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NEWBORNS FUNGAL INFECTIONS: ASSOCIATED FACTORS AND CLINICAL-EPIDEMIOLOGICAL PROFILE

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ABSTRACT

Objective: Invasive Fungal Infections (IFI) are among the main causes of morbidity and mortality in newborns. In this way, the objective of this research is to analyze the frequency of fungal infections in newborns admitted to the Neonatal Intensive Care Unit (NICU) in a public Hospital of Itaperuna city, Rio de Janeiro State, Brazil, identifying associated factors and describing its clinical and epidemiological characteristics. **Study design:** This is an observational, descriptive, and analytical study, with data collected from the medical records of hospitalized newborns. Subsequently, in order to identify the role of the variables as associated factors for neonatal fungal infection, a Multivariate Logistic Regression model was carried out using the presence of Candida spp. infection as the response variable. Comparative analyzes were carried out considering the odds ratio (OR), 95% confidence interval (95% CI) and p value, obtained during the bivariate logistic regression analysis. **Results:** This study consisted of 78 newborns patients, of which 23.08% (18/78) were positive for Candida species´ infection. In the final model, two factors were found to be associated with Candida spp. newborns fungal infections: caesarean delivery (OR:7.6; 95%CI:1.13-51.24) and exclusive parental nutrition for days (OR:1.1; 95%CI:1.03-1.17). **Conclusions:** Knowledge about newborns fungal infections associated factors can help to optimize these patients' management, as well as contributing to reduce the high rates of fungal infections in this group of patients.

Keywords: Newborns. Fungal infections. *Candida* spp. Associated factors. Clinical-epidemiological profile.

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INTRODUCTION

Invasive Fungal Infections (IFI) are among the main causes of morbidity and mortality in newborns.[1-3] Facing that, understanding the risk factors and the disease pathogenesis is the key to prevent invasive candidiasis.[2] IFI are multifactorial, highlighting an increase in newborns (NB) who survive premature births and chemotherapy for cancer treatment.[4] Other factors reported in the literature are the prolonged length of stay in hospitals, mainly in the Neonatal Intensive Care Unit (NICU), low birth weight, use of broad-spectrum antibiotic therapy and invasive therapeutic devices.[5,6]

Most IFI are due to *Candida* or *Aspergillus* species but other species of fungi have been identified.[1,7] Reported neonatal mortality attributable to neonatal invasive candidiasis in low- and middle-income countries varies from 20% to 50%, being significantly higher compared to high-income countries.[3,7] Epidemiological data on infections caused by *Candida* species are still scarce, especially in Latin America, and little attention has been given to candidiasis in low-birth-weight newborns with abdominal commitment.[8] Appropriate identification and treatment are required to enhance antifungal drugs activity and reduce its toxicity.[1,9,10] Successful management of neonatal candidiasis includes appropriate antifungal chemotherapy and supportive care, as well as preventive measures to reduce the risk of systemic candidiasis.[11]

It is critical that each neonatal intensive care unit examine its invasive fungal infection rates and promotes evidence-based prevention, including antifungal prophylaxis, in high-risk patients.[3,12] This way, the aim of this research was to analyze the frequency of fungal infections and to identify the probable associated factors, describing the clinical and epidemiological characteristics of newborns admitted to the Neonatal Intensive Care Unit (NICU) in a public Hospital of Itaperuna city, Rio de Janeiro, Brazil.

MATERIALS AND METHODS

This is an observational, descriptive, and analytical study, with data collected from the medical records of hospitalized newborns. The research was carried out at a Public Hospital, located in the central region of Itaperuna city, state of Rio de Janeiro, Brazil.

Data from 738 (seven hundred and thirty-eight) medical records, in Hospital, from December 2018 to March 2022, were analyzed and positive blood culture for *Candida* spp. results were collected, as well as data from newborns with potential associated factors for fungal infections. These records were available with prior hospital authorization. The

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newborns were identified by the medical record number, sex, age and initials of their names or by a symbol.

Despite of total number of medical records, only 78 were eligible due to the fact that the others had incomplete medical records data.

