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ORIGINAL ARTICLE

Fluconazole for prevention of systemic infection in extremely low birth weight infants with Candidal colonization

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Abstract

Objetive: To evaluate the association of candidal colonization and systemic candidiasis in extremely preterm infant (EPTI). Analyse if fluconazole can prevent systemic candidiasis in previously colonized EPTI. **Methods:** Prospective cohort study of EPTI (birth weight less than 1000 grams), in a Brazilian neonatal intensive care unit (NIUC), at University Hospital, between April, 2012 to April, 2014. Oropharyngeal and rectal swab, and tracheal secretions (in intubed) were collecte for fungal culture on 3rd, 10th, 17th, 24th and 30th days of life. EPTI with positive culture for Candida spp. received fluconazole. Was considered systemic candidiasis those who presented: sepsis with positive blood culture, pneumonia with positive tracheal secretion and changed chest X-ray, and urinary tract infection with positive urine culture. **Results:** Fity-six infants were evaluated, median weight of 826 grams (435-980), median gestacional age of 27 weeks (23.1-34.1), 23 (43,1%) infants were colonized with Candida ssp. Among 10 infants with candidiasis, 7 (70%) were colonized with Candida. Five (21,7%) infants received fluconazole an from these, one (20%) developed systemic candidiasis (p = 0,6411). The lethality rate was 33,9% and there was one death between EPTI with systemic candidiasis (p = 0,0761). **Conclusion:** Most infants with systemic candidiasis were previously colonized with Candida. Fluconazole have prevented systemic candidiasis in colonized EPTI.

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INTRODUCTION

Fungal infections are frequently observed in neonatal intensive care units. Currently, with the survival of preterm infants with increasingly lower birth weights and gestational age, the incidence of neonatal fungal infection is increasing; *Candida albicans* is responsible for approximately 75% of fungal infections. As a result, candidemia is now the third most common cause of late-onset sepsis in very low birth weight newborns (VLBWNs; birth weight less than 1,500 g), affecting about 10% of this population, and in up to 15% of extremely low weight newborns (ELBWNs; birth weight less than 1,000 g); a high mortality rate - between 25% and 50% - is associated with these infections[1-3].

The incidence of systemic candidiasis in VLBWNs admitted to 16 units of the Brazilian Neonatal Network was 13% during 2009 - 2010 (range, 0% - 35%). In the present service, which is part of the Network, *Candida* spp. was identified in 11.5% of blood cultures of late-onset sepsis collected during the investigation; these data are similar to the international literature, which shows 10% - 12% of late-onset sepsis caused by *Candida* spp[4].

Fungal infection may be acquired by the fetus during pregnancy, during birth, and in the neonatal period. The newborn (NB) is predisposed to infection due to the characteristic immune immaturity and as a result of exposure to risk factors that facilitate colonization and systemic invasion by various pathogenic microorganisms[1,5,6].

Colonization by *Candida* spp. in newborns occurs mainly by transmission through the birth canal. Using molecular techniques, the vertical transmission of *C. albicans*, *C. parapsilosis*, and *C. glabrata* was documented in term and preterm NBs. Maternal vulvovaginitis by *Candida* spp. is a risk factor for colonization and potential neonatal infection. Intrauterine infections are rare: by ascending infection through the birth canal or transplacental transmission.

In the postnatal period, colonization also occurs when species colonizing the maternal skin come into contact with the skin and oral mucosa of the NB. In cases of mastitis by *Candida ssp.*, there is an increased risk of transmission of this pathogen. Although maternal transmission is the most common way of acquiring this pathogen, infection may also occur during healthcare, which is an important source for the acquisition of different species of *Candida*.

The latter is considered the main form of *C. parapsilosis* transmission, due to high rates of colonization of this species on the hands of healthcare professionals. Perinatal transmission may result in colonization, congenital infection, mucocutaneous candidiasis, and even systemic infection in NBs[7].

Systemic candidiasis may have insidious onset or present quickly with signs and symptoms that may be confused with bacterial sepsis. Clinical findings are varied and include fluctuating body temperature, food intolerance, hypoactivity, abdominal distension, alterations in blood sugar levels (hypoglycemia or hyperglycemia), heart rate instability (tachycardia or bradycardia), worsening respiratory pattern (tachypnea, bradypnea, or apnea), arterial hypotension, jaundice, and hepatosplenomegaly.

The diagnosis of systemic candidiasis requires a high index of suspicion. Some authors consider that if the patient exhibits clinical deterioration in the presence of broad-spectrum antibiotics with no apparent cause, especially in the presence of risk factors, an associated fungal infection should be suspected[7-10].

