Epidemiology of and risk factors for neonatal candidemia at a tertiary care hospital in western China

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Abstract

Background: The prevalence and clinical characteristics of neonatal candidemia are poorly understood in western China. The aim of our study was to evaluate the epidemiological features of neonatal candidemia in the Liuzhou Maternity and Child Healthcare Hospital.

Methods: A retrospective case-control study was conducted between January 2012 and November 2015. Electronic databases were reviewed and data on Candida species were isolated from blood cultures and candidemia incidence, risk factors, and mortality were extracted. Univariate and multivariate logistic regression analysis were performed to identify risk factors associated with candidemia.

Results: During the 4-year period, candidemia was identified in 69 newborns, for an incidence rate of 13.6 per 1000 admissions. Prolonged antibiotic therapy duration [odds ratio (OR), 95% confidence interval (95% CI) = 1.06, 1.01–1.10], total parenteral nutrition [OR, 95% CI = 6.03, 2.10–17.30] and neurodevelopmental impairment (OR, 95% CI = 7.34, 1.18–45.80) were all associated with increased odds of candidemia development in infants (P value was 0.010, 0.001, 0.033, respectively). The overall mortality rate was 7.2% in the candidemia group.

Conclusions: Prolonged duration of antibiotic therapy, presence of total parenteral nutrition and neurodevelopmental impairment were the major risk factors associated with neonatal candidemia. This study highlights the importance of the early detection, diagnosis and treatment of neonatal candidemia.

Keywords: Neonate, Candidemia, Case-control study, Risk factors

Background

Candidiasis is one of the leading causes of bloodstream infections in neonatal intensive care units (NICUs) and associated with high morbidity and mortality. It has been estimated that 2.4–9.0% of mortality [1, 2] and 25.0% of morbidity [3] in the NICU setting may be attributable to Candida infections.

Because of their immature specific and nonspecific immune systems, neonates may be vulnerable to invasive candidemia. Several factors have previously been identified as contributing to an increased incidence of neonatal candidemia, including prolonged endotracheal intubation, indwelling medical catheterization, parenteral nutrition, use of broad-spectrum antibiotics, and prolonged antibiologic therapy duration. Because of the lack of specific signs and symptoms and sensitive and specific laboratory tests for the diagnosis of Candida infection, early diagnosis of candidemia remains crucial and is a challenge for both pediatricians and microbiologists. Therefore, the aims of the present study were to evaluate the incidence and epidemiology of candidemia in infants and determine the risk factors and clinical outcomes associated with candidemia to help pediatricians select effective preventive measures and medical treatment for neonatal candidemia.

Methods

This retrospective study was conducted at the 60-bed NICU of the Liuzhou Maternity and Child Healthcare Hospital, which is the largest neonatal care center in Liuzhou. Between 1000 and 1200 neonates are admitted...
to this NICU each year. Candidemia was defined by a
blood culture that yielded any Candida species. Micro-
biology laboratory and clinical records from two elec-
tronic databases were reviewed. The following data
were extracted: admission age, gender, gestational age,
birth weight, delivery mode, necrotizing enterocolitis,
neurodevelopmental impairment, maternal underlying
diseases, abdominal surgery, mechanical ventilation, in-
dwelling central venous catheterization, endotracheal
intubation, rescue history, total parenteral nutrition,
hospitalization duration, use of carbapenems, use of
vancomycin, multiple antibiotic (≥3 classes of antibi-
otics) use, antibiotic therapy duration and outcome of
candidemia. For each case, one neonate with negative
blood culture results was matched based on the follow-
ing factors to serve as a control: admission age, gender,
gestational age, and birth weight. These data were also
extracted as previously described.

Microbiologic methods
All microbiological testing was completed using standard
methodology. Candida were isolated from blood cultures
using the BacT/Alert 3D rapid culture and monitoring
system (BioMérieux). Candida species were identified
using API 20C AuX (BioMérieux).