Explanatory variables: newborn sex, birth weight, length of hospitalization, umbilical catheterization, antibiotic, parenteral nutrition and mechanical ventilation usage, blood transfusion, congenital malformation, number of consultations, gestational age, type of birth.

Response variable: presence of *Candida* spp. infection (Yes versus No).

This research was approved by the Human Research Ethics Committee of the Santa Casa de Belo Horizonte Hospital, under CAAE: 96368618.2.0000.5138.

STATISTICAL ANALYSIS

Initially, an exploratory analysis was carried out using the Shapiro-Wilk test to determine data normality with continuous distribution. Considering the data non-parametric nature, median measurements, interquartile ranges (P25 and P75), and minimum and maximum values were obtained. For categorical variables, frequency measurements (n) and percentage (%) referring to each category were calculated.

In order to identify the role of variables as associated factors neonatal fungal infection, Multivariate Logistic Regression was performed using the presence of *Candida* spp.´ infection as the response variable. Comparative analyzes were carried out considering the odds ratio (OR), 95% confidence interval (95% CI) and p value, obtained during the bivariate logistic regression analysis. To compose the multivariate model, all variables present in the database were crossed with the response variable and items that presented a p value ≤ 0.3 were included in the initial multivariate logistic model (full model). Variables with more than two categories were transformed into dummy variables. Variables that presented collinearity or low frequency (<80%) were excluded from the multivariate analysis. Subsequently, the Backward method was used, starting from the complete model with successive discarding of the variables that, adjusted in relation to the others, did not present a significance level of p<0.05. The variables that presented a level of statistical significance (p<0.05) and significant OR, according to the 95% CI, remained in the final multivariate logistic model. To define the final models, the likelihood ratio test was used, according to Hosmer & Lemeshow (1989).[13]

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In all analyzes performed, the differences obtained were considered statistically significant when the *p* value was less than 0.05 ($p<0.05$). Statistical analyzes were performed using the Stata® program (version 14.0, Stata Corporation, College Station, TX, USA).

RESULTS

The present study consisted of 78 newborns patients. Among them, males were the most prevalent (51.28%). In relation to the number of consultations, the majority of pregnant women received prenatal care incompletely (74.36%), with the third trimester of pregnancy (62.82%). Also, cesarean section (71.79%) and the Normal Apgar score (97.44%) were the most prevalent among newborns. The majority of the patients had low birth weight (55.13%), followed by patients characterized as extremely low birth weight (37.18%). Newborns with normal weight (from 2,500 to 3,999 kg) were the minority in the present study (7.69%) (Table 1).

Table 1. Descriptive analysis of clinical data, considering the general study population (n=78)

General study population (*n*=78)		*n*	%
Sex (n=78)			
	Masculine	40	51.28
	Feminine	38	48.72
Number of consultations (n=78)			
	7 or more (complete prenatal care)	20	25.64
	Up to 6 (incomplete prenatal care)	58	74.36
Gestational Age (categories) (n=78)			
	2nd Trimester (from 15 to 28 weeks)	29	37.18
	3rd Trimester (from 29 to 42 weeks)	49	62.82
Gestational Age (weeks) (n=78)			
	Median (P25-75)	29 (27 - 31)	
	Min - Max	22 - 39	
Type of birth (n=78)			
	Vaginal	22	28.21
	Cesarean section	56	71.79
Apgar score (n=78)			
	Normal (from 7 to 10 in the 5th minute)	76	97.44
	Moderately abnormal or low (< 6 in the 5th minute)	2	2.56
Birth weight (categories) (n=78)			
	Normal (de 2,500 a 3,999 kg)	6	7.69
	Low weight (1,000 a 2,499 kg)	43	55.13
	Extremely low (< 0,999 kg)	29	37.18
Birth weight (g) (n=78)			
	Median (P25-75)	1,082.50 (860 – 1,275)	
	Min - Max	320 – 3,700	
Total length of stay (days) (n=78)			
	Median (P25-75)	56.5 (40 - 88)	
	Min - Max	2 - 665	
Total length of stay (categories) (n=78)			

