

Risk factors and lethality associated with Neonatal Candidemia in a neonatal unit

Factores de riesgo y letalidad asociados a Candidemia Neonatal en una unidad de neonatología

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Abstract

Objective: To identify the main risk factors associated with neonatal candidemia. **Patients and Method:** A retrospective paired case-control study was conducted from January 2014 to December 2016. The cases were patients with isolation in blood culture and/or cerebrospinal fluid of *Candida* spp. after their first 48 hours in the hospital and the controls cases were neonates chosen from the statistical census of neonatology paired according to their admission date (30-day range), birth weight, gestational age, and discharge condition (alive or deceased). For each case, we select two controls. The risk factors evaluated were intrahospital stay over seven days, use of broad-spectrum antibiotics, mechanical ventilation, parenteral nutrition longer than five days, invasive procedures such as central venous access and abdominal and thoracic surgeries, necrotizing enterocolitis and growth of bacterial microorganisms in blood culture before candidemia. **Results:** During the study period, 141 patients developed candidemia. 49% of the cases corresponded to *Candida parapsilosis* with the highest associated lethality rate. The multivariate analysis identified as risk factors hospital stay longer than seven days (OR = 17.0, 95% CI = 2.36-122.4), use of umbilical lines (OR = 9.04, 95% CI = 1.55-52.5), abdominal and/or thoracic surgery (OR = 12.4, 95% CI = 1.76-87.3), and treatment with Meropenem (OR = 4.62, 95% CI = 1.34-15.9). **Conclusion:** Prolonged intrahospital stay longer than seven days and thoracic and/or abdominal surgery were the most significant risk factors in this study for the development of neonatal candidemia.

Keywords:

Neonate;
Candidemia;
Risk factors;
Fluconazole;
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Introduction

Candida infections are currently associated with increased mortality in the neonatal population; thus it is necessary to evaluate the main risk factors associated with this infectious process.

Patients in neonatal intensive care units (NICU) are colonized by *Candida* species shortly after birth. Colonization is found mainly in the gastrointestinal and respiratory tracts in the first two weeks of life due to vertical transmission associated with childbirth. After two weeks of life, the most frequent colonization site is the skin, this can be related to the manipulation of the patient by health personnel^{1,2}.

Risk factors for candidemia in premature patients are associated with gastrointestinal tract immaturity, colonizing strain virulence, immunological deficiencies and immaturity, and incomplete epidermis development that weakens physical and immunological barriers facilitating invasion. After having access to mucous membranes or the bloodstream, *Candida* shows a predilection for the invasion of the central nervous system, kidneys, liver, spleen, heart, and retina, with complications compromising the function of these organs^{3,4}.

Candida is the main cause of invasive fungal infections in the NICU and is the third most commonly isolated microorganism in blood cultures in late neonatal sepsis. It is estimated to cause 2-4% of infections in early neonatal sepsis and 10-12% in late neonatal sepsis⁵.

Neonatal candidiasis significantly increases mortality and morbidity, with a mortality rate between 15 and 60%, which is higher in extremely low-birth-weight (ELBW) infants (less than and equal to 1,000 grams)⁵.

The objective of this study was to determine the main risk factors associated with candidemia in neonates seen at the *Hospital del Niño Dr. José Renán Esquivel de Panamá* (DRJRE).

Patients and Method

A retrospective paired case-control study was conducted between January 2014 and December 2016. Due to the previously known high prevalence of candidemia in the institution's neonatal unit, a period of three years was chosen for this study.

The cases were all neonates who had blood culture and/or cerebrospinal fluid with isolation of *Candida* after 48 hours of hospitalization in the neonatal unit of the Hospital del Niño DRJRE, admitted during the study period. Controls were taken from the statistical census of the neonatal unit matched by admission date,

birth weight, gestational age, and discharge condition. For multiple pregnancies, only one of the children was selected as the control group. Clinical records were then evaluated in the archives of Hospital del Niño DRJRE.

