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Fungal colonization in newborn babies of very low birth weight: a cohort study

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Abstract

Objectives: To learn about the profile of fungal colonization and related risk factors in premature newborns.

Methods: Prospective cohort, from April 04, 2010 to April 31, 2011, with 44 patients admitted to the neonatal intensive care unit, born at the hospital maternity, weighing less than 1,500 g. On admission, data were collected on pre-natal care and childbirth. Clinical and laboratory information, nasal and rectal swabs, and peripheral blood cultures were collected on days 1,7,10 and 14 of stay in neonatal intensive care unit and then, every 7 days until discharge or death. For statistical analysis, we used chi-square test, Fisher exact test, Kaplan-Meier and logistic regression model.

Results: The incidence of colonization was 13.5/1,000 patients/day. The incidence of candidemia was 0.9/1,000 patients/day. The average hospitalization time was 30.5 days (±20.27), and the onset of colonization occurred, in average, at 11.13 days (±8.82). Vaginal delivery was found to be an independent risk factor for the development of fungal colonization during hospitalization (p = 0.042, odds ratio = 4.38, 95% confidence interval [95%CI] = 1,13-16,99). Likewise, leukocytosis (> 30,000/mm^3) on admission was an indicator for the simultaneous presence of fungal colonization (p = 0.048). The presence of bronchopulmonary dysplasia tends to be a factor of higher probability for the development of colonization (p = 0.067). The most affected colonization site was the rectal mucosa: 89.09 versus 10.9% of the nasal mucosa.

Conclusion: Vaginal delivery and leukocytosis over 30,000/mm^3 on admission were found to be risk factors for fungal colonization during hospitalization.

J Pediatr (Rio J). 2012;88(3):211-6: Candidiasis, candidemia, prematurity, Neonatal Intensive Care Unit.

Introduction

The increased incidence of opportunistic infections in neonatal intensive care units (NICU) is remarkable.[1] An example is fungal sepsis, defined as the isolation of *Candida* spp. in any sterile body site, which has a major effect on neonatal morbidity and mortality,[2] reaching mortality rates of up to 60%,[3] especially in newborns (NB) of very (< 1,500 g) and extremely (< 1,000 g) low birth weight.[2] The incidence of candidemia is inversely proportional to birth weight and gestational age (GA),[4] ranging from 2.6 to 3.1% in NBs of very low birth weight and from 5.5 to 10% in NBs of extremely low birth weight.[5] The main causative agent of fungal sepsis is *Candida albicans*, though other non *albicans* species increased their incidence in recent years, including *Candida tropicalis*, *Candida parapsilosis*,

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Candida krusei, *Candida glabrata*, *Candida lusitaniae* and *Candida guilliermond.*[6]

The most prevalent risk factors mentioned in literature are related to the conditions of delivery, prematurity and its consequences, the presence of invasive devices and the use of broad-spectrum antibiotics; however, the major and main factor is the previous colonization by *Candida* spp.[5,7-12]

It is known that colonization precedes candidemia in 42% of cases,[7] most frequently in oral and intestinal mucosa. Transmission can occur vertically, during birth, on the passage through the birth canal (mainly *C. albicans*), or horizontally, by the hands of health care professionals (mainly *C. parapsilosis*).[4,10,13]

Prevalence of *C. parapsilosis* in children is higher than in the adults: 40 *versus* 33%, due to the high rate of colonization found on the hands of health care professionals who assist NBs in NICUs.[13,14]

The onset of colonization in the critical NB happens early; 10% of them become colonized in the first week of hospitalization, and in up to four weeks, 64% have already been colonized.[14]

The development of fetal and neonatal medicine in terms of management and monitoring of prematurity rendered possible the birth of ever more immature fetuses. These individuals go through long periods of hospitalization, undergoing invasive procedures, which per se increase the chances and, precisely, the rates of fungal colonization. Thus, once colonization is the major risk factor for the development of sepsis, the aim of this study was to understand the profile of fungal colonization of this population and other risk factors associated with this condition.