Statistical analysis
SPSS version 20.0 (SPSS Inc. Chicago, IL, USA) was used
for data analysis. Comparisons between the case and
control groups were performed using univariate analysis
methods. All variables with P < 0.05 were selected for
inclusion in the multivariate logistic regression model to
identify predisposing risk factors associated with neo-
natal candidemia.

Ethical considerations
Local ethics approval was obtained.

Results
Five thousand and seventy-five newborns were admitted
to the NICU from January 2012 to November 2015, and
69 newborns developed candidemia. In the case group,
the gestational age ranged from 27 weeks to 41 weeks and
birth weight ranged from 800 g to 3350 g. Of the 33
infants with extremely low birth weight (ELBW < 1000 g),
10 developed candidemia; of the 449 newborns were very
low birth weight (VLBW < 1500 g), 38 developed candi-
demia. The overall candidemia incidence was 13.6 per 1000
admissions. The highest candidemia incidence was ob-
served among ELBW infants (303.0 per 1000 ELBW in-
fants). The candidemia incidence among VLBW infants
was 84.6 per 1000 VLBW infants. The overall mortality
rate in the candidemia group was 7.2%, while the mortality
rate in the control group was 1.4%.

The most and almost equally prevalent pathogens iden-
tified were Candida albicans and Candida glabrata, with
30 (34.5) and 23 (33.3%) episodes of candidemia attributed
to Candida albicans and Candida glabrata, respectively.
The remaining episodes of candidemia were caused by
Candida tropicalis (14, 20.3%), Candida parapsilosis
(1, 1.4%) and Candida kefyr (1, 1.4%).

Patient demographics, clinical characteristics, and
prognosis were compared between the candidemia and
non-candidemia groups and are summarized in Table 1.
There were no significant differences in the following
variables between case and control patients: gestational
age, birth weight, admission age, gender and delivery
mode.

In the univariate logistic regression analyses, factors sig-
nificantly associated with candidemia were necrotizing
enterocolitis (P = 0.025), neurodevelopmental impair-
ment (P = 0.006), maternal underlying diseases (P =
0.035), mechanical ventilation (P = 0.011), central ven-
ous catheterization (P = 0.007), intubation (P = 0.013),
total parenteral nutrition (P = 0.000), prolonged
hospitalization duration (P = 0.000), carbapenem use
(P = 0.000), multiple antibiotic use (P = 0.000), antibiotic
therapy duration (P = 0.000), and the mortality due to can-
didemia (P = 0.043).

Forward step-wise multivariate logistic regression was
used to evaluate the risk factors for candidemia identi-
fied as significant in the univariate analyses, as shown
in Table 2. The results of this analysis showed that total
parenteral nutrition [odds ratio (OR) = 6.03, 95% confi-
dence interval (95% CI = 2.10–17.30, P = 0.001], anti-
biotic therapy duration (OR = 1.06, 95% CI = 1.01–1.10,
P = 0.010), and neurodevelopmental impairment (OR =
7.34, 95% CI = 1.18–45.80, P = 0.033) were significant
predictors of candidemia in the multivariate model.

Discussion
Candida species have emerged as a leading pathogenic
cause of bloodstream infections in neonates [1–3]. The
overall incidence of candidemia in our study was 13.6
per 1000 admissions. This incidence was lower than that
reported in a previous study conducted by Benjamin et
al. [1], in which a higher incidence (9%) was reported. In
the present study, we found that the overall incidence of
candidemia among VLBW infants was 84.6 per 1000 ad-
missions, and in the ELBW group, the candidemia inci-
dence was 303.0 per 1000 admissions. These findings are
consistent with the results of a study based on surveil-
lance data collected in England between 2004 and 2010,
which reported that ELBW infants had the highest risk of
invasive Candida infection of the neonates evaluated
[2]. During the 4-year period evaluated in our study,
only 33 ELBW infants survived and were admitted to
the NICU after delivery. One likely reason for the
The observed discrepancy is that the prevalence of VLBW, especially ELBW, among infants is much higher in developed countries than in China [4]. These studies highlighted the importance of infection control and early identification of potential risk factors for the prevention of candidemia among high risk infants.

