

ORIGINAL ARTICLE

Risk Factors for Candidemia in Newborns in the University Reference Hospital

Fatores de Risco para Candidemia em Neonatos em um Hospital Universitário de Referência

Factores de Riesgo de Candidemia en Recién Nacidos en un Hospital Universitario de Referencia

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ABSTRACT

Background and objectives: Newborn admitted to neonatal unit are at high risk of acquiring hospital infections and Candida infections are associated with several preventable risk factors. **Methods:** Paired case-control study was carried out in a neonatal referral unit of a university hospital. Data were collected by trained professionals from the Hospital Infection Control Service. The analysis of risk factors was performed using the Statistical Package for the Social Sciences software. The study was approved by the Ethics Committee. **Results:** 3,087 admissions and 108 patients were selected (36 cases with Invasive Candidemia and 72 controls). The prevalence of Candidemia was 1.2% and the incidence density was 0.48 per 1000 patients per day. Parenteral nutrition, mechanical ventilation, central venous catheter and use of aminoglycosides showed statistical significance associated with Invasive Candidemia in the univariate analysis. The multivariate analysis showed that newborns who received parenteral nutrition, Odds ratio 3.52 Confidence interval (95%) 1.11-11.16 and urinary catheters Odds ratio 3.91 Confidence interval (95%) 1.66-9.23 had a higher risk of developing Candidemia. **Discussion:** Good practices are necessary for the administration of parenteral nutrition and insertion and maintenance of urinary catheters to avoid fungal infections since the risk was greater in neonates who used these devices.

Keywords: Fungal infection; *Candida* spp.; Invasive Candidiasis; Candidemia; Neonates; Risk Factors.

RESUMO

Justificativa e objetivos: Recém-nascidos internados em unidade neonatal apresentam alto risco de contrair infecções hospitalares e infecções por *Candida* estão associadas a vários fatores de risco evitáveis. **Métodos:** Foi realizado um estudo caso-controle pareado em uma unidade de referência neonatal de um hospital universitário. Os dados foram coletados por profissionais treinados do Serviço de Controle de Infecção Hospitalar. A análise dos fatores de risco foi realizada por meio do software Statistical Package for the Social Sciences. O estudo foi aprovado pelo Comitê de Ética. **Resultados:** foram selecionados 3.087 internações e 108 pacientes (36 casos com candidemia invasiva e 72 controles). A prevalência de candidemia foi de 1,2% e a densidade de incidência foi de 0,48 por 1000 pacientes por dia. Nutrição parenteral, ventilação mecânica, cateter venoso central e uso de aminoglicosídeos apresentaram significância estatística associada à candidemia invasiva na análise univariada. A análise multivariada mostrou que os recém-nascidos que receberam nutrição parenteral, Odds ratio 3,52 Intervalo de confiança (95%) 1,11-11,16 e odds ratio de cateteres urinários 3,91 Intervalo de confiança (95%) 1,66-9,23

tiveram maior risco de desenvolver Candidemia. **Discussão:** Boas práticas são necessárias para a administração de nutrição parenteral e a inserção e manutenção de cateter urinário para evitar infecções fúngicas, uma vez que o risco foi maior nos neonatos que utilizaram esses dispositivos.

Palavras-chave: Infecção fúngica; *Candida spp.*; Candidíase Invasiva; Candidemia; Recém-Nascidos; Fatores de Risco.