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		n	%
	Up to 15 days	11	14.10
	From 15 days to 3 months	48	61.54
	> 3 months	19	24.36
Peripherally inserted central puncture (n=78)			
	No	18	23.08
	Yes	60	76.92
Umbilical Catheterization (n=78)			
	No	9	11.54
	Yes	69	88.46
Umbilical Catheterization (days) (n=78)			
	Median (P25-75)	5 (3 - 8)	
	Min - Max	0 - 15	
Antibiotic use (n=78)			
	No	3	3.85
	Yes	75	96.15
Antibiotic use (number of regimens) (n=78)			
	Median (P25-75)	3 (2 - 4)	
	Min - Max	0 - 5	
Antifungal prophylaxis (n=78)			
	No	9	11.54
	Yes	69	88.46
Invasive mechanical ventilation (n=78)			
	No	8	10.26
	Yes	70	89.74
Non-invasive mechanical ventilation (n=78)			
	No	18	23.08
	Yes	60	76.92
Use of H3 blockers (n=78)			
	No	78	100.00
	Yes	0	0.00
Blood transfusion (n=78)			
	No	25	32.05
	Yes	53	67.95
Associated congenital malformation (n=78)			
	No	69	88.46
	Yes	9	11.54
Total parenteral nutrition (n=78)			
	No	10	12.82
	Yes	68	87.18
Total parenteral nutrition (days) (n=78)			
	Median (P25-75)	8 (3 - 16)	
	Min - Max	0 - 46	
Clinical outcome (n=78)			
	Hospital discharge	60	76.92
	Death	18	23.08

n: absolute frequency; %: percentage; P25: interquartile range 25; P75: interquartile range 75.
Min: minimum value; Max: maximum value.

The median total length of hospitalization was 56.5 days (P25 = 40 and P75 = 88 days), with a minimum length of 2 (two) and a maximum of 665 days. Among the categories used in this study, it was observed that the total length of hospitalization was from 15 days to 3 months represented most of the sample analyzed (61.54%). The majority of the newborns underwent peripherally inserted central puncture (76.92%) and the umbilical

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catheterization procedure (88.46%), the latter with a median time of 5 days (minimum of 0 and maximum of 15 days).

Antibiotics usage was reported in 96.15% of the cases, with the median number of therapeutic regimens used was 3 (three) (minimum of 0 and maximum of 5 regimens). The use of H3 blockers was not reported in any sample in the present study. The majority of the patients underwent antifungal prophylaxis (88.46%), invasive (89.74%) and non-invasive (76.92%) mechanical ventilation and blood transfusion (67.95%).

Associated congenital malformation was observed in only nine patients (11.54%). Regarding exclusively parenteral nutrition, 87.18% of newborns had this procedure, with a median time of 8 days (minimum of 0 and maximum of 46 days). Considering the clinical outcome of these patients, 23.08% of the newborns died (18/78) (Table 1).

The Table 2 presents the comparative analysis of the clinical variables, considering the presence or absence of *Candida* spp.´ infection. Among the 78 newborns evaluated, 23.08% (18/78) were positive for this fungus species. Significant differences (in individual associations) were observed in the following variables: gestational age (weeks), birth weight (g), hospitalization time (days), number of antibiotic regimens used, total parenteral nutrition time, blood transfusion and associated congenital malformation (p <0.05).

Table 2. Comparative analysis of clinical data, considering infection by *Candida* spp.

	***Candida* spp.**							
	No (n=60)		**Yes (n=18)**		**Odds Ratio**	**CI 95%**		***p* valor**
	n	**%**	***n***	**%**				
Sex (n=78)								
Masculine	30	50,00	10	55.56	1.0	---	---	---
Feminine	30	50,00	8	44.44	0.8	0.28	2.31	0.679
Number of consultations (n=78)								
7 or more (complete prenatal care)	13	21.67	7	38.89	1.0	---	---	---
Up to 6 (incomplete prenatal care)	47	78.33	11	61.11	0.4	0.14	1.34	**0.148**[a]
Gestational Age (weeks) (n=78)								
Median (P25-75) Min - Max	29 (27 - 30,5) 22 - 38		29 (28 - 38) 24 – 39		1.2	1.02	1.35	**0.029**[*a]
Type of birth (n=78)								
Vaginal	20	33.33	2	11.11	0.3	0.05	1.20	**0.083**[a]
Cesarean section	40	66.67	16	88.89	1.0	---	---	---
Birth weight (g) (n=78)								
Median (P25-75) Min - Max	1,075 (845 – 1,230) 320 – 2,855		1,407.50 (880 – 2,800) 595 – 3,700		1.0	1.00	1.00	**0.004**[*a]

