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Candida Colonization in Low Birth Weight and Very Low Birth Weight Infants in a Neonatal Intensive Care Unit

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Background: *Candida* colonization is a major risk factor for invasive candidiasis in premature infants in the neonatal intensive care unit (NICU).

Objectives: The purpose of this study was to determine the rate, risk factors, and sources of colonization in low birth weight (LBW) and very low birth weight (VLBW) infants in an NICU.

Patients and Methods: All cases were classified in to 1 of 2 groups: LBW and VLBW. A questionnaire that collected demographic data was completed for each case. Swabs were obtained from the ear, umbilicus, and rectum, as well as catheters, tracheal tubes, and nasogastric tubes. Samples were cultured on Sabouraud dextrose agar. The data were analyzed using SPSS software. A P value < 0.05 was considered significant.

Results: A total of 102 cases were examined in this study. The mean weight of the infants was 1720 ± 474 gr (range 850 - 2500 gr). Positive *Candida* cultures were isolated in 19 (31.7%) cases in the LBW group and 20 (47.6%) cases in the VLBW group. In addition, 36 (35.3%) cases showed signs of sepsis. The mortality rate was 1.7% (n = 1). The umbilicus and rectum were the most common sites for *Candida* colonization in both groups. The analysis also indicated that the duration of hospitalization, prolonged use of corticosteroids, central venous catheters, total parenteral nutrition, and mechanical ventilation were associated with candidiasis infection in VLBW infants while prolonged use of corticosteroids and central venous catheters were major risk factors associated with candidiasis infection in LBW infants.

Conclusions: These results show that maturity and birth weight are related to a decrease in the risk of developing a candidiasis infection.

Keywords: Candida; Neonatal Intensive Care Units; Risk Factor

1. Background

Colonization by *Candida* species is a major risk factor for invasive candidiasis in premature and low birth weight (LBW) infants in the neonatal intensive care unit (NICU). In addition, the incidence of *Candida* colonization has increased steadily over the last two decades (1) and premature and LBW infants are more susceptible to systemic fungal infections because of invasive interventions, immune system immaturity, and prolonged use of antimicrobials (2). Invasive candidiasis in neonates is also a major cause of late onset sepsis in infants with very low birth weight (VLBW) and accounts for 1.6% - 12% of all cases (3-5). Furthermore, invasive candidiasis may lead to mortality or neurodevelopment damage (6-13).

Candida albicans is the most commonly isolated *Candida* species in colonized infants. However, in the past decade, colonization with other species has increased and has been attributed to advancements in technology, life support systems, and relative immunodeficiency in the neonate, as well as horizontal transmission from the hands of health care workers and vertical transmission from maternal vaginal infection. Known risk factors for candidiasis infection include low birth weight (< 1,500 gr), prolonged use of broad-spectrum antibiotics, parenteral alimentation, intravenous fat emulsion, *Candida* colonization, a previous episode of mucocutaneous candidiasis, the presence of a central lines, prior colonization with another microbes, and prolonged urinary catheterization (14-19). However, published literature regarding candidemia in NICUs in developing countries, such as Iran, is limited (20, 21).

2. Objectives

The purpose of this study was to determine the rate, risk factors, and sources of colonization by various *Candida* species in LBW and VLBW infants in the NICU.

3. Patients and Methods

This descriptive, observational study examined LBW and VLBW preterm neonates that were hospitalized in the NICU between February and May 2013 at the Imam Hossien university hospital in Tehran, Iran. A questionnaire that included demographic data (e.g. mother's age and gravid status as well as the neonate's sex, birth weight, gestational age, and cause of admission to the NICU) and laboratory data

(e.g. results of Gram-stains and fungal cultures) was completed for each case. The prolonged use of broad-spectrum antibiotics and steroids as well as septicemia and patient morbidity and mortality were also recorded.

All cases in this study were classified into 1 of 2 groups according to birth weight (LBW if 1,500 gr > weight ≥ 2,500 gr; VLBW if weight ≥ 1,500 gr). Swabs from the ear, umbilicus, and rectum, as well as catheters, tracheal tubes, and nasogastric tubes (if present) were obtained within 24 hours of NICU admission and every week thereafter until the neonate was discharged. Samples were cultured on Sabouraud dextrose agar (Sigma Chemical Co., St Louis, MO, USA).

The data were analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). The Fisher's exact or chi-square test and the Student's t test were used to assess statistical associations between variables in the two groups. Demographic characteristics, medical data, and laboratory test data were subjected to a multivariate analysis. Continuous data are presented as mean ± standard deviation. A P value < 0.05 was considered significant.

The study was approved by the university's ethics committee prior to initiation, and the protocols conformed to the ethical guidelines of the 1975 Helsinki declaration. All parents were informed about the study protocol and written consent was obtained from all parents.