In our study, the majority of candidemia episodes were caused by *C. albicans* (43.5%) and *C. glabrata* (33.3%). Previous studies, especially those conducted in western countries, have frequently reported that *C. albicans* was the most common causative agent of neonatal candidemia, followed by *C. parapsilosis* [2]. In contrast with the results of some previous studies, the results of our study paralleled those of a previous study conducted by Xia et al. [4], who reported that *C. albicans* was the species most commonly identified in Chinese 11 NICU centers, followed by *C. glabrata*. These results were consistent with the fact that the predominant causative agents of candidemia may vary by geographic region [5].

Previous studies have revealed that prophylactic or empiric therapy with antifungal agents, especially fluconazole, may be associated with changes in *Candida* ecology and antifungal agent susceptibility [6]. According to the microbiological data evaluated in our study, all of the tested *Candida* isolates were susceptible to fluconazole, amphotericin B and voriconazole. Fluconazole is considered as the first line antifungal agent in our hospital. Previously, a study showed that pre-exposure to fluconazole was a predisposing factor for *C. glabrata* infection [7], which may

### Table 1 Clinical characteristics of neonates with and without candidemia

| Variable                      | Case mean (95% CI) or n(%) | Control mean (95% CI) or n(%) | P value | Odds ratio (OR) (95% CI) |
|-------------------------------|----------------------------|-------------------------------|---------|-------------------------|
| Demographics                  |                            |                               |         |                         |
| Gestational age (wks)         | 31.7(28.2, 35.2)           | 31.6(27.8, 35.4)              | 0.763   |                         |
| Birth weight (g)              | 1514.4(852.0, 2176.3)      | 1529.3(856.5, 2202.1)         | 0.894   |                         |
| Male gender, n(%)             | 44(63.8)                   | 41(59.4)                      | 0.600   | 1.20(0.61–2.39)         |
| Admission age                 | 1.1(0.8, 1.4)              | 1.5(1.2, 4.2)                 | 0.149   |                         |
| Risk factors                  |                            |                               |         |                         |
| Vaginal delivery              | 28(40.6)                   | 33(47.8)                      | 0.392   | 0.75(0.38–1.46)         |
| Necrotizing enterocolitis     | 16(23.2)                   | 6(8.7)                        | 0.025   | 3.17(1.16–8.68)         |
| Neurodevelopmental impairment| 14(20.3)                   | 2(2.9)                        | 0.006   | 8.52(1.86–39.14)        |
| Maternal underlying diseases  | 31(44.9)                   | 19(27.5)                      | 0.035   | 2.15(1.06–4.37)         |
| Abdominal surgery             | 10(14.5)                   | 3(4.4)                        | 0.057   | 3.67(0.96–13.99)        |
| Mechanical ventilation        | 43(62.3)                   | 28(40.6)                      | 0.011   | 2.42(1.22–4.80)         |
| Central venous catheter       | 40(58.0)                   | 24(34.8)                      | 0.007   | 2.59(1.30–5.15)         |
| Intubation                    | 31(44.9)                   | 17(24.6)                      | 0.013   | 2.50(1.21–5.15)         |
| Rescue history                | 35(50.7)                   | 26(37.7)                      | 0.124   | 1.70(0.86–3.35)         |
| Total parenteral nutrition    | 58(84.1)                   | 23(33.3)                      | 0.000   | 10.55(4.66–23.85)       |
| Hospitalization duration (d) | 46.6(23.3, 69.9)           | 24.5(5.7, 43.3)               | 0.000   |                         |
| 3rd cephalosporins use        | 39(57.4)                   | 29(42.0)                      | 0.074   | 1.86(0.94–3.65)         |
| Carbapenems use               | 50(72.5)                   | 15(21.7)                      | 0.000   | 9.47(4.35–20.64)        |
| Vancomycin use                | 10(14.5)                   | 5(7.2)                        | 0.179   | 12.17(0.70–6.72)        |
| Multiple antibiotic use       | 37(53.6)                   | 9(13.0)                       | 0.000   | 7.71(3.31–17.95)        |
| Antibiotic therapeutic duration (d) | 33.5(14.7, 52.3) | 13.8(2.5, 25.1)               | 0.000   |                         |
| Outcome                       |                            |                               |         |                         |
| Cure                          | 16(23.2)                   | 32(46.4)                      | reference | reference              |
| Improvement                   | 43(62.3)                   | 33(47.8)                      | 0.013   | 2.61(1.23–5.53)         |
| Exacerbation                  | 5(7.2)                     | 3(4.3)                        | 0.128   | 3.33(0.71–15.74)        |
| Death                         | 5(7.2)                     | 1(1.4)                        | 0.043   | 10.00(1.08–92.94)       |