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Total length of stay (days) (n=78)								
Median (P25-75)	58.5 (46.5 - 90)		28.5 (7 - 81)		1.0	0.96	1.00	**0.017**[*a]
Min - Max	4 - 665		2 – 127					
Umbilical Catheterization (days) (n=78)								
Median (P25-75)	5 (3 - 7)		5.5 (3 - 9)		1.0	0.85	1.19	0.942
Min - Max	0 - 15		0 – 10					
Peripherally inserted central puncture (n=78)								
No	16	26.67	2	11.11	1.0	---	---	---
Yes	44	73.33	16	88.89	2.9	0.60	14.09	**0.185**[a]
Antibiotic use (number of regimens) (n=78)								
Median (P25-75)	2.5 (2 - 4)		4 (4 - 4)		2.4	1.32	4.52	**0.004**[*a]
Min - Max	0 - 5		2 – 5					
Total parenteral nutrition (days) (n=78)								
Median (P25-75)	7 (3 - 11)		17.5 (6 - 27)		1.1	1.02	1.14	**0.008**[*a]
Min - Max	0 - 38		0 – 46					
Invasive mechanical ventilation (n=78)								
No	7	11.67	1	5.56	1.0	---	---	---
Yes	53	88.33	17	94.44	2.2	0.26	19.57	0.464
Non-invasive mechanical ventilation (n=78)								
No	14	23.33	4	22.22	1.0	---	---	---
Yes	46	76.67	14	77.78	1.1	0.30	3.76	0.922
Blood transfusion (n=78)								
No	23	38.33	2	11.11	1.0	---	---	---
Yes	37	61.67	16	88.89	5.0	1.05	23.65	**0.044**[*a]
Associated congenital malformation (n=78)								
No	58	96.67	11	61.11	1.0	---	---	---
Yes	2	3.33	7	38.89	18.5	3.38	100.87	**0.001**[*a]

[n] absolute frequency; [%] percentage; [P25] percentile 25; [P75] percentile 75.
[Min] minimum value; [Max] maximum value; [CI 95%] 95% confidence interval. [*] Significant difference (*p*<0.05).
[a] Variables with p value less than or equal to 0.3 (*p*≤0.3), selected for the full multivariate logistic regression model.

According to the results obtained for this sample, each gestational week slightly increased the chances of newborns having a fungal infection caused by *Candida* spp. (OR: 1.2; 95%CI: 1.02 – 1.35; p=0.029). Patients with longer hospitalization also had a higher chance of infection. According to this results, each day of hospitalization increased the chance of newborns contracting *Candida* spp. (95%CI: 0.96 – 1.00; p=0.017). Regarding antibiotics usage, each regimen used increased 2.4 times the chances of fungal infection (95% CI: 1.32 – 4.52; p=0.004). The more days of Total Parenteral Nutrition (TPN), higher the newborns chances of infection: each day of TPN increased 1.1 times the chances of patients becoming infected by *Candida* spp. (95%CI:1.02 – 1.14; p=0.008). Babies undergoing blood transfusion were 5 times more likely to have neonatal fungal infection compared to patients who were not transfused (95% CI: 1.05 – 23.65; p=0.044). Newborns with associated congenital malformations also had an 18.5-fold increased chance of infection compared to patients without this condition (95%CI: 3.38 – 100.87; p=0.001) (Table 2).

