which 33 were cases of extreme low birth weight (ELBW) (defined as < 1,000 g). A total of 76 episodes of candidemia were identified in 48 VLBW and ELBW infants. Of those episodes, 23 (47.9%) and 5 (10.4%) infants experienced 2 and more than 2 episodes of candidemia, respectively. Approximately one-third (30.3%) of the neonates with ELBW had at least 1 episode of candidemia. The incidence of candidemia was 106.9 per 1,000 admissions (Fig 1). The incidence increased from 65.8 per 1,000 in 2012 to 158.9 per 1,000 in 2015. *C albicans* was the leading causative pathogen of candidemia, and it was isolated in 39.6% of the cases, followed by *C glabrata* (33.3%) and *C tropicalis* (27.1%).

Risk factors

As expected, gestational age (29.6 weeks vs 30.2 weeks; $P = .189$), birth weight (1,148.1 g vs 1,154.6 g; $P = .874$), male gender ($P = .673$), and admission age ($P = .315$) did not differ significantly between the cases and controls.

The univariate analysis of the 28 potential risk factors of candidemia in the current study revealed that neurodevelopmental impairment ($P = .010$), maternal underlying disease ($P = .014$), mechanical ventilation ($P = .008$), presence of a central venous catheter ($P = .043$), central venous catheter duration ($P = .001$), intubation ($P = .037$), intubation duration ($P = .001$), rescue history ($P = .025$), total parenteral nutrition ($P = 0.000$), total parenteral nutrition duration ($P = 0.000$), hospitalization duration ($P = 0.000$), carbapenem use ($P = 0.000$), multiple antibiotic use ($P = 0.000$), antibiotic therapy duration ($P = 0.000$), prophylaxis antifungal therapy ($P = .001$), and antifungal therapy duration ($P = 0.000$) were all associated with candidemia (Table 1). Based on the multivariate logistic regression analysis, infants with candidemia infections were more likely to have been administered carbapenems (OR, 11.39; 95% CI, 3.28-39.54), to have received total parenteral nutrition (OR, 10.16; 95%

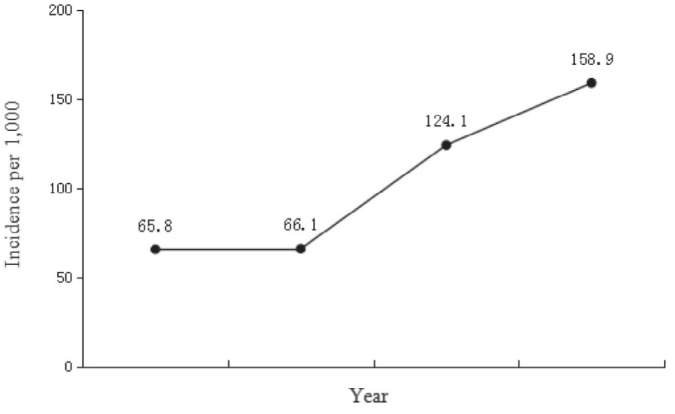

Fig 1. Annual change in incidence (per 1,000 admissions) of candidemia in Liuzhou Maternity and Child Health Care Hospital, 2012-2015.