### Table 2 Multivariate analysis for candidemia

| Risk factor                  | Odds ratio | 95% CI      | P value |
|------------------------------|------------|-------------|---------|
| Total parenteral nutrition   | 6.03       | 2.10–17.30  | 0.001   |
| Antibiotic therapeutic duration (d) | 1.06 | 1.01–1.10  | 0.010   |
| Neurodevelopmental impairment| 7.34       | 1.18–45.80  | 0.033   |
partly explain the observed discrepancy regarding the distribution of *Candida* among neonates, as most NICUs have been reported to use liposomal amphotericin B when administering prophylactic or empiric therapy [2].

Central venous catheterization and total parenteral nutrition were identified as significant predisposing factors for the development of candidemia in our study. The majority of the infected neonates had received central venous catheterization (58.0%), endotracheal intubation (44.9%), and total parenteral nutrition (84.1%). The multivariate logistic regression model results suggested that total parenteral nutrition was the factor most highly associated with increased odds of candidemia. *Candida* species are notorious for their capacity to attach to foreign materials (such as invasive and indwelling devices) and form biofilms, which may be associated with high virulence and act as a biological barrier that prevents the penetration of antifungal agents and protects the fungal cells from the host’s immune responses. This fact may explain why invasive and indwelling medical devices have been identified as factors consistently associated with increased risk of candidemia [5, 8].

Broad-spectrum antibiotic use has also been described as a risk factor for candidemia [2, 9, 10]. In our department, the majority of candidemia cases had received broad-spectrum antibiotics, such as carbapenems (72.5%), and 53.6% of patients received multiple antibiotics. The median antibiotic therapy duration was 33.5 days (range 14.7–52.3 days). A previous study conducted by Kaufman et al. [11] showed that decreased use of carbapenem may be associated with decreased incidence of invasive fungal infections. It has been reported that prolonged exposure to broad-spectrum antibiotics not only increases the risk of developing neonatal candidemia [12] but also may be associated with the development of refractory candidemia [13]. The widespread use of antibacterial agents may suppress bacterial flora and increase *Candida* colonization density [14]. The results of our study were consistent with those of a previous investigation conducted in 11 NICUs, which revealed that broad-spectrum antibacterial agents were commonly used for prophylactic or empiric therapy in China [4]. This finding highlights the need to evaluate the antimicrobial burden in local NICUs in China.

Our study revealed that neonatal candidemia was associated with neurodevelopmental impairment. Several studies have also reported this conclusion. Two large prospective cohort studies reported that systemic candidiasis was associated with increased risk of death and/or neurodevelopmental impairment [15, 16] in extremely low birth weight infants. Experimental data suggests that the cytokine-mediated inflammatory responses mediated elicited by infection may be neurotoxic and contribute to brain damage. However, data regarding cytokine-mediated inflammatory responses to specific pathogens and their relationship with adverse neurodevelopmental outcomes are limited [17, 18]. It is of importance to evaluate potential mechanisms by which to reduce inflammatory responses and the risk of brain damage associated with candidemia in future research.