Regarding hospitalizations period, the data obtained revealed that in most cases the onset of fungal infection occurred between the first and 10th day of hospitalization, and between the 11th and 20th day of hospitalization. Regarding treatment, 50% of newborns (9/18) were treated within a period of 11 to 20 days, 44.44% between one and 10 days (8/18), and only one patient received treatment for 41 to 50 days (5.56%). Blood culture was considered positive in 88.89% of cases (16/18).

To compose the full multivariate logistic regression model, variables with a *p* value up to 0.3 were considered, that is, variables that in the bivariate analysis were considered as potential factors associated with *Candida* spp. infection. Considering these criteria, the following variables were pre-selected from the database: number of consultations, gestational age (days), type of delivery, birth weight (g), total hospitalization time (days), umbilical catheterization (days), peripherally inserted central puncture, antibiotics usage (number of regimens), total parenteral nutrition (days), blood transfusion and associated congenital malformation (see Table 2).

After excluding variables with non-significant *p-values* and odds ratios, the results obtained in the final logistic regression model indicated that the variables “type of delivery” and “time of total parenteral nutrition” were associated factors for neonatal *Candida* spp.´ infection. According to the OR values obtained, newborns born by cesarean section were 7.6 times more likely to be infected by *Candida* spp. than babies born via vaginal delivery (95%CI= 1.13 – 51.24; p=0.037). In relation to total parenteral nutrition, longer the number of days that newborns undergo this procedure, higher the chances of fungal infection. In other words, one day of total parenteral nutrition increases 1.1 times the chances of infection (95%CI= 1.03 – 1.17; p=0.003) (Table 3).

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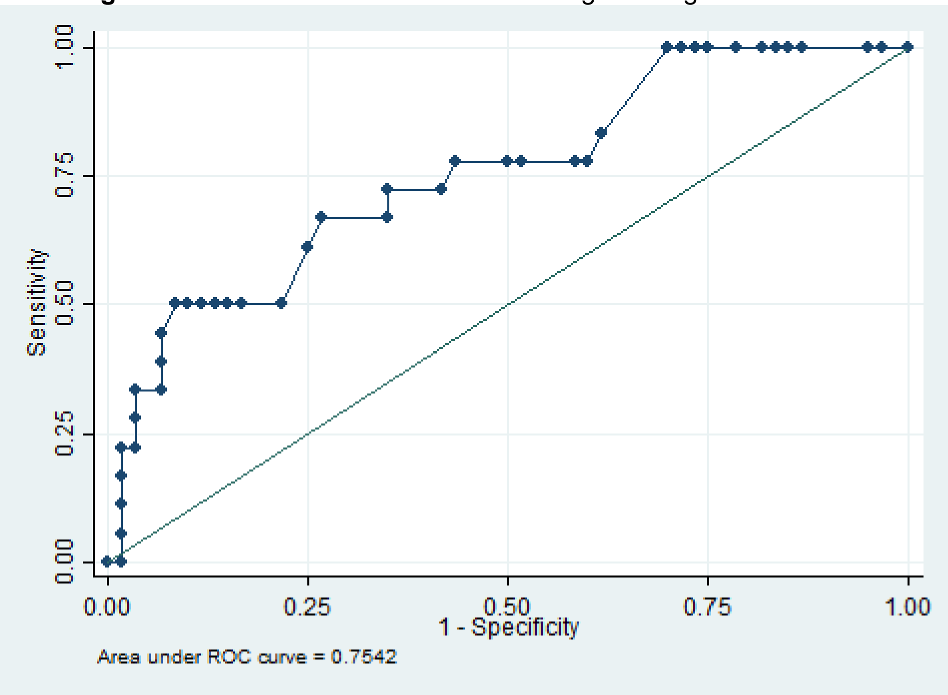
Table 3. Logistic Regression (factors associated with fungal infection by *Candida* spp.) Final Model

Logistic Regression (*Candida* spp.)			
Explanatory variables	**Final Model**[**] **Odds Ratio**	**CI 95%**	***p* value**
Type of cesarean birth	7.6	1.13 – 51.24	**0.037**[*]
Total Parenteral Nutrition (days)	1.1	1.03 – 1.17	**0.003**[*]

[CI 95%] 95% confidence interval. [*]significant values of *p* ($p<0.05$).
[**] Log likelihood = -35.17 / No. of observations = 78 / Pseudo R^2 = 0.17 / *Correctly classified* = 82.05%.