RESUMEN

Antecedentes y objetivos: Los recién nacidos ingresados en la unidad neonatal tienen un alto riesgo de contraer infecciones hospitalarias y las infecciones por *Candida* están asociadas con varios factores de riesgo prevenibles. **Métodos:** Se realizó un estudio de casos y controles pareado en una unidad de referencia neonatal de un hospital universitario. Los datos fueron recolectados por profesionales capacitados del Servicio de Control de Infecciones Hospitalarias. El análisis de los factores de riesgo se realizó mediante el software Statistical Package for the Social Sciences. El estudio fue aprobado por el Comité de Ética. **Resultados:** se seleccionaron 3.087 ingresos y 108 pacientes (36 casos con candidemia invasiva y 72 controles). La prevalencia de candidemia fue del 1,2% y la densidad de incidencia fue de 0,48 por 1000 pacientes por día. La nutrición parenteral, la ventilación mecánica, el catéter venoso central y el uso de aminoglucósidos mostraron significancia estadística asociada con candidemia invasiva en el análisis univariado. El análisis multivariado mostró que los recién nacidos que recibieron nutrición parenteral, Odds ratio 3.52 Intervalo de confianza (95%) 1.11-11.16 y sondas urinarias Odds ratio 3.91 Intervalo de confianza (95%) 1.66-9.23 tenían un mayor riesgo de desarrollar Candidemia. **Discusión:** Son necesarias buenas prácticas para la administración de nutrición parenteral y la inserción y mantenimiento de catéteres urinarios para evitar infecciones fúngicas ya que el riesgo fue mayor en los neonatos que utilizaron estos dispositivos.

Palabras clave: Micosis; *Candida spp.*; Candidiasis Invasiva; Candidemia; Recién-Nacido; Factores de Riesgo.

INTRODUCTION

Newborn (NB) admitted to neonatal unit are at high risk of acquiring hospital infections because of their immature immune systems. With technical advances in neonatology and invasive procedures, the survival rates of premature newborns with extremely low birth weight increased.^{1,2}

Among fungal infections, *Candida spp.* are the most common health-related pathogens. The most common *Candida* species that cause fungal infections in newborns are *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. albicans*, and together they represent 95.4% of candidemia cases. The distribution of species varies according to the geographical location and the age of the patient.³

The international literature reveals that the incidence of candidemia is between 1.4 and 3.6 per 1000 newborns, and the main risk factors for candidemia are external factors related to the care provided in the neonatal unit, such as gestational age, low weight at birth, mechanical ventilation, use of broad-spectrum antibiotics, antifungal prophylaxis, normal birth, parenteral nutrition, presence of central catheters and previous surgery.²⁻⁵ However, few national studies have been conducted to assess candidemia in newborns.

The aim of this study was to determine the risk factors for candidemia in newborns admitted to the neonatal referral unit and to propose care measures to prevent candidemia.

METHODS

This is an observational case-control study, conducted from January 2008 to December 2018 in a neonatal referral unit in a University Hospital in Belo Horizonte / Minas Gerais, with facilities such as intensive care, intermediate care and kangaroo.

All newborns hospitalized for more than 48 hours in the neonatal unit and with positive blood culture for *Candida spp.*, defined as a result of candidemia, were included. Neonates with gastrointestinal malformations admitted to the neonatal unit were excluded because they have a higher risk of developing intestinal infection. Neonates without candidemia were matched for gestational age with a difference of up to 1 week before or after and hospitalized in the same week as neonates with candidemia. Controls were considered in the proportion of 1: 2; the controls were selected sequentially (1 before and 1 after the case) and all had a negative culture for candidemia. Considering Candidemia prevalence, a sample with a minimum of 30 cases was calculated with 5% accuracy and a 95% confidence interval.

Data collection was carried out systematically by specialized and trained professionals from the Hospital Infection Control Service (HICS) of the institution, which has surveillance protocols in critical sectors, including the neonatal unit. In addition to demographic information, the collection of variables according to Ordinance nº. 2.616, of May 12, 1998, is mandatory and includes demographic variables, infection rates and density of incidence of infections, topographic infections, infection and density of incidence of infections associated with devices, surgical site infections, profile of microorganisms and sensitivity to antimicrobials, use of antimicrobials, lethality associated with infections and parenteral nutrition. The independent variables analyzed were sex, birth weight, previous use of antimicrobials (ATM), number of previous treatments with antimicrobials, use of central venous catheter (CVC), use of mechanical ventilation (MV), use of internal urinary catheter (IUC), use of parenteral nutrition (PN) and previous surgery.

Descriptive analysis was performed with frequency and percentage of categorical variables and mean and median of continuous variables with normal and abnormal distribution, respectively. The univariate analysis of the risk factors was performed using the χ^2 and Fisher Exact tests of the categorical variables, and the multivariate analysis of the risk factors was performed with poisson regression and the variables with $p < 0.20$ in the univariate analysis. The level of significance was set at $p < 0.05$. The endemic alert level (2 DS) or outbreak (3 DS) is shown in the control table with the density of candidemia incidence.