The sample was calculated using OpenEpi program having a 95% confidence level, 80% detection probability, with two controls per case, a hypothetical proportion of controls with exposure of 4%, a hypothetical proportion of cases with exposure of 13%, and odds ratios of 3.59 obtaining a minimum size of 76 cases according to Kelsey and 89 according to Fleiss, and a minimum size of 152 control samples according to Kelsey and 178 according to Fleiss, making a total of 267 patients.

Reference population and study place

The study was conducted in the neonatal unit of the Hospital del Niño DRJRE, with capacity for 90 patients (two intensive care units for 14 patients each, three intermediate care units for 20 to 24 patients each, and an isolation unit for two patients), to which 6,755 neonates were admitted during the study period.

The extremely low-birth-weight (ELBW) is defined as a newborn weighing less than 1,000 grams, the very-low-birth-weight (VLBW) as a newborn weighing less than 1,500 grams, and the low birth weight (LBW) as a newborn weighing less than 2,500 grams⁶.

During the study, all patients under 1,250 grams received a dose of fluconazole prophylaxis at 3mg/kg using the intravenous route every 48 hours, the first dose given on the third day of life and continuing prophylaxis for six weeks. This protocol has been applied in the institution since 2009.⁷

Microbiological Method

Blood specimens were inoculated into BacT/AlerT PF Plus pediatric aerobic bottles (Biomérieux, France), then incubated in the BacT/AlerT 3D automated system for five days. The blood volume extracted for blood culture was determined according to the weight of the patient: 1 ml for weights less than or equal to 1000 grams, 2 ml for weights from 1001 to 3000 grams, and 4 ml for weights more than 3001 grams. Bottles that were positive were Gram stained, and each sample with microscopic yeasts evidence was subcultured in sabouraud agar medium and incubated at 35 +/- 2 ° C for 24 hours. Phenotypic identification and susceptibility testing for each isolation were performed using the Vitek®2 system (Biomérieux, France) with YST, AST and YBC cards. The cerebrospinal fluid sample was inoculated in thio-

glycolate broth and incubated at 37°C for 72 hours. As yeasts grew in the solid medium, the identification process and susceptibility testing were carried out in the same way as blood culture.

Analysis plan

Initially, a descriptive analysis of the cases and controls characteristics was carried out. Variables proposed as risk factors in the literature were selected, and the presence or absence of these associations was established in the neonatal unit. Through the comparison between cases and controls, a univariate analysis was performed estimating the Odds Ratio (OR) as the extent to which these risk factors predispose patients to develop candidemia, defining as statistically significant a p -value < 0.05 . All variables with a p -value < 0.05 were selected for inclusion in the multivariate logistic regression model. The analysis was performed using the statistical software STATA 14.

The development of this study is guided by the international ethical guidelines for epidemiological studies developed by the World Health Organization (February 2008)⁸. The study was approved by the bioethics committee of the institution and by the bioethics committee of the Ministry of Health. Written permission was obtained from both committees to review clinical records.

Results

A total of 6755 newborns were admitted to the neonatal unit from January 2014 to December 2016 of which 2801 (41.5%) were admitted to the NICU and 3954 (58.5%) to the intermediate care unit.

A total of 836 positive blood cultures were reported, of which 328 episodes (39.2%) were Gram-negative microorganisms, 263 (31.5%) fungi, and 245 (29.3%) Gram-positive ones. Out of the 263 blood cultures reported with fungal growth, 141 patients were identified with episodes of candidemia, however, seven patients were excluded as they presented *Candida* growth prior to 48 hours of hospitalization, making a total of 134 patients with candidemia in the group of cases. Three patients (2%) presented *Candida* isolation in cerebrospinal fluid. The control group consisted of 268 patients.

The candidemia incidence was 20 per 1000 admissions, with the highest rate in ELBW patients (406.6 per 1000 ELBW neonates). The increase was from 15 per 1000 admissions in 2014 to 30 per 1000 admissions in 2015, having a decrease by 2016 to 18 per 1000 admissions.