Prolonged hospitalization and the necessary interventions in these VLBWNs favor colonization and fungal infection. In a multicenter study, Saiman et al.[11] isolated fungi in blood culture and gastrointestinal tract of patients in intensive care units, and demonstrated a relationship between colonization of the gastrointestinal tract and fungemia.

As colonization often precedes infection, several studies have examined strategies to identify colonization in NBs, enabling early prevention of systemic fungal infections in VLBWNs[1].

Due to the severity of systemic candidiasis, with high rates of morbidity and mortality, strategies to reduce the incidence of colonization (and, therefore, of invasive disease) have been sought. Although simple, it is important to emphasize the need for hand hygiene among healthcare professionals, especially considering that the transmission *Candida* spp. through the hands of these professionals has been clearly demonstrated[3,11,12].

This purpose of this study was to perform surveillance cultures in ELBWNs for early detection of *Candida* spp. Colonization and thereby administer prophylactic fluconazole to the colonized. Thus, the incidence of colonization with *Candida* spp. in ELBWN was determined, and the use of prophylactic fluconazole in preventing invasive candidiasis in colonized ELBWN was assessed.

METHODS

This prospective cohort study included all ELBWNs admitted to the neonatal ward of a University Hospital in Paraná, Brazil, between April 2012 and April 2014.

The variables studied were as follows: birth weight, gestational age, sex, use of broad-spectrum antibiotics, mechanical ventilation use, central catheter use, use of parenteral nutrition, colonization by *Candida* spp., presence of mucocutaneous and/or invasive candidiasis, and use of prophylactic and/or therapeutic antifungal medication.

A tracheal aspirate or swab of oropharyngeal secretions (in non-intubated NBs) was collected, and a rectal swab for culturing for *Candida* spp. was collected on the 3rd, 10th, 17th, 24th, and 30th days of life, while the NB used a tracheal tube and/or central venous catheter.

The swabs and homogenized tracheal aspirate were inoculated into tryptic soy broth containing vancomycin 6 µg/ml, ciprofloxacin 8 mg/ml, and colistin 17.2 µg/ml, incubated

for 24 h at 35°C. The broths were subcultured on chromogenic agar for *Candida* spp. screening, and remained in the incubator for 48 h. The yeasts that grew in the cultures were identified at the level of genus and species.

The NB was considered to be colonized by *Candida* spp. in case of any positive culture. If symptoms of infection were present, blood cultures, urine culture (by vesical catheter or suprapubic aspiration), and cerebrospinal fluid (CSF) culture were collected.

The diagnosis of invasive or systemic candidiasis considered the growth of *Candida* spp. in cultures of blood, urine, spinal fluid, or other sterile site. A urine culture was considered positive in the presence of any colony count in urine collected by suprapubic puncture or ≥ 1,000 colonies/ml in urine collected by vesical catheter. CSF was considered to be positive in the presence of pleocytosis, biochemical alterations, or positive *Candida* spp. culture in a CSF collected within 4 days of the diagnosis of invasive candidiasis.

Mucocutaneous candidiasis (oral and dermatitis) were defined as the presence of lesions in the skin and mucous membranes with isolated *Candida* spp. *Candida spp.* pneumonia was considered as invasive candidiasis and defined as respiratory deterioration, need to increase the ventilation parameters, increased tracheal secretions, persistent radiological abnormalities on serial X-rays, positive qualitative culture for *Candida* spp. in tracheal aspirates, and response to specific treatment[8,13].

For colonized and asymptomatic NBs, using a central venous catheter and/or endotracheal tube, fluconazole (3 mg/kg/day) was administered intravenously for 3 weeks or for a shorter duration if the NBs were no longer under central vascular catheter or mechanical ventilation use.

Symptomatic NBs and those with positive blood and/or urine culture for *Candida* spp. were treated with fluconazole, amphotericin B deoxycholate, liposomal amphotericin, or micafungin.

Data were analyzed using Epi Info version 3.4. Categorical variables were analyzed by chi-squared or Fisher's exact test, considering $p < 0.05$ as significant.

This study was approved by the institutional Ethics Committee for Research Involving Human Beings.

RESULTS

This study evaluated 56 ELBWNBs: mean weight of 816 g (435-980), and median of 27 weeks of gestational age (23.1 to 34.1); 55.4% of the NBs were female. Of the 56 NBs included, 23 (41.1%) were colonized by *Candida* spp. and ten (17.9%) had positive swabs and/or tracheal aspirates on the third day of life. *Candida* spp. was isolated in 26.8% of the oropharyngeal secretion swabs, 32.1% of the rectal swabs, and in 14.3% of tracheal secretions; fungal colonization in more than one site were common. The isolated species observed in the colonized NBs are shown in Figure 1; three of them were colonized by more than one species of *Candida*.