As was identified in mainland China, the situation related to neonatal candidemia observed in this study was also not optimistic. Studies have previously reported incidence rates of candidemia ranging from 0.74 [4] to 15.7% [19] and mortality rates ranging from 8.9 [20] to 26.3% [21] in neonatal patients in mainland China. Our results were consistent with those of previous investigations [4, 19, 22, 23] suggesting that very low birth weight was an independent factor associated with the development candidemia. Previous studies have identified *C. albicans* as the predominant pathogen causing candidemia in neonatal patients in China [4, 22]. Risk factors previously reported to be associated with neonatal candidemia in China have included intubation [20], use of medical catheters [20, 21, 23], use of high-level antibiotics [20, 21], prior surgeries [20, 21], prolonged antibiotic use [21], and preterm birth with low birth weight [4, 19, 22, 23].

The limitations of the current study were inherent given its retrospective nature. The single center design and small sample size may have compromised the statistical power of the study. Furthermore, the diagnosis of neurodevelopmental impairment was mostly based on ophthalmological, otological, and radiological findings and not systematically evaluated using the Gross Motor Functional Classification Score and cognitive and motor scales of the Bayley Scales of Infant Development-III (BSID-III) [16]. Follow-up data regarding neurodevelopmental impairment in the infants included in this study were not available. Further studies should focus on this aspect of candidemia risk. Nevertheless, these data provide information regarding the epidemiology of neonatal candidemia in western China. It is crucial for local pediatricians to promote the prevention, early detection and treatment of candidemia in high risk neonates.

**Conclusions**

In conclusion, our findings suggest that prolonged antibiotic therapy duration, presence of total parenteral nutrition and neurodevelopmental impairment were associated with increased odds of neonatal candidemia. The identification of risk factors associated with increased odds of neonatal candidemia emphasizes the need for early detection, diagnosis and treatment of *Candidiasis* infections in NICUs.

**Abbreviations**

95% CI: 95% confidence interval; BSID-III: Bayley scales of infant development-III; C. Albicans: Candida albicans; C. Glabrata: Candida glabrata; C. Parapsilosis: Candida Parapsilosis; ELBW: Extremely low birth weight; NICUs: Neonatal intensive care units; OR: Odds ratio; VLBW: Very low birth weight
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Availability of data and materials
We declare that the data supporting the conclusions of this article are fully described within the article.

Authors’ contributions
JC and JF designed the study and drafted an outline. JC, YJ, BW, YD, SX, PQ and JF participated in data analysis, draft of initial manuscript and approved the final content of this manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Lizhou Maternity and Child Health Care Hospital Ethics Committee approved the study. The Ethics Committee also permitted the authors to use the neonatal records to write this article.