Statistical Package for the Social Sciences (SPSS) software version 24.0 was used for statistical analysis.

The Institution's Research Ethics Committee approved this research (CAAE: 58973616.2.0000.5149).

RESULTS

In the ten-year period, 3,087 newborns were hospitalized for more than 48 hours in the unit, totaling 75,653 patients per day, all of whom underwent blood culture, with 36 cases (positive blood cultures for *Candida spp.*) and 72 controls (negative blood cultures for *Candida spp.*). With the inclusion of 108 neonates in the study.

The descriptive analysis of the 108 newborns showed that 57 (52.78%) were male, 49 (45.37%) were female and 2 (1.85%) had ambiguous genitalia. The average gestational age was 31.41 weeks with a range of 24 - 40 weeks and the average weight was 1,665.23 g with a range of 515-4,015. The median of the 1-minute Apgar was 7 and the 5-minute Apgar was 9.

Table 1. Incidence density of Healthcare-Associated Infections by ranges of weight in case and control groups in a reference Neonatal Unit, Minas Gerais, Brazil, 2008-2018.

Weight (g)	CASES			CONTROLS		
	Patient-day n(%)	\$HAIs Total n (%)	\$HAIs Incidence Density	Patient-day n(%)	\$HAIs Total n (%)	\$HAIs Incidence Density
< 750	124 (15.35)	10 (22.73)	80.6	254 (9.21)	10 (14.92)	39.4
751-1.000	193 (23.89)	13 (29.54)	67.4	961 (34.84)	24 (35.82)	25
1.001-1.500	59 (7.30)	2 (4.55)	33.9	647 (23.46)	19 (28.36)	29.4
1.501-2.500	314 (38.86)	13 (29.54)	41.4	506 (18.35)	9 (13.43)	17.8
> 2.500	118 (14.60)	6 (13.64)	50.6	390 (14.14)	5 (7.46)	12.8
Total	808	44	54.5	2758	67	24.3

\$HAIs – Healthcare-Associated Infections

Table 1 shows the incidence density (ID) of health-associated infections (HAI) in the neonatal unit of the present study, stratified by weight and group (case and control). Previously, the HAI ID was higher in the case group ($p < 0.001$), and when comparisons were made according to the weight ranges, the HAI ID was again higher in the weight range of 751-1,000 g ($p < 0.001$).

The prevalence of candidemia was 1.2%. When stratified by weight, there was a higher prevalence (14.7%) in newborns weighing ≤ 750 g. The other weights had a much lower prevalence: 1.1% in the range of 751 g to 1,000 g; 4.6% in the range from 1,001 to 1,500 g; 0.2% in the range of 1,501 g to 2,500 g; and 0.2% above 2,500 g.

The average of 1,000 800 patients per day and is shown in the control chart in figure 1. There was a significant difference in candidemia ID between the weight ranges, with greater identity in patients weighing < 750 g ($p < 0.001$).

It was found that of 108 patients, 75 (69.4%) used antimicrobials. Of these, 62 received more than two antimicrobials and the most used were aminoglycosides 57 (76%), ampicillin 46 (61.3%) and vancomycin 37 (49.3%). One hundred patients used cvc for an average of 19.76 days; 82 (75.9%) received PN for an average of 8.53 days; The MV was used in 83 (76.8%) patients for an average of 13.84 days. IUC was less used - 35 (32.40%) patients for an average of 2.95 days.

Surgical procedures were performed in 45 (41.7%) 59 surgeries were performed and 59 surgeries were performed, separated by the system; musculoskeletal system ($n = 3$), cardiovascular system ($n = 10$), head, eyes, ears, nose and throat

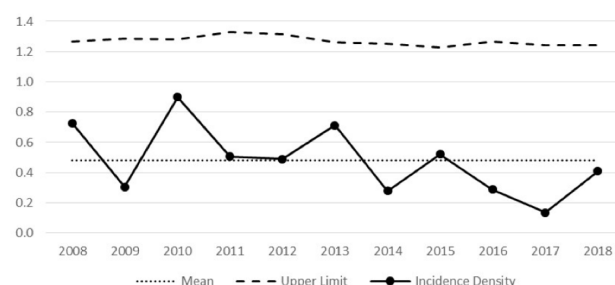


Figure 1. Incidence Density Chart for Candidemia per 1,000 patients-day, in a reference Neonatal Unit, Minas Gerais, Brazil, 2008-2018.