Materials and methods

This is a prospective cohort study conducted from April 1st, 2010 to April 31st, 2011, at the NICU of a mid-sized tertiary hospital in the city of Curitiba, which has a total of 10 neonatal beds. The study included all NBs weighing below 1,500 g, born in the maternity and hospitalized in the NICU, whose guardians signed an informed consent form at the time of entry into the NICU, giving permission for the serial collection for scientific purposes. To perform the analysis, we obtained approval from the Ethics Committee Research of the base hospital (no. 152/2010).

Initially, data such as the GA and method employed for its determination, sex, birth weight, Apgar indicator value and method of Parkim for the evaluation of GA (though currently little used, it remains as the chosen method of the hospital where the study was conducted), type of delivery, incidents, need for reanimation and methods used, presence of meconium, corticoids use and prenatal follow-up by the expectant mother.

Throughout hospitalization, nasal and rectal mucosa materials were collected, with the help of sterile swab pre-moistened with sterile saline and with Trypticase Soy Broth, respectively. The blood samples of 0.5-1.0 mL were collected by peripheral venipuncture and inoculated into appropriate flask. In each collection, rules of procedure were respected in order to prevent contamination of the material. All samples were placed in the automated trading system Bact/Alert120® at the microbiology laboratory of the hospital for 14 days. After this period, the Gram coloration was used, which if negative for the presence of bacteria, the material was led to culture on the Agar Sabouraud plate. In the event of colonies growing in this medium, they were again cultured on chromogenic agar medium at 25 °C for identification of the species *C. albicans* and *C. tropicalis*. The white-colored colonies were brought to the automated Vitek System® for identification of other species of *Candida* spp. The test for susceptibility to antifungal agents in positive blood cultures was simultaneously carried out. The absence of microorganism growth after 14 days on Bact/Alert120® system defined the sample as negative.

The materials were collected at D1 (day of birth and admission to the NICU), D7, D10, D14 and, thereafter, every 7 days until discharge or death. In those days the following information was also collected: type of invasive ventilation (IV), use of antibiotics, use of total parenteral nutrition (TPN), length of stay, umbilical arterial (UAC) and venous (UVC) catheterization, central catheter peripherally inserted (CCPI), orogastric tube (OT), presence of oral and/or genital moniliasis, value of C-reactive protein (CRP), leukocyte count above 30,000/mm^3 or below 6,000/mm^3 and platelet count lower than 50,000/mm^3.

We defined: genital/anal moniliasis as macules, papules and/or erythematous pustules, with confluent areas, distributed in perineal region; oral moniliasis as whitish adherent plates with erythematous base when removed, located in the oral mucosa, tongue, gums, palate and cheeks; candidemia as the isolation of *Candida* spp. in any sterile site, such as blood, urine, or central nervous system; colonization as the microbiological growth of *Candida* spp. in material extracted from the nasal or perianal mucosa, however without presenting clinical symptoms that reflect infection; bronchopulmonary dysplasia (BPD) as iatrogenic chronic pulmonary disease, developed by prolonged use of oxygen therapy or mechanical ventilation in preterm NBs and defined as the dependence on oxygen in concentrations above 21% for a period of time longer or equal to 28 days.[15]

For the analysis, all data mentioned above were considered and crossed among each other on the scheduled days for the collection of material. P values < 0.05 indicated statistical significance, and $p < 0.1$, indicated a trend towards significance. The data that presented marginal p values were subjected to multivariate analysis. For these crosses,

the chi-square test, the Fisher exact test and the logistic regression model were considered. All information gathered was analyzed through the Statistica v.8.0 software.

The free time of colonization (in percentage) and the evolution of the number of colonized over the analyzed period were expressed by the Kaplan-Meier method. For statistical purposes, D35 has been established as the last day for analysis, because it is the period with greatest number of hospitalized patients. The results obtained in this study were expressed in frequencies and percentages. Incidence rates were calculated by 1,000 patients/day.

Results

Over the analyzed period, 309 NBs were hospitalized in the NICU, with an occupancy rate of 1,110 patients/day. Of these, 45 met the criteria for inclusion in the study, but one was excluded due to incomplete sampling. There was a variation along the sampling period (D1 = 44; D7 = 38; D10 = 37; D14 = 35; D21 = 32; D28 = 25; D35 = 18) due to hospital discharges or deaths. The mean hospital stay was 30.5±20.27 days. Descriptive statistics of variables in the epidemiological and clinical profile of the sample are presented in Table 1.