Table 1
Clinical characteristics of neonates with and without candidemia

Variable	Case	Control	*P* value	Odds ratio
Demographic characteristic				
Gestational age, wk	29.6 (27.6-31.6)	30.2 (28.2-33.2)	.189	
Birth weight, g	1,148.1 (953.9-1342.3)	1,154.6 (950.5-1358.7)	.874	
Male gender	19 (39.6)	17 (35.4)	.673	
Admission age	1.6 (1.6-4.7)	1.0 (0.9-1.1)	.315	
Risk factors				
Necrotizing enterocolitis	10 (20.8)	4 (8.3)	.092	2.89 (0.84-9.98)
Neurodevelopmental impairment	12 (25.0)	1 (2.1)	.010	15.67 (1.95-126.12)
Maternal underlying diseases	25 (65.8)	13 (34.2)	.014	2.93 (1.25-6.86)
Respiratory distress	18 (37.5)	13 (27.1)	.277	1.62 (0.68-3.83)
Vaginal birth	28 (58.3)	24 (50.0)	.413	0.72 (0.32-1.60)
Fetal membrane rupture, h	30.3 (33.5-94.1)	24.2 (40.2-88.6)	.644	
Congenital disease	25 (52.1)	12 (25.0)	.007	3.26 (1.37-7.74)
Abdominal surgery	3 (6.3)	2 (4.2)	.648	1.53 (0.25-9.61)
Mechanical ventilation	34 (70.8)	21 (43.8)	.008	3.12 (1.34-7.26)
Central venous catheter	28 (58.3)	18 (37.5)	.043	2.33 (1.03-5.29)
Central venous catheter duration	18.9 (10.5-27.3)	13.6 (10.5-16.5)	.001	1.17 (1.07-1.30)
Intubation	23 (47.9)	13 (27.1)	.037	2.48 (1.06-5.81)
Intubation duration	16.6 (11.9-21.3)	13.1 (8.5-17.6)	.001	1.18 (1.07-1.31)
Pulmonary surface active substance use	15 (31.3)	7 (14.6)	.057	2.66 (0.97-7.29)
Steroid use	12 (25.0)	7 (14.6)	.205	1.95 (0.69-5.49)
Rescue history	32 (66.7)	21 (43.8)	.025	2.57 (1.12-5.88)
Antacid use	7 (14.9)	2 (4.2)	.094	4.03 (0.79-20.49)
Total parenteral nutrition	45 (93.8)	20 (41.7)	.000	21.00 (5.71-77.21)
Total parenteral nutrition duration	23.2 (18.0-28.4)	13.4 (10.2-16.7)	.000	1.64 (1.35-2.00)
Hospitalization duration, d	54.8 (32.5-77.1)	28.8 (8.9-40.9)	.000	1.06 (1.03-1.09)
Third-generation cephalosporin use	29 (61.7)	20 (41.7)	.052	2.26 (0.99-5.13)
Carbapenem use	42 (87.5)	13 (27.1)	.000	18.85 (6.45-54.74)
Vancomycin use	9 (18.8)	4 (8.3)	.145	2.54 (0.72-8.90)
Piperacillin tazobactam use	46 (95.8)	41 (85.4)	.099	3.93 (0.77-19.98)
Multiple antibiotic use	31 (64.6)	8 (16.7)	.000	9.12 (3.48-23.86)
Antibiotic therapeutic duration, d	38.9 (19.8-58.0)	15.5 (5.5-27.5)	.000	1.11 (1.06-1.16)
Prophylaxis antifungal therapy	41 (85.4)	26 (54.2)	.001	4.96 (1.86-13.23)
Antifungal therapeutic duration, d	8.8 (3.4-14.1)	1.9 (0.4-4.2)	.000	2.08 (1.56-2.76)
Outcome				
Survived	43 (89.6)	1 (97.9)	Reference	Reference
Death	5 (10.4)	1 (2.1)	.128	5.46 (0.61-47.62)

NOTE. Values are presented as mean (95% confidence interval), n (%), or odds ratio (95% confidence interval).

Table 2
Multivariate analysis of candidemia

Risk factor	Odds ratio	95% confidence interval	*P* value
Carbapenem use	11.39	3.28-39.54	.000
Total parenteral nutrition	10.16	2.25-45.94	.003
Hospitalization duration, d	1.04	1.01-1.07	.024

CI, 2.25-45.94), and to have experienced a prolonged hospitalization (OR, 1.04; 95% CI, 1.04, 1.01-1.07) (Table 2).

Clinical outcomes of candidemia

Five case infants (10.4%; 5 out of 48) and 1 control infant (2.1%) died during hospitalization. Univariate logistic regression revealed that there was no significant difference in mortality between the 2 groups due to candidemia ($P = .128$).

DISCUSSION

Invasive candidiasis remains the third most common cause of nosocomial bloodstream infections in neonatal intensive care units. Premature or VLBW infants are known to be at a higher risk of developing candidemia. It was reported that the incidence of candidemia was inversely related to birth weight in premature infants, with a 2%-5% incidence in VLBW and 15%-20% in ELBW infants.[2,12,13] The incidence of neonatal candidemia in this study was 106.9 per 1,000 VLBW infant admissions. The majority of the infections (30.3%; 10 out of 33) (and all of the deaths) occurred in ELBW infants and in VLBW infants (8.5%, 38 out of 449), confirming that extreme prematurity is associated with the highest risk of developing candidemia. Neonates themselves are known to be a risk factor for candidemia infection. ELBW infants in particular are reported to have a 10-fold higher risk of developing bloodstream *Candida* infection during their first year of life.[14] The incidence in our data was significantly higher than that reported in England (1.88%) and North America (6.9%).[4,15] Antifungal prophylaxis has recently been recommended in our hospital, and medical practices such as vascular catheters, broad-spectrum antibiotic prophylaxis, pulmonary surface active substance use, and even frequent blood culturing have also been recently introduced in our hospital to monitor and rescue ELBW infants. Moreover, surveillance mechanisms and neonatal demographic characteristics such as ethnicity and the high prevalence of congenital disease (which is known to occur in Guangxi, China) may help to explain these discrepancies.