($n = 2$), central nervous system ($n = 13$), digestive system and abdominal surgery ($n = 29$) and genitourinary system ($n = 2$).

Eleven (30.55%) patients with candidemia died. When stratifying deaths by weight, we found 3 weighing up to 750 g, 2 weighing between 751 and 1,000 g, 3 weighing between 1,501 and 2,500 g, and 3 weighing more than 2,500 g, with no difference in mortality between weight ranges.

The variable use of PN, MV, IUC and aminoglycosides showed greater significance in the univariate analysis for greater risk of candidemia with statistical association in the univariate analysis. These variables and those analyzed in the multivariate analysis ($p < 0.20$) are shown in table 2.

Table 2. Risk factors univariate analysis ($p < 0.20$) for candidemia in a reference Neonatal Unit, Minas Gerais, Brazil, 2008-2018.

Risk factors	Case	Control	$\chi^2 p$	τOR	IC 95%
Gender n(%)					
Male	16 (44.4)	41 (58.6)	0.167*		
Female	20 (55.6)	29 (41.4)			
Parenteral nutrition n(%)					
Yes	32 (88.9)	50 (69.4)	0.026*	3.52	1.11 – 11.16
No	4 (11.1)	22 (30.6)			
Mechanical ventilation n(%)					
Yes	34 (94.4)	49 (68.1)	0.02*	7.98	1.76 – 36.11
No	2 (5.6)	23 (31.9)			
Delay bladder catheter n(%)					
Yes	19 (52.8)	17 (47.2)	0.01*	3.91	1.66 – 9.23
No	16 (22.2)	56 (77.8)			
Previous surgery n(%)					
Yes	19 (52.8)	27 (37.5)	0.130*	1.86	0.83 – 4.19
No	17 (47.2)	45 (62.5)			
Aminoglycosides n(%)					
Yes	33 (91.7)	54 (75)	0.039*	3.67	1.00 – 13.41
No	3 (8.3)	18 (25)			

Ampicilin n(%)					
Yes	27 (75)	43 (59.7)	0.117*	2.02	0.83 – 4.92
No	9 (25)	29 (40.3)			
4th generation cephalosporin n(%)					
Yes	7 (19.4)	5 (6.9)	0.100**	3.23	0.95 – 11.04
No	29 (80.6)	67 (93.1)			
Glycopeptide n(%)					
Yes	20 (55.6)	27 (37.5)	0.074*	2.08	0.92 – 4.70
No	16 (44.4)	45 (62.5)			
Macrolide n(%)					
Yes	2 (5.6)	0	0.109**	0.32	0.24 – 0.42
No	34 (94.4)	72 (100)			
Metronidazole n(%)					
Yes	5 (13.9)	2 (2.8)	0.040**	5.64	1.04 – 30.70
No	31 (86.1)	70 (97.2)			
Oxacillin n(%)					
Yes	11 (30.6)	13 (18.1)	0.141*	1.99	0.79 – 5.06
No	25 (69.4)	59 (81.9)			

¶p= Significance level; τOR= odds ratio; ¶CI 95%= Confidence Interval 95%; * chi-squared test and ** Fisher's test

Table 3. Risk factors multivariate analysis for candidemia with statistical significance in a reference Neonatal Unit, Minas Gerais, Brazil, 2008-2018.

Risk factors	β	¶p	τOR	¶CI 95%
Parenteral nutrition	-0.231	0.025	3.52	1.11 - 11.16
Delay bladder catheter	-0.276	0.005	3.91	1.66 - 9.23

Legend: β=Statistical power; ¶p=Significance level; τOR= odds ratio; ¶CI 95%= Confidence Interval 95

In the multivariate analysis of categorical variables, the use of NP, previous surgery, IUC, MV and antimicrobials (aminoglycosides, ampicillin, beta-lactams, fourth generation cephalosporin, glycopeptides, macrolides, metronidazole and oxacillin) were found to be significant factors for the development of candidemia (Table 2).