4. Results

A total of 102 neonates were enrolled for participation in this study. Fifty-five (53.9%) were male, 47 (46.1%) were female, and the mean weight was 1,720 ± 474 gr (range 850 - 2,500 gr). LBW infants (n = 60) had a mean weight of 2,063 ± 276 gr (range 1,550 - 2,500 gr) while VLBW (n = 42) had a mean weight of 1,230 ± 165 gr (range 850 - 1,500 gr). Table 1 summarizes the demographic data and compares the results between the two groups. A statistically significant difference between the two groups was found for gestational age, cause of hospitalization, use of broad-spectrum antibiotics, and having a tracheal tube.

Table 1. Demographic and Neonatal Characteristics in LBW and VLBW Groups [a,b]

Parameters	LBW (n = 60)	VLBW (n = 42)	P Value
Gender			
Male	30 (50)	25 (59.5)	0.342
Female	30 (50)	17 (40.5)	
Age of mother, y	27.3 ± 5.3 (range 18 - 45)	28.6 ± 4.6 (range 18 - 37)	0.216
Gravid status			
First	31 (51.7)	25 (59.5)	0.165
Second	17 (28.3)	4 (9.5)	
Third	6 (10)	6 (14.3)	
Forth	5 (8.3)	6 (14.3)	
Fifth	1 (1.7)	0	
Sixth	0	1 (2.4)	
Cause of admission			
Prematurity	33 (55)	30 (71.4)	0.011 [c]
Pneumonia	1 (1.7)	2 (4.7)	0.156
ROP	2 (3.3)	2 (4.7)	0.852
Dehydration	1 (1.7)	0	1
PROM	2 (3.3)	1 (2.4)	0.641
IUGK	2 (3.3)	1 (2.4)	0.646
Respiratory distress	8 (13.3)	5 (11.9)	0.064
Icter	8 (13.3)	1 (2.4)	0.003 [c]
TTN	1 (1.7)	0	1
Preeclampsia	1 (1.7)	0	1
Illness	1 (1.7)	0	1
Gestational age, w	34 ± 2.7 (range 28 - 41)	29.6 ± 2 (range 23 - 35)	< 0.001 [c]
Duration of hospitalization, d	7.6 ± 6.4 (range 2 - 40)	14.7 ± 10.6 (range 2 - 46)	0.317
Septicemia	20 (33.3)	16 (38.1)	0.620
Using broad-spectrum antibiotics	46 (76.7)	41 (97.6)	0.003 [c]
Using steroids	7 (11.7)	10 (23.8)	0.105
Tracheal tube	3 (5)	11 (26.2)	0.003 [c]
Mortality	1 (1.7)	0	1

[a] Abbreviations: LBW, low birth weight; IUGR, intrauterine growth restriction; PROM, premature rupture of membrane; ROP, retinopathy of prematurity; TTN, transient tachypnea of the newborn; VLBW, very low birth weight.
[b] Data are presented as No (%) or mean ± SD.
[c] This P Value was considered significant.

Positive *Candida* cultures were found in 19 (31.7%) cases in the LBW group and 20 (47.6%) cases in the VLBW group. In our study, 36 (35.3%) cases (20 cases in the LBW group and 16 cases in the VLBW group) showed signs of sepsis. The mortality rate was 1.7% (n = 1). Results of the organism cultures showed that the umbilicus and rectum were the most common sites for *Candida* colonization in both groups (Table 2).

In the risk factor analysis for candidiasis infection, the multivariate logistic regression did not show any significant correlation between the prolonged use of antibiotics or urinary catheterization with candidiasis infection in either group. However, duration of hospitalization (OR = 3.143, 95% confidence interval [CI]: 1.562 - 6.324), prolonged corticosteroid use (OR = 3.182, 95% CI: 1.452 - 6.114), central venous catheters (OR = 1.401, 95% CI: 0.831 - 3.451), total parenteral nutrition (OR = 2.345, 95% CI: 0.887 - 3.946), and mechanical ventilation (OR = 1.479, 95% CI: 0.984 - 1.699) were associated with candidiasis infection in VLBW infants while prolonged corticosteroid use (OR = 3.400, 95% CI: 1.241 - 5.423) and central venous catheters (OR = 1.125 95% CI: 0.773 - 2.676) were major risk factors associated with candidiasis infection in LBW infants (Table 3).

Table 2. Results of Organism Cultures in the LBW and VLBW Groups [a,b]

Parameters	LBW (n = 60)	VLBW (n = 42)	P Value
Ear			
Negative culture	24 (40)	10 (23.8)	0.088
Gram-positive	26 (43.3)	19 (45.2)	0.773
Gram-negative	15 (25)	13 (31)	0.462
Candida	4 (6.7)	7 (16.7)	0.193
Umbilicus			
Negative culture	25 (41.7)	13 (30.9)	0.271
Gram-positive	18 (30)	11 (26.2)	0.675
Gram-negative	21 (35)	14 (33.3)	0.861
Candida	8 (13.3)	14 (33.3)	0.016 [c]
Rectum			
Negative culture	16 (26.7)	12 (28.5)	0.832
Gram-positive	7 (11.7)	5 (11.9)	0.971
Gram-negative	36 (60)	18 (42.8)	0.088
Candida	12 (20)	13 (30.9)	0.206
Catheter			
Negative culture	45 (75)	26 (61.9)	0.496
Gram-positive	8 (13.3)	5 (11.9)	0.764
Gram-negative	5 (8.3)	0	0.159
Candida	2 (3.3)	1 (2.3)	1
Tracheal tube			
Negative culture	0	6 (14.2)	–
Gram-positive	1 (1.7)	0	–
Gram-negative	1 (1.7)	5 (11.9)	–
Candida	1 (1.7)	0	–

[a] Abbreviations: LBW, low birth weight; VLBW, very low birth weight.
[b] Data are presented as No (%).
[c] This P value was considered significant.

