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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.

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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. It is reported that invasive candidiasis develops in 2%-5% of VLBW infants. 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 azole³ 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}

E-mail address: cjclzsfy@126.com (J. Chen). Financial support: None. Conflicts of Interest: None to report. JF and XW contributed equally to this work. 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).

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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 II⁹ 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%

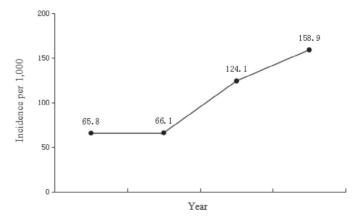


Fig 1. Annual change in incidence (per 1,000 admissions) of candidemia in Liuzhou Maternity and Child Health Care Hospital, 2012-2015.

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