Multivariate analysis (Table 3) showed that patients who used PN or IUC had a higher risk of developing candidemia, and the fit model was good (Hosmer and Lemeshow with $p = 0.99$).

DISCUSSION

The prevalence of candidemia in our study was 1.2%. The highest incidence was in 2010 and, when stratified by weight, the highest incidence was among newborns weighing ≤ 750 g as observed in other studies.⁶⁻⁹ This is justified by the immaturity of the immune system and the weakness of physical barriers.⁷ Multicenter study composed of case control studies and prospective cohort carried out in 13 Neonatal Intensive Care Units in 9 Canadian cities from 2001 to 2006 with 139 newborns (49 cases and 90 controls) stratified by weight, the incidence rate was 1.5% for newborns $<1,500$ g (95% CI: 0.09-3.26), 2.2% for newborns -births $<1,000$ g (95% CI: 1.02-3.39) and 4.2% for newborns <750 g (95% CI: 1.23-7.66) in the 5-year period.⁶ In Brazil, a prospective cohort study conducted from 2012 to 2014 in another referral hospital in Minas Gerais showed an incidence rate of 5.25%.⁸

The period of greatest occurrence of candidemia found in this study was in 2010 with 1 million cases per 1,000 patients per day and the occurrence of 6 cases, but it did not reach the alert level (2SD).

The use of ATM changes the flora, favors colonization and, consequently, the proliferation of *Candida* spp. Studies carried out in several countries have shown the use of antibiotics, mainly of a broad spectrum, as an important predictor of candidemia. In the USA, a multicenter cohort study, retrospective from 2001 to 2010 and composed of 530,162 newborns, evaluated the risk factors for invasive candidiasis among newborns weighing $<1,500$ g. There were 330 cases of candidemia and the use of broad-spectrum antibiotics was considered a significant factor that affected the outcome (OR 1.6 95% CI: 1.1-2.4). The same result was found in 2010 by Benjamin et al,⁴ in a multicenter study also carried out in the USA by Lee et al⁹ composed of 6,833 newborns (OR 1.98 95% CI: 1.37-2.28) and by Chen et al¹⁰ in a 2016 study carried out in China with 5,075 hospitalized newborns and 69 cases of candidemia (OR 1.06 95% CI: 1.01-1.10). In this study, the antimicrobials that were inserted in the multivariate analysis were aminoglycosides, ampicillin, fourth generation cephalosporin, glycopeptides, macrolides, metronidazole and oxacillin, but there was no statistical significance in the multivariate analysis, which may have been influenced by the high number of prescribed antimicrobials prematurity, low weight and malformations of newborns admitted to this unit.

It is a reference unit for fetal medicine and newborns with malformations in the gastrointestinal tract that require surgery for correction. Digestive and abdominal surgeries were performed more frequently, although they were not significantly associated with the outcome. Previous studies in the same neonatal unit show that surgery is a risk factor for laboratory confirmed infections, which prolongs the use of invasive devices and NP, also identified as risk factors.¹¹⁻¹²

Invasive devices are risk factors for infection by *Candida* spp.¹³⁻¹⁵ In this study, the MV associated with the use of endotracheal tubes had significance only in the univariate analysis with an average time of use of 13.84 days, which corroborates with the literature that presents the use of MV for more than 5 days as risk factor. In a case-control study carried out in Turkey, from 2000 to 2007, 2,420 newborns were admitted and 28 were diagnosed with candidemia and the average time for MV use was 5.5 days, with a standard deviation of 6.6 and $p = 0.004$.⁴ Humidification of mechanical ventilators is a source of inoculation of microorganisms in the trachea

because condensed water can accumulate in the ventilator circuit, which can become contaminated during care and thus colonize the patient's trachea. Other sources of inoculation of contaminated material in the trachea are contaminated nebulizers and endotracheal aspirations not performed using appropriate techniques.¹⁶