Figure 1 presents the ROC curve of the post-test assessment of the adequacy of the Multivariate Logistic Regression model. According to the ROC curve, 75.42% of neonatal fungal infections caused by *Candida* spp. were explained by this model.

Figure 1. ROC curve of the Multivariate Logistic Regression model.



DISCUSSION

Candidemia is a significant problem in the hospital environment and is associated with high morbidity and mortality rates, prolonged hospitalization and high healthcare costs.[14] The incidence of candidemia is worldwide increasing, requiring best care, frequent monitoring and management.[1,7] It is very common in newborns, especially those caused by *C. albicans*.[6,15,16] The species *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei* in several studies have been considered responsible for most episodes of candidemia.[6,15-17] Although it is important to identify the species responsible for candidemia in newborns admitted in the NICU, in this study were considered all patients infected with

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Candida spp. (a general designation that includes all species of the genus *Candida*), once there is no species identification in the medical records of the NB analyzed.

This result did not make possible to compare the incidence of the *C. albicans* species in our study with that of other studies that report *C. albicans* as the primary cause and most frequent species isolated in samples of different countries such as the United States, Northern Europe, Australia[18], China[17], and Latin America[6,8,18]. Considering the epidemiology in different regions, *C. albicans* is also dominant, in adults and especially in newborns infections, notably in those with a history of NICU admission.[19-23] However, Raja (2021), reported that non-albicans species of *Candida* were predominant in men aged > 65 years, due to long periods of NICU stay and surgical intervention.

According to Riceto et al. (2015), virulence factors depend on host defense mechanisms and virulence factors which characterize the causative microorganism.[24] These factors have been widely investigated in order to explain differences in the pathogenicity of various fungal isolates, including *Candida* spp., as well as to understand the parasite-host relationship. Perhaps for this reason, candidemia is considered quite complex in nature, due to several factors inherent to fungal mechanisms.[25-27]

According to the literature, several factors associated with invasive candidiasis in newborns contribute to high rates of fungal infections, mainly prematurity, very low birth weight, use of vascular catheters, parenteral nutrition, administration of broad-spectrum antibiotics, abdominal surgery, prolonged hospitalization and mechanical ventilation and, among extremely low birth weight (ELBW) newborns (<1000g) the incidence is even higher.[6,28-30] In this study, several associated factors for fungal infections in newborns were evaluated, but only two were actually associated, namely: cesarean section (OR:7.6; 95% CI:1.13-51.24) and total parenteral nutrition (in days) (OR:1.1; 95%CI:1.03-1.17).

In relation to cesarean birth, a possible explanation is that such patients are not exposed to the maternal genitourinary flora at birth, leaving this group more susceptible to infections, not only fungal but also by other pathogens. Total parenteral nutrition (in days) is justified by the fact that such patients need an intravenous access creating a site of infection. Another reason is the fact that children on TPN do not receive a diet via enteral route, which inhibit bacterial gastrointestinal colonization, making these patients more susceptible to opportunistic agents.

All patients with known risk factors for candidemia who received prophylactic fluconazole were considered. The majority of patients had low birth weight (55.13%) and extremely low birth weight (37.18%) and, with normal weight (7.69%) between 2,500 and 3,999kg. The normal Apgar score (97.44%) was prevalent among newborns. The majority underwent invasive (89.74%) and non-invasive (76.92%) mechanical ventilation and blood transfusion (67.95%).