The incidence of colonization was 13.5/1,000 patients/day, with onset, on average, after 11±9 days of life. The Kaplan-Meier curve depicting time until first colonization indicates that the estimated percentage of cases without colonization after 1 week was of 81.4%, progressing to 49.3% at the end of follow-up (Figure 1).

In three swab samples, there was growth of other kinds of fungi: *Aspergillus* spp. and *Penicillium* spp., probably due to the environmental contamination.

In univariate analysis, the parameters without statistical significance for the development of colonization at some point during the period studied were: sex, birth weight, GA, rupture of amniotic membrane, length of amniotic membrane rupture, weight, Apgar < 5 at 5th minute,

Table 1 - Clinical and epidemiological profile

Variables/Classification	Frequency	%
Gender		
Female	20	45.5
Gestational age (weeks)		
Less than or equal to 30	39	88.6
Between 31 and 34	5	9.1
Greater or equal to 35	1	2.3
Birth weight (g)		
Below 1,000	16	36.4
Between 1,001 and 1,500	28	63.6
Type of delivery		
Cesarean	29	65.9
Prenatal (number of visits)		
Less than 6 or unregistered	33	75.0
Greater or equal to 6	11	25.0
Prenatal Corticosteroids		
Yes	34	77.3
Amniotic membrane rupture		
Less than 18 hours	7	36.8
Between 18 and 24 hours	1	5.3
Between 25 and 48 hours	1	5.3
Between 49 and 72 hours	2	10.5
Greater than 72 hours	8	42.1
Urinary Tract Infection		
Yes	13	31.7
Vaginal candidiasis		
Yes	2	4.7
Pregnancy-induced hypertension		
Yes	12	27.3

reanimation, meconium, use of corticoids, number of prenatal consultations and parameters relating to pregnancy, such as the presence of urinary tract infection (UTI), pregnancy-induced hypertension, candidiasis, chorioamnionitis and drug use. Likewise, patent ductus arteriosus, necrotizing enterocolitis, hyaline membrane disease, bone disease, retinopathy, sepsis, jaundice, asphyxia, and periventricular hemorrhage, antibiotics use (regardless of number of schemes), TPN, UAC, UVC, CCPI and OT were not associated with colonization (Table 2).

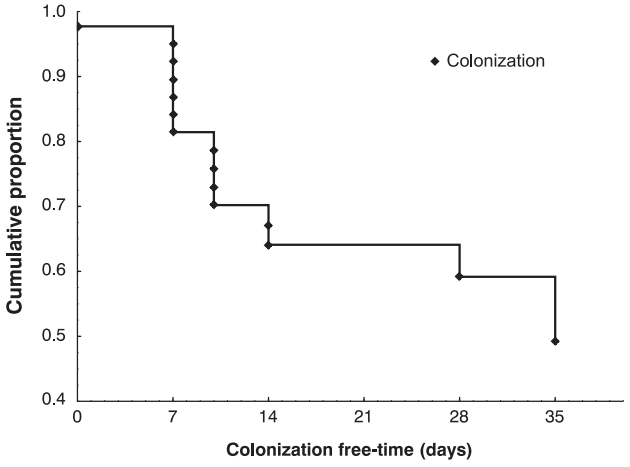

Figure 1 - Description of time until the first occurrence of colonization (Kaplan-Meier Curve)

Leukocytosis on admission (> 30,000/mm^3) was related to the simultaneous presence of colonization (p = 0.048) in some of the analyzed sites. The presence of BPD is associated to colonization. NBs with BPD tend to a greater chance of being colonized (p = 0.067; risco relativo – RR = 2.27). Normal delivery offers more risk of colonization than the cesarean delivery. (p = 0.048; RR = 2.21). The results of the univariate analysis are presented in Table 2.