The use of CVC was a risk factor presented in several studies. However, our study did not confirm this device as a higher risk factor for candidemia, despite 92.6% of newborns using CVC. A prospective, multicenter study, carried out in 8 countries in Latin America (Argentina, Brazil, Chile, Colombia, Ecuador, Honduras, Mexico and Venezuela) from 2008 to 2010, studied 302 patients, 89 newborns and 213 children. CVC was a risk factor and had a similar proportion in both groups; newborns versus children (70.8% vs. 62.4%, $p = 0.17$).¹⁷ The time of use promotes the adhesion of *Candida* spp. in the catheter and can form a biofilm, causing invasive candidiasis. Thus, it is strongly recommended, with a moderate quality of evidence, that the catheter should be removed early when the infection is presumed to be related to the device.¹⁸

Although CVC was not a significant factor for candidemia in this study, the catheter-related sepsis clinical ID was 4.6 per 1,000 live births, and catheter-related laboratory sepsis was 16.6 per 1,000 live births during that period. The presence of this device requires packages for assistance from the team for its insertion and maintenance to avoid infections related to the catheter.

In the multivariate analysis, the IUC was the only device whose use was associated with a significant risk of candidemia, although it was used by only 32.4% of patients and the average duration of use (2.95 days) was low. It is a poorly presented factor in studies with newborns, although it is common in studies carried out in adults and children. Prolonged use of IUC increases peri-urethral colonization and microorganisms use the surface of the catheter to rise into the bladder causing urinary tract infection. The improper handling of the closed system can be one of the causes of the proliferation of microorganisms in the urinary tract, increasing the risk of candidiasis and, consequently, invasive candidiasis. Although the use of IUC is not frequent in the neonatal unit examined in this study, it is necessary to review practices to prevent catheter-related urinary tract infections according to the recommendations of the National Healthcare Safety Network NHSN on how to ensure early removal.^{16,19} Preventive measures should be implemented to reduce the risk of developing candidemia among hospitalized newborns, such as encouraging hand washing to remove visible dirt and transient flora before and after procedures and handling the device, in addition to monitoring through observations and raising the team's awareness of the importance of hand hygiene. In general care neonatology units, the recommendation is hygiene with soap and water or 70% alcohol. In neonatal intensive care units where the risk of infection is greatest, the use of chlorhexidine is recommended.¹ Removal of the IUC when the fungal infection is diagnosed is strongly recommended.¹⁶⁻¹⁸

Parenteral nutrition was another factor that showed a significant association in the multivariate analysis, and patients who used PN had a higher risk of candidemia than the others. Fu et al in a retrospective case-control study conducted in China with 449 newborns with very low birth weight (<1,500 g) showed that patients who used PN were 10 times more likely to develop candidemia, (OR, 10.16; 95% CI, 2.25 - 45.94).²⁰

Lipid present in solutions of PN are responsible for the growth of microorganisms and are associated to pH solution; the higher the pH, the higher the risk.²¹ The parenteral nutrition preparation requires strict care by the team to avoid

contamination of the solution.¹⁸⁻²²

The use of aseptic techniques in the preparation and installation of PN to ensure a closed system with an exclusive CVC to avoid frequent handling of the device is strongly recommended. The early introduction of enteral nutrition, when possible, in the preference of breast milk, which contains antibodies against *Candida*, decreases the time of use of NP.²³

Despite the low prevalence, invasive candidiasis is an important infection in newborns because it increases morbidity and mortality, and measures are needed to avoid increasing its incidence in the unit. The mortality rate from candidemia ranges from 15% to 60% in international studies, with the highest rate among babies weighing less than 1000g.^{13,24-25} In this study, the mortality rate was 30% and there was no difference between weight ranges.

One of the limitations of this study is the retrospective design and the lack of information such as the use of PN that was not part of the HICS database. To minimize information bias, all physical and electronic records were analyzed to verify the use of PN.

The study shows that candidemia is associated with the use of IUC and PN. This implies that the adoption of good practices for the insertion, handling and early removal of CIC together with the appropriate use of NP reduces infection rates. In addition, the awareness and training of nursing professionals is essential to reduce infection rates.

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