New drugs can change the perspective regarding antifungal treatment, as well as their prophylaxis role, changing empirical and preventive approaches in the future.[31] In addition to prophylactic and preventive strategies, empirical treatment is another established approach mainly in neutropenic, hematological patients with persistent fever refractory to broad-spectrum antibiotics and those after abdominal surgery with suspected complications such as perforations or leaks.[32] However, this approach has not been recommended due to the lack of data showing a survival benefit, except for high-risk patients without previous antifungal prophylaxis.[10]

It is worth mentioning that amphotericin B can cause direct vasoconstriction and reduction in renal blood flow, as well as changes in the tubular cell membrane permeability. And, there may also be an increase in serum creatinine, associated with tubular acidosis, with characteristics of hyperchloremic metabolic acidosis, hyponatremia, hypokalemia and hypomangnesemia. Devarajan and Basu (2017) suggest that over 80% of patients undergoing therapy with amphotericin B, with a decreased renal function, the incidence of Acute Kidney Injury induced by amphotericin B is high, especially if administered in a cumulative dose.[33]

Maertens and colleagues (2023) state that empirical antifungal therapy has been considered the standard treatment for high-risk neutropenic patients with persistent fever. However, it is highlighted that this therapy for patients at risk of IFI during the first weeks of high-risk neutropenia is not yet well established.[34] For Ygberg et al. (2012) empirical antifungal therapy is more indicated for newborns[35] and Kanda et al. (2020) in the same sense, also suggest preventive therapy[36].

On the other hand, studies indicate prophylaxis with fluconazole[6,37,38], micafungin in invasive candidiasis caused by common *Candida* species.[39] But preventive treatment has been more recommended compared to empirical treatment, as it is less specific.[10] In this study, the majority of newborns received antibiotics (96.15%), underwent antifungal prophylaxis (88.46%), with a minimum length of stay of 2 days and a maximum of 665 days. A relatively high number of incomplete prenatal care was identified (74.36%), perhaps this is a contributing factor to hospitalizations and even deaths (18/78) and the majority were

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cesarean deliveries (71.79%). However, this does not mean that all low-birth-weight newborns are necessarily born by cesarean section. However, according to Moreira et al. (2018), cesarean section is one of the factors associated with low birth weight.[40]

Concerning invasive (89.74%) and non-invasive (76.92%) mechanical ventilation and blood transfusion (67.95%), the results proved to be higher than some studies.[6,22,23] The use of H3 blockers was not reported in this study. As for malformation in only 11.54%, parenteral nutrition (87.18%) with a median duration of 8 days and a range from 0 to 46 days.

It was observed that the majority of newborns underwent peripherally inserted central puncture (76.92%) and umbilical catheterization (88.46%), the latter with a median time of 5 days (minimum 0 and maximum 15 days).

Last of all, it is important to remind that the greatest difficulty in studies on invasive fungal infections in low-birth-weight newborns refers to the limitation of obtaining a representative sample of the disease well diagnosed. This is because, throughout this study, it was observed that the number of undiagnosed cases was high, considering that the sensitivity of blood cultures is low, generating false negative results. This perception is aligned with other studies.[28,36]

CONCLUSION

When analyzing fungal infections in 78 records of newborns in the Neonatal Intensive Care Unit in a public Hospital of Itaperuna city, RJ, Brazil, it was observed that most had fungal infections and the majority had low birth weight, followed by those with extremely low birth weight and the minority with normal weight.

In the final model, presenting statistical significance, fungal infections (*Candida* spp.) were associated with cesarean section births and longer Total Parenteral Nutrition (TPN) days.

Although the majority of patients had fungal infections, as expected, it was noticed that in many cases the clinical diagnosis was not confirmed, according to information contained in the analyzed medical records, it can be attributed to the low blood culture sensitivity.

From the study carried out, it is important to establish a clinical protocol to attend this population, guaranteeing regular consultations for pregnant women, and refining the

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information to be entered in the records of newborns, as all information is extremely important. Prevention is still the best choice.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR'S CONTRIBUTION

Ana Paula Frizzo: Conception and design of the study, Acquisition of data. Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted.

Rachel Basques Caligiorne*: Conception and design of the study, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted.

Luciana Araújo Marques: Drafting the article, Final approval of the version to be submitted.

Sônia Maria de Figueiredo: Drafting the article, Final approval of the version to be submitted.

Thais Almeida Marques-Silva: Conception and design of the study, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted.

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