In the common evaluation of the variables (multivariate analysis), we adjusted a logistic regression model including as explanatory variables the type of delivery and BPD, which showed p < 0.25 in univariate analysis. Leukocytosis was not included in this analysis because no NB with absence of leukocytosis had colonization. The results indicate that, independently, the presence of BPD is significantly associated to colonization (p = 0.046; odds ratio [OR] = 5.44; 95%

Table 2 - Association between colonization and some of the variables assessed in prenatal and postpartum

Variable/Classification	n	Colonization		p* value
		No	Yes	(univariate)
Delivery				
Cesarean	29	22 (75.9%)	7 (24.1%)	
Normal	15	7 (46.7%)	8 (53.3%)	0.092
Gender				
Male	24	16 (66.7%)	8 (33.3%)	
Female	20	13 (65%)	7 (35%)	1
Gestational age (weeks)				
≤ 30	39	26 (66.7%)	13 (33.3%)	
≥ 31	5	3 (60%)	2 (40%)	1
Weight (g)				
< 1,000	16	9 (56.3%)	7 (43.8%)	
> 1,001	28	20 (71.4%)	8 (28.6%)	0.340
Pre-birth corticoids				
No	10	7 (70%)	3 (30%)	
Yes	34	22 (64.7%)	12 (35.3%)	1
Prenatal				
No	7	6 (85.7%)	1 (14.3%)	
Yes	36	22 (61.1%)	14 (38.9%)	0.391
Bronchopulmonary dysplasia				
No	34	25 (73.5%)	9 (26.5%)	
Yes	10	4 (40%)	6 (60%)	0.067
Leukocytosis				
≤ 30,000	39	39 (100%)	0 (0%)	
> 30,000	2	1 (50%)	1 (50%)	0.048

* Fisher exact test or chi-square test, p < 0.05.

confidence interval [95%CI] = 1.03-28.67). Vaginal delivery also presented statistical significance, increasing the probability of colonization at some point. (p = 0.047; OR = 46; 95%CI = 1.02-20.4).

Birth weight showed a significant tendency for the outcome death (p = 0.085). Males had a greater tendency to death compared to females (p = 0.173). In analyzing the number of deaths, the highest numbers were obtained in NBs of mothers without prenatal care, (p = 0.081) and in those who had UTI (p = 0.073) during pregnancy.

The colonization at some point during the hospitalization does not present association with the outcome death. (p = 0.171).

The incidence of fungal sepsis in our sample was of 1/44 NBs (2.2%), amounting to 0.9/1,000 patients/day. This NB had GA lower than 30 weeks, birth weight lower than 1,000 g and previous colonization by *Candida albicans* in rectal and nasal site (same species later found in blood culture). Laboratory tests revealed: high CRP (> 15 mg/dL), leukopenia (< 6,000/mm^3) and thrombocytopenia (< 50,000/mm^3). This NB was the only one to receive empirical therapy with fluconazole and, after the microbiological confirmation of diagnosis, treatment with amphotericin B. Nevertheless, there was progression to death.

Discussion

Regarding the incidence of colonization, in our study, we found a percentage of 15.9% (7/44) until the seventh day of hospitalization and of 31.8% (14/44) until the 28th day, numbers diverging from the 10 and 64% mentioned in the literature for the same periods.[16]

Borges et al. found an incidence of candidemia, with microbiological criteria, of 0.4/1,000 patients/day,[11] however our sample is of 0.9/1,000 patients/day. This demonstrates that despite a relatively small sample, we had almost twice the expected.

Of the 55 samples with *Candida* spp., 49 (89.09%) were originated in the rectal mucosa and six (10.9%) in the nasal mucosa. This proves that the rectal colonization was more frequent in our study than the 74% found in literature.[11]

In both sites, *C. albicans*, considered the most virulent of the *Candida* spp. for its strong association with death,[13] was the most prevalent, followed by: *C. parapsilosis*, considered the less virulent[17]; a combination of more than one type of *Candida* spp.; and *C. glabrata*. No species of *C. lusitaniae* or *C. guilliermondi* was isolated, what is in line with literature, where they are described as virtually absent in the pediatric population.[13]

In our study, mortality was of 27.2%, more relevant in the male sex: 75% (9/12) versus 25% (3/12) for females. Of such deaths, only two (13.33%) presented colonization at some point.