When evaluating the persistence of candidemia (defined as blood culture by *Candida* six days after

starting antifungal therapy)⁵ versus non-persistence, it was found that there was no relationship between persistence and mortality, which was 59% in persistent candidemia versus 63% in the non-persistent one.

General characteristics of cases and controls

Table 1 shows the gender, gestational age, birth weight, and discharge status characteristics which were similar in cases and controls.

Out of 273 infants with ELBW and VLBW (< 1500 g), 91 (33%) developed candidemia, and of 68 infants with LBW (< 2500 g), 24 (35%) developed candidemia. During the study, 191 (100%) of patients under 1250 grams received fluconazole prophylaxis, developing candidemia in 80 patients (42%).

An overall 62% candidemia fatality rate was found. Table 2 describes the fatality by species.

Table 1. Clinical characteristics of cases and controls

Variable	Cases n = 134	Control n = 268	P Value
Demographics			
Gender			
Male	81 (60.5%)	165 (61.5%)	0.82
Gestational age			
< 28 weeks	42 (31.3%)	67 (25.0%)	0.17
< 32 weeks	80 (59.7%)	159 (59.3%)	0.94
< 36 weeks	106 (79.1%)	208 (77.6%)	0.73
Birth weight (g)			
< 1500 g	91 (67.9%)	182 (67.9%)	1.00
< 2500 g	115 (85.8%)	226 (84.3%)	0.69
Discharge Condition			
Alive	51 (38.0%)	103 (38.0%)	-
Deceased	83 (62.0%)	165 (62.0%)	-

Case and Controls (ratio of 1: 2), were matched according to gestational age, birth weight, date of admission and discharge condition.

Table 2. Fatality rate of candidemia by species

Species	Fatality (%)
<i>Candida parapsilosis</i>	68%
<i>Candida guilliermondii</i>	67%
<i>Candida albicans</i>	55%
<i>Candida tropicalis</i>	55%
<i>Candida haemulonii</i>	50%
<i>Candida lusitanae</i>	50%

Patients admitted in the neonatal nursery from 2014 to 2016.

Candida parapsilosis caused 66 (49%) episodes of candidemia, second is *Candida albicans* with 44 (33%) episodes, followed by *Candida tropicalis* with 11 (8%) episodes, *Candida* with 7 (5%) episodes, other species caused 9 (7%) episodes, and *Candida guilliermondii*, *Candida haemulonii* and *Candida lusitanae* caused 3 (2%), 2 (1.4%), 2 (1.4%) episodes respectively.

Univariate Analysis

Initially, the variables were evaluated independently, highlighting possible risk factors for candidemia on an individual basis (Table 3). When performing the univariate paired analysis, it was observed that the same variables remained as risk factors, statistically significant for candidemia, identifying inpatient stay longer than seven days, the use of broad-spectrum antibiotics, admission to NICU, and exposure to mechanical ventilation, the use of parenteral nutrition for more than five days, invasive procedures such as placement of central venous access and abdominal and thoracic surgeries, necrotizing enterocolitis, and bacterial microorganism growth in blood culture prior to candidemia. Out of the statistically significant risk factors, those that represent a higher risk are length of stay longer than seven days, use of parenteral nutrition for more than five days, and exposure to abdominal surgeries (Table 4).

Multivariate Analysis

In the multivariate analysis, risk factors identified were inpatient stay longer than seven days, the use of umbilical catheters, surgery, and treatment with meropenem (Table 5).

Discussion

The study was able to evaluate the most important risk factors associated with candidemia in patients hospitalized in the neonatal unit: inpatient stay longer than seven days, the use of umbilical catheters, surgery, and treatment with meropenem. Although there are limitations in assessing risk factors, we decided to conduct a paired case-control study to reduce possible bias.