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Candidiasis Infection [a]

Parameters	Odd Ratio (95% Confidence Interval)	P Value
Duration of hospitalization, d		
LBW group	2.430 (0.984 - 4.988)	0.078
VLBW group	3.143 (1.562 - 6.324)	0.006 [b]
Prolonged use of antibiotics		
LBW group	1.735 (0.886 - 3.400)	0.108
VLBW group	1.331 (0.674 - 2.692)	0.297
Prolonged use of corticosteroid		
LBW group	3.400 (1.241 - 5.423)	0.010 [b]
VLBW group	3.182 (1.452 - 6.114)	0.018 [b]
Central venous catheters		
LBW group	1.125 (0.773 - 2.676)	0.021 [b]
VLBW group	1.401 (0.831 - 3.451)	0.014 [b]
Prolonged urinary catheterization		
LBW group	2.036 (1.110 - 2.836)	0.443
VLBW group	2.744 (1.019 - 3.251)	0.104
Total parenteral nutrition		
LBW group	1.599 (1.184 - 2.048)	0.054
VLBW group	2.345 (0.887 - 3.946)	0.011 [b]
Mechanical ventilation		
LBW group	1.011 (0.558 - 1.001)	0.471
VLBW group	1.479 (0.984 - 1.699)	0.049 [b]

[a] Abbreviations: LBW, low birth weight; VLBW, very low birth weight.
[b] This P value was considered significant.

5. Discussion

Candidiasis is a major cause of mortality and morbidity in preterm infants. The first step in the pathogenesis of invasive candidiasis is colonization, and prematurity as well as low birth weight are two major risk factors for fungal colonization (9, 22). In the present study, positive *Candida* cultures were found in 19 (31.7%) cases in the LBW group and 20 (47.6%) in the VLBW group. Similarly, the frequency of *Candida* colonization was higher in the VLBW group than in the LBW group. This may be related to immunodeficiencies (such as decreased neutrophil function or a relative, quantitative deficiency of protective maternal IgG antibodies to *Candida)* in VLBW preterm infants (23). In our study, 36 (35.3%) cases (20 in the LBW group and 16 in the VLBW group) showed signs of sepsis. The mortality rate 1.7% (n = 1). In addition, the frequency of colonization observed in our study was higher than the frequency found by Ali et al. (27%) (24) and Saiman et al. (28.2%) (25). In a similar study examining the frequency of candidiasis in VLBW infants, Adams-Chapman et al. reported 31% of patients had sepsis due to *Candida* (26) while Singh et al. reported an even higher rate (74.4%) of *Candida* colonization (27). It is possible that the variation in results is related to differences in management protocols as well as the nature and intensity of routine antifungal, antiseptic measures applied in a particular setting.

Previous studies have suggested that *Candida* colonization of the skin and gastrointestinal tract is a main cause of systemic candidiasis in preterm infants (28). Results of organism cultures in the present study showed similar results and found that the umbilicus and rectum were common sites for *Candida* colonization in both groups (LBW group: 13.3% and 20%, respectively; VLBW group: 33.3% and 30.9%, respectively). Several studies have suggested that gastrointestinal and respiratory tract colonization predominantly occurs during the first week after birth and that the gastrointestinal tract can serve as a reservoir from where the fungus can spread, particularly if there is a breach in the mucosal lining and poor local colonization resistance (29, 30).

In our study, the major risk factors associated with candidiasis infection for VLBW infants were duration of hospitalization, prolonged use of corticosteroids, central venous catheters, total parenteral nutrition, and mechanical ventilation while the major risk factors for LBW infants were prolonged use of corticosteroids and central venous catheters. These results indicate that maturity

and birth weight are related to a decrease in the risk of developing a candidiasis infection. In addition, antenatal care provisions for birth term infants may have been a protective factor for neonatal candidemia. Moreover, the presence of regular antenatal visits may have led to earlier detection and treatment of maternal fungal colonization resulting in the reduction of neonatal colonization and dissemination in preterm infants.

This study reviewed candidemia related sepsis in a local NICU setting and identified the epidemiological features, frequency, and risk factors of candidiasis infection as well as the antifungal and clinical outcomes for inpatient infants. These findings can serve as a template for the development of local guidelines regarding the prevention and appropriate treatment of candidal sepsis in intensive care units.

Candidemia in the NICU is a common problem and is frequently associated with sepsis. In this study, the major risk factors were the duration of hospitalization, central venous catheters, total parenteral nutrition, and mechanical ventilation. However, antenatal care demonstrated a protective impact on neonatal fungal infections in our setting.

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