In the literature, the most prevalent *Candida* species causing candidemia has shifted over time from *albicans* to non-*albicans* species and varied geographically and by age, including *tropicalis*, *parapsilosis*, and *glabrata*.[16-20] In the current study, non-*albicans* accounted for the most number of cases (*glabrata* 33.3% and *tropicalis* 27.1%), although *albicans* was the most common species (39.6%). As reported, the presence of *albicans* isolated from the bloodstream was consistent with the pattern seen around the world and in China, not only in adult groups but also in neonate groups.[16-20] There have recently been reports that among the non-*albicans* species, the

leading causative pathogen of candidemia in children is *parapsilosis*, whereas it is *glabrata* in adult patients.[21,22] However, in the current study, *glabrata* was the second most frequently isolated strain in neonates and was the most commonly encountered non-*albicans* strain in our study as well. This pattern is consistent with previous studies on Chinese neonate groups.[20]

Many studies have suggested that the increased use of azole antifungal agents, especially fluconazole, has determined the increased distribution of non-*albicans* candida and that the decrease in *C albicans* with azole use may imply changes in the candida etiology.[19,23,24] At the same time, demographic differences, medical practices, and therapeutic decision making may have also contributed to the distribution of *Candida* species in bloodstream infections. Therefore, the predominant causative species of candidemia may vary by geographical region.

In our study, the most common risk factor associated with candidemia was carbapenem use as prophylaxis (OR, 11.39; 95% CI, 3.28-39.54). The mean duration of antibiotic use was 38.9 days, and multiple antibiotics were used in 31 cases (64.6%). Previous observations are consistent with the view that prolonged broad-spectrum antibiotic use such as third-generation cephalosporin and carbapenems (meropenem and imipenem) predispose VLBW infants to candidemia.[25] Carbapenems were likely to have been increasingly used in neonatal intensive care units in recent years. The long-term use of these broad-spectrum antibiotics in routine empirical therapy may lead to the overgrowth of opportunistic *Candida* by depleting the competitive pressure exerted by the normal bacterial flora. Receiving broad-spectrum antibiotics is the most consistently identified risk factor associated with candidemia among neonatal groups, including VLBW infants.[4,26]

The second predisposing factor for the development of candidemia in our study was total parenteral nutrition (OR, 10.16; 95% CI, 2.25-45.94). The majority of the infected neonates had received total parenteral nutrition (93.8%), central venous catheters (58.3%), and endotracheal intubation (47.9%). Our findings were consistent with other investigations, which revealed that an independent risk factor for candidemia was *Candida* sp colonization due to medical catheters and colonization in multiple sites, regardless of whether the host was an adult, neonate, or VLBW infant.[7,25,27] The use of medical catheters has raised concern about the emergence of candidemia because they may facilitate the introduction of *Candida*, and the capability of *Candida* sp to attach to foreign material and form biofilms leads to horizontal transmission and protects them from immune responses and antifungal agents.[19,28] Identifying the medical catheter as responsible for candidemia is of great importance in terms of medical decision making, because the early removal of these catheters could be expected to eliminate intravenous pathogens and decrease candidemia infection. A previous observation confirmed that delayed catheter removal (> 1 day after initiating antifungal therapy) may contribute to an increased risk of death or neurodevelopmental impairment in ELBW infants.[29]

Prolonged hospitalization has been implicated as a risk factor for the development of candidemia because it provides the opportunity for *Candida* colonization to occur in hospitalized patients. In our study, the mean duration of hospitalization before the development of candidemia was 20.3 days. A few studies have suggested that prolonged hospital stays could contribute to the development of candidemia and increases in cost.[19,21]

Half of the ELBW infants (50%; 5 out of 10) diagnosed with candidemia died before 37 weeks postconceptional age. It has been reported that the attributable mortality of candidemia in infants ranges between 43% and 54%, and the mortality in ELBW infants with candidemia is much higher.[30,31] This highlights the urgent need to diagnose candidemia early and to reduce infants' exposure to potential risk factors.

The main limitations of this study were that it was conducted in a single neonatal intensive care unit and the number of subjects was limited. Additionally, this study was performed retrospectively, and bias was thus unavoidable. Multicenter, prospective surveillance systems are essential to determine the epidemiology and potential risk factors of candidemia in VLBW infants to improve the prevention, diagnosis, and treatment of this disease in the future.

CONCLUSIONS

This study found that the incidence of candidemia in VLBW infants was 106.9 per 1,000 admissions. Non-*albicans Candida* species were predominant (60.4%). Carbapenem use, total parenteral nutrition, and prolonged hospitalization were found to be independently associated with the development of candidemia in VLBW infants. The medical policies in our neonatal intensive care unit should focus on decreasing the use of broad-spectrum antibiotics, especially carbapenems, removing catheters early on and initiating the appropriate treatment to reduce the hospitalization duration, which could reduce the incidence of candidemia.

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