The hospital incidence rate of *Candida* in the study was 20 per 1000 admissions, which is higher when comparing with other studies such as Feja et al. ⁶ in New York, Fu et al. ⁹ and Chen et al. ¹⁰ in China, and Pinhat et al. ¹¹ in Brazil, being 15.9, 13.6, 10.6 and 9.0 per 1000 admissions respectively. Among the possible reasons associated with the high incidence of candidemia in our institution, we can mention daily overcrowding (census above capacity), the small number of doctors and nurses (numerical ratio per patient), the pathologies high complexity, to be a national reference

Table 3. Risk Factors for Candidemia in neonates hospitalized in the Hospital del Niño, January 2014 to December 2016. Unpaired Bivariate Analysis

Variable	Cases n = 134	Controls n = 268	Odds Ratio No Matched	P Value
Length of stay				
> 7 days	131	139	40,5 (12,9-202,6)	0,00
NICU	130	230	5,3 (1,8-21,1)	0,00
Mechanic ventilation	128	202	6,9 (2,9-20,1)	0,00
Medications				
Broad spectrum antibiotic				
Piperacillin/Tazobactam	118	85	15,8 (8,6-30,2)	0,00
Meropenem	107	42	21,3 (12,0-37,8)	0,00
NPT				
> 5 days	132	185	29,6 (7,6-251,6)	0,00
Procedures				
Invasive				
Umbilical lines	101	155	2,2 (1,3-3,6)	0,00
Percutaneous	84	32	12,3 (7,2-21,3)	0,00
Central venous catheter	21	7	6,9 (2,7-19,7)	0,00
Surgery				
Abdominal	37	10	9,8 (4,5-22,9)	0,00
Thoracic	9	5	3,7 (1,1-14,6)	0,01
Necrotizing Enterocolitis	25	19	3,0 (1,5-6,0)	0,00
Bacterial Isolation previous blood culture candidemia	34	35	2,2 (1,2-3,9)	0,00

NICU: Neonatal intensive care unit; NPT: Parenteral nutrition.

Table 4. Risk Factors for Candidemia in neonates hospitalized in the Hospital del Niño, January 2014 to December 2016. Matched Bivariate Analysis

Variable	Odds Ratio Matched	Confidence interval 95%	P Value
Length of stay			
> 7 days	54.9	13.4-224.7	0.00
NICU	6.0	2.0-17.5	0.00
Mechanic ventilation	9.1	3.5-23.5	0.00
Medications			
Broad spectrum antibiotic			
Piperacillin/Tazobactam	3.1	2.3-3.9	0.00
Meropenem	2.8	2.1-3.5	0.00
NPT			
> 5 days	30.2	7.3-125.1	0.00
Procedures invasive			
Umbilical lines	2.8	1.6-4.9	0.00
Percutaneous	10.9	6.0-19.7	0.00
Central venous catheter	6.7	2.7-16.8	0.00
Surgery			
Abdominal	16.5	5.8-46.6	0.00
Thoracic	5.0	1.3-19.1	0.01
Enterocolitis Necrotizante	2.9	1.5-5.4	0.00
Bacterial Isolation previous blood candidemia	2.0	1.2-3.4	0.00

NICU: Neonatal intensive care unit; NPT: Parenteral nutrition.

Table 5. Risk Factors for Candidemia in neonates hospitalized in the Hospital del Niño, January 2014 to December 2016. Matched Multivariate Analysis

Variable	Odds Ratio Matched	Confidence interval 95%	P Value
Gestational age < 32 weeks	14,2	1,5-128,4	0,01
Birth Weight < 1000 g	8,5	1,6-44,3	0,01
Length of stay	17,0	2,3-122,4	0,00
NICU	0,4	0,0-2,8	0,36
Percutaneous	1,2	0,3-3,9	0,69
NPT	6,1	0,5-68,9	0,13
Umbilical lines	9,0	1,5-52,5	0,01
Central venous catheter	1,4	0,2-8,8	0,67
Surgery	12,4	1,7-87,3	0,01
Broad spectrum antibiotic			
Meropenem	4,6	1,3-15,9	0,01
Piperacillin/Tazobactam	3,7	0,9-14,8	0,05

NICU: Neonatal intensive care unit; NPT: Parenteral nutrition.

center, and the indiscriminate use of broad-spectrum antibiotics. According to the obtained results, we recommend reducing the use of broad-spectrum antibiotics, especially carbapenem antibiotics, improving aseptic techniques when placing and using umbilical catheters, and trying as much as possible to reduce the inpatient stay to reduce the incidence of candidemia in the institution.