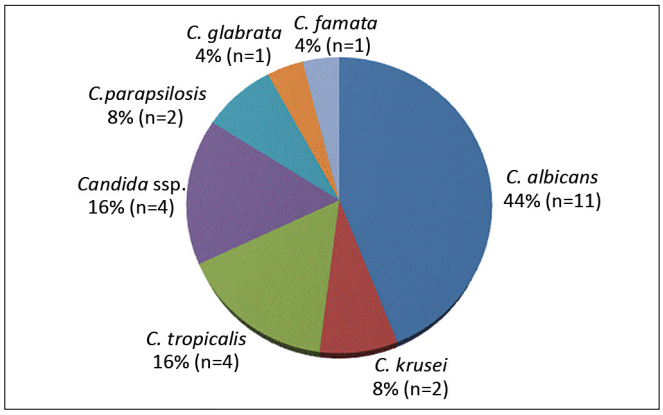

Figure 1. Candida species responsible for the colonization in extremely low birth weight newborns.

Eight (14.3%) were diagnosed with mucocutaneous candidiasis, six (75%) of whom were previously colonized by *Candida* spp. ($p = 0.0435$), and there was an association between mucocutaneous candidiasis and invasive fungal infection ($p = 0.0269$).

Ten (17.8%) ELBWNs presented invasive candidiasis (IC); in six (60%) of these, the interval between the first positive culture colonization and invasive disease was ≤ 7 days. The median age at which children developed IC was 24 days (9-39). All the children with systemic fungal infection were on mechanical ventilation; IC was not associated with mechanical ventilation ($p = 0.6720$). All the children with IC used a central catheter and received parenteral nutrition (PN), but there was no association between the use of PN and IC ($p = 0.8214$), nor between the use of central catheter and IC ($p = 0.6720$).

No association between the use of broad-spectrum antibiotics and IC ($p = 0.1790$) was observed in the present study.

Among the ten ELBWNs with IC, seven (70%) were previously colonized and three (30%) were not colonized by *Candida* spp. ($p = 0.0456$) (Figure 2). The IC were: four cases of (40%) urinary tract infections; three (30%), meningitis; two (20%), sepsis; and one (10%), pneumonia.

The *Candida* spp. responsible for IC are shown in Figure 3. Six NBs (60%) with invasive fungal infection presented the same species of *Candida* in previously performed swabs and/or tracheal aspirates, and in sterile material culture (blood/urine). In one NB, the *Candida* spp. in the previous swab was not identified (*Candida* spp.), and *C. parapsilosis* was isolated in the blood culture. Three NBs with IC had negative prior swab and/or tracheal aspirates.

CSF was collected in eight (80%) patients with IC; among these, five NBs (62.5%) had suspected sepsis and three had altered CSF (cellularity and/or biochemical) with meningitis diagnosis. Among the four ELBWNs with urinary tract infection, two presented altered CSF; it was not collected in one patient. The patient with pneumonia also did not undergo CSF collection.

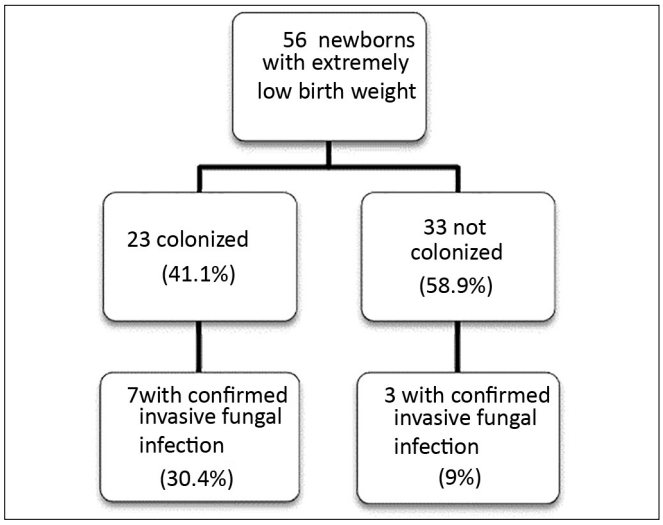

Figure 2. Colonization and infection by Candida spp. in extremely low birth weight newborns.