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References
1. Benjamin Jr DK, Stool BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010;126(6):65–73.
2. Oser C, Vergnano S, Naidoo R, et al. Neonatal invasive fungal infection in England 2004–2010. Clin Microbiol Infect. 2014;20(9):E41–47.
3. Benjamin Jr DK, Stool BJ, Fanneroff AA, National Institute of Child Health and Human Development Neonatal Research Network, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117(4):92–99.
4. Xia H, Wu H, Xiao S, et al. Invasive candidiasis in preterm neonates in China: a retrospective study from 11 NICUS during 2009–2011. Pediatr Infect Dis J. 2014;33(10):10–9.
5. Zhang XB, Yu SJ, Yu JX, et al. Retrospective analysis of epidemiology and prognostic factors for candidiasis at a hospital in China, 2000–2009. Jpn J Infect Dis. 2012;65:510–5.
6. Filotti J, Spirohug K, Pantelidias CP, et al. Invasive candidiasis in pediatric intensive care patients: epidemiology, risk factors, management, and outcome. Intensive Care Med. 2007;33:1272–83.
7. Lortholary O, Desnos-Olliver M, Srton M, French Mycosis Study Group, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117(4):92–99.
8. Xia H, Wu H, Xiao S, et al. Invasive candidiasis in preterm neonates in China: a retrospective study from 11 NICUS during 2009–2011. Pediatr Infect Dis J. 2014;33(10):10–9.
9. Zhang XB, Yu SJ, Yu JX, et al. Retrospective analysis of epidemiology and prognostic factors for candidiasis at a hospital in China, 2000–2009. Jpn J Infect Dis. 2012;65:510–5.
10. Filotti J, Spirohug K, Pantelidias CP, et al. Invasive candidiasis in pediatric intensive care patients: epidemiology, risk factors, management, and outcome. Intensive Care Med. 2007;33:1272–83.
11. Lortholary O, Desnos-Olliver M, Srton M, French Mycosis Study Group, et al. Recent exposure to caspofungin or flucanazole influences the epidemiology of candidemia: a prospective multicenter study involving 2441 patients. Antimicrob Agents Chemother. 2011;55:532–8.
12. Sigh J, Deep A. Invasive candidiasis in pediatric intensive care units. Indian J Pediatr. 2009;76:1033–44.
13. Chang YJ, Choi IR, Shin WS, et al. The control of invasive Candida infection in very low birth weight infants by reduction in the use of 3rd generation cephalosporin. Korean J Pediatr. 2013;56:68–74.
14. Cotten CM, McDonald S, Stoll B, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2008;118:717–22.
15. Kaufman DA. Challenging issues in neonatal candidiasis. Curr Med Res Opin. 2010;26:1769–78.
16. Cullen L, Lamagni TL, Brocklehurst P, et al. Invasive fungal infection in very low birthweight infants: national prospective surveillance study. Arch Dis Child Fetal Neonatal Ed. 2006;91:188–92.
17. Natarajan G, Luc-Botica M, Aranda JV. Refractory neonatal candidemia and high-dose micafungin pharmacotherapy. J Perinatol. 2009;29:738–43.
18. Kelly MS, Benjamin Jr DK, Smith PB. The epidemiology and diagnosis of invasive candidiasis among premature infants. Clin Perinatol. 2015;42:105–17.
19. Stoll BJ, Hansen NI, Adams-Chapman I, National Institute of Child Health and Human Development Neonatal Research Network, et al. Neurodevelopmental and growth impairment among extremely low-birthweight infants with neonatal infection. JAMA. 2004;292:2357–65.
20. Adans-Chapman I, Bann CM, Das A, Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network, et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. J Pediatr. 2013;163:61–7.
21. Schelonka RL, Maheshwari A, Carlo WA, et al. T cell cytokines and the risk of bloodstream infection in extremely low birth weight infants. Cytokine. 2011;53:249–55.
22. Baier RJ, Loggins J, Yamanandara K. IL-10, IL-6 and CD14 polymorphisms and sepsis outcome in ventilated very low birth weight infants. BMC Med. 2006;4(1):
23. Wu Z, Liu Y, Feng X, Liu Y, Wang S, Zhu X, Chen Q, Pan S. Candidemia: incidence rates, type of species, and risk factors at a tertiary care academic hospital in China. Int J Infect Dis. 2014;22:4–8.

Neurodevelopmental and growth impairment among extremely low-birthweight infants with neonatal infection. JAMA. 2004;292:2357–65.
Adans-Chapman I, Bann CM, Das A, Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network, et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. J Pediatr. 2013;163:61–7.
Schelonka RL, Maheshwari A, Carlo WA, et al. T cell cytokines and the risk of bloodstream infection in extremely low birth weight infants. Cytokine. 2011;53:249–55.
Baier RJ, Loggins J, Yamanandara K. IL-10, IL-6 and CD14 polymorphisms and sepsis outcome in ventilated very low birth weight infants. BMC Med. 2006;4(1):
Wu Z, Liu Y, Feng X, Liu Y, Wang S, Zhu X, Chen Q, Pan S. Candidemia: incidence rates, type of species, and risk factors at a tertiary care academic hospital in China. Int J Infect Dis. 2014;22:4–8.

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