A total of 49% of candidemia cases were caused by *Candida parapsilosis* similar to that exposed in the studies of Yu et al.¹², Rodríguez et al.¹³, Neu et al.¹⁴, Celebi et al.¹⁵, and Caggiano et al.¹⁶. In contrast, other studies such as Feja et al.⁶, J. Fu et al.⁹, Chen et al.¹⁰, Saiman et al.¹⁷, Robinson et al.¹⁸, Juyal et al.¹⁹, Hsu et al.²⁰, and Márquez et al.²¹, the predominant species was *Candida albicans*.

The overall mortality rate in the neonatal unit of our institution, in patients weighing less than 2500 grams, is 10% (source: neonatal database). During the study period, the overall fatality rate due to candidemia was 62%. *Candida parapsilosis* was responsible for the highest number of episodes and fatality due to candidemia.

The *Candida parapsilosis* virulence factors include biochemical characteristics and metabolic processes such as the production of phospholipases, the synthesis and storage of fatty acids, great affinity for synthetic surfaces (greater than *Candida albicans*), and differences in the structure and composition of biofilms, which contribute to the increase in the number of cases observed in recent years²²⁻²⁴. In addition, lower susceptibility to different antifungals, such as amphotericin B, fluconazole, and caspofungin, along with the emergence of multi-resistant strains, contributes to the higher incidence of this species compared to other species of *Candida*²⁵.

No relationship was found in the study between persistence of candidemia and mortality, similar to that obtained by Robinson et al.¹⁸, Levy et al.²⁶, and Benjamin et al.²¹.

Multivariate analysis identified the following risk factors: inpatient stay, use of umbilical catheters, surgery, and treatment with meropenem. These risk factors appear as statistically significant in the literature. Surgical intervention as a risk factor has been previously mentioned in the study by Ávila-Agüero et al.²⁸ based on the skin and epithelial barrier disruption for *Candida* invasion of the bloodstream. Inpatient stay and the use of meropenem have been identified as risk factors in studies by Fu et al.⁹, Chen et al.¹⁰, Yu, et al.¹², Saiman et al.¹⁷, Stoll et al.²⁹, Benjamin et al.³⁰, and Hsu et al.³¹. It has been found that carbapenem antibiotics (Meropenem) may contribute to the proliferation of opportunistic microorganisms such as *Candida* by reducing the competitive pressure exerted by normal bacterial flora.⁹ A study by Kaufman et al.³² showed that decreased use of carbapenem antibiotics is associated with decreased incidence of *Candida* infections.

In the study, the main risk factor was inpatient stay since it enables *Candida* to colonize patients. These results coincide with those found in other neonatal units^{33,34}.

In addition, the umbilical catheters placement was identified as a risk factor for the development of candidemia since it facilitates the *Candida* introduction and attachment to foreign material, therefore, it forms biofilms that lead to its horizontal transmission³⁵⁻³⁷.

It is noteworthy to highlight the high incidence of candidemia observed in patients weighing less than 1250 grams despite fluconazole prophylaxis. Possible explanations for this finding include a high degree of

horizontal transmission due to a failure to comply with biosecurity standards, overcrowding in the neonatal units, and complexity of the neonatal population in the region. Future studies are needed to assess these possibilities.

The strengths of the study include adequate selection and definition of cases and controls, good access to clinical records, and control of biases during statistical analysis.

The importance of identifying factors that increase the likelihood of developing candidemia is highlighted when considering the impact they have on morbidity and mortality in the neonatal population. It is therefore mandatory to make a timely diagnosis and start treatment early.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

The authors declare not having any conflict of interests. Rodrigo DeAntonio is an employee of GSK Vaccines. Own opinions are expressed in this article and do not reflect opinions or views from GSK Vaccines.

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