To Pimentel et al.,[16] the incidence of death due to *Candida* spp. is greater in males. In the present study, colonization was proportionally higher in girls, and they are, thus, at increased risk of fungal sepsis, and therefore, have a greater chance of death.

Little is mentioned in literature about the incidence of death due to fungal sepsis among NBs of mothers who had not received adequate prenatal care or who have had UTI during pregnancy. However, these conditions proved to be a significant trend: p = 0.081 and p = 0.073, respectively.

Similarly, the incidence of vaginal candidiasis, ranging from 20-30% of all pregnancies, generally does not produce obstetrical complications.[13] We had only two (4.7%) cases, one of which evolved with positive cultures after the 14th day of hospitalization. Vaginal delivery has proved to be very relevant, compared to cesarean section, concerning the development of colonization. Both facts suggest that many cases of vaginal candidiasis are not being diagnosed and/or treated properly during prenatal care, which would increase the transmission of *Candida* spp. during passage through the birth canal. This is confirmed by Kaufman et al., Hinrichsen et al. and Baley et al. in their studies.[10,14,18]

Leukocytosis on admission was an indicator for the concomitant presence of colonization (p = 0.048), considered the main risk factor for fungemia.[5,7-12] This correlation makes us assume that infants considered potentially infected at birth, be it by premature rupture of membranes, UTI, maternal candidiasis or other factors, present more chances, due to immaturity of the immune system, of being colonized on admission.

Contrary to the literature,[7,8] in the present study, the risk factors for the development of colonization – birth weight, Apgar < 5 at 5th minute, use of antibiotics, GA, TPN, UAC, UVC, CCPI and OT – did not present statistical significance.

The isolation of *Candida* spp. in blood culture translates into greater risk of death at progress when compared to the presence of bacterial growth.[1] We found that among patients with positive fungal blood cultures (16/44), 12.5% (2/16) evolved to death, against 100% of those with positive blood cultures. However, we cannot say that mortality rates are higher in the fungal sepsis than in the bacterial sepsis, due to the limited number of the sample.

For us, although only one patient out of the 44 analyzed has developed candidemia, there was a significant tendency towards the presence of colonization at some point for the evolution to death (p = 0.171). According to the risk factors described above, this only patient with candidemia was exposed to the following: birth weight lower than 1,000 g, GA lower than 30 weeks, previous colonization by *C. albicans* in intestinal and oral sites, CCPI, TPN, IV, thrombocytopenia, leukopenia and use of more than three broad-spectrum antibiotics. The empirical therapy

was initiated with fluconazole based on insidious clinical worsening, associated with worsening of laboratory exams and previous fungal colonization, as suggested by literature.[7,13,19] After positive microbiological results of the material, it was decided to suspend fluconazole and start amphotericin B, but the newborn evolved to death.

The fact that the blood culture has low sensibility and takes longer than 14 days for growth and cultivation causes negative blood cultures not to exclude the diagnosis of candidemia.[19,20] The sum of these factors may have delayed the start of antifungal therapy and changed the prognosis of the newborn.

The incidence of fungal sepsis varies between hospitals and services; in NBs smaller than 1,000 g, it is between 4-15%.[21] This prevalence is influenced both by the complexity of patients and the adoption of prevention measures, the control of risk factors during hospital care, and the experience of the service in question. The establishment of antifungal prophylaxis for NBs under exposure to a large number of risk factors (such as the only NB who had candidemia) should take into consideration these peculiarities, and it should be carefully discussed, especially due to the still controversial bibliographic basis.[1,9,19,21]

Therefore, we should be cautious and careful at indicating this behavior, always assessing risks and benefits, since studies demonstrate that waiting longer than 3 days for the beginning of antifungal therapy increases the mortality rate by 50%.[1,14]

In this context, it is necessary to create protocols, such as the task force of the Italian Society of Fungal Sepsis, to start antifungal prophylaxis in pregnant women and/or NBs with higher chance of developing candidemia.

Although consisting of a small sample, this study becomes another important tool in the assistance provided to preterm infants, once it does not present strong indications for the establishment of routine empirical prophylaxis and therapy, since most colonized NBs evolved well clinically, and deaths were not related to prior colonization in the period analyzed ($p = 0.171$).

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