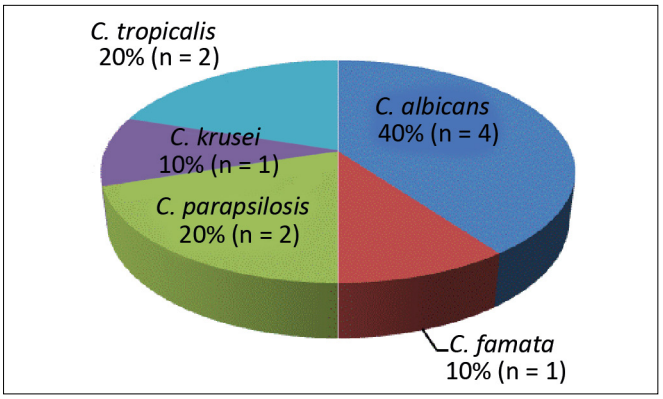

Figure 3. Candida species responsible for invasive infection in extremely low birth weight newborns.

Among the 23 colonized NBs, five (21.7%) received fluconazole prophylaxis; of these, one (20%) developed candidemia ($p = 0.6411$). Among all colonized NBs, 15 (65.2%) received antifungal treatment; among the 33 non-colonized NBs, 23 (69.7%) received antifungal treatment (Figure 4).

Different antifungal medications were prescribed: seven (70%) received fluconazole; five (50%), amphotericin B deoxycholate; five (50%), liposomal amphotericin B; and two (20%), micafungin. Nineteen (33.9%) out of the 56 ELBWNs died; this outcome was observed in one (10%) ELBWN with IC ($p = 0.0761$) and in 11 (47.8%) among the 23 colonized ELBWNs ($p = 0.0612$).

DISCUSSION

The use of antifungal agents such as nystatin, miconazole, and more recently, fluconazole, has been studied in the prophylaxis of invasive fungal infection. Nystatin and miconazole are topical antifungal agents without systemic distribution. The results of studies on this topic are controversial[14-17].

The first randomized clinical trial on prophylaxis with oral nystatin (100,000 U, three times a day) included NBs weighing less than 1,250 g, on mechanical ventilation, with the use of nystatin until up to 1 week after extubation. There was a significant reduction in the incidence of fungal sepsis, but there was no difference in mortality between the treatment and control groups[14].

Another study compared VLBWNs and ELBWNs who received prophylactic oral nystatin or miconazole. Those who received nystatin showed significantly less invasive candidiasis when compared with the control group. In turn, those who received miconazole had a lower rectal colonization rate, but this did not influence the incidence of neonatal candidiasis[16].

Since 2001, the number of reports in the literature on the beneficial use of fluconazole prophylaxis to prevent colonization and infection by *Candida* spp. in VLBWNs has been increasing. Fluconazole is characterized by its excellent concentration in tissue and fluids; it has a long half-life and acts on the main species of *Candida*[18-22].The safety and efficacy of prophylaxis with fluconazole has been reported in four randomized controlled studies[18-20].

Violaris et al. compared the safety and efficacy of oral prophylaxis with nystatin and fluconazole in VLBWNs and found a higher mortality in the group using nystatin; nonetheless, the authors did not mention aspects related to colonization and surveillance cultures[23]. Aydemir et al. found no difference in the incidences of colonization, fungal infection, and mortality in a study of VLBWNs that compared the use of prophylactic nystatin with prophylactic fluconazole[24].

Kaufman et al. conducted a double-blinded prospective randomized study with prophylactic fluconazole or placebo for the first 6 weeks of life in patients with birth weight < 1,000 g to assess the prevention of colonization and invasive disease by *Candida* spp. During the period of prophylactic fluconazole use, fungal colonization was documented in 60% of the placebo group and in 22% of the group receiving prophylactic fluconazole ($p = 0.002$)[22].

Invasive fungal infection, in which the fungi was isolated in blood, urine, or CSF, was observed in 10 of 50 patients (20%) of the placebo group and in none of the 50 patients of the group treated with fluconazole ($p = 0.008$). Eight of the ten patients (80%) who developed sepsis showed colonization by the same species of *Candida,* similar to the present study, in which 85.7% of patients had the same kind of *Candida* in swab and/or tracheal secretion and sterile liquid. Kaufman et al. observed no side effects with fluconazole; no development of resistance was observed in the study period[22].

Despite evidence of reduced incidence of colonization and neonatal fungal infection in newborns at high risk of invasive candidiasis, many authors still do not recommend universal implementation of prophylaxis with fluconazole for ELBWNs.

The major concern of the experts is the risk of inducing medium and long-term resistance to azoles for the species *C. albicans* and *C. parapsilosis*, which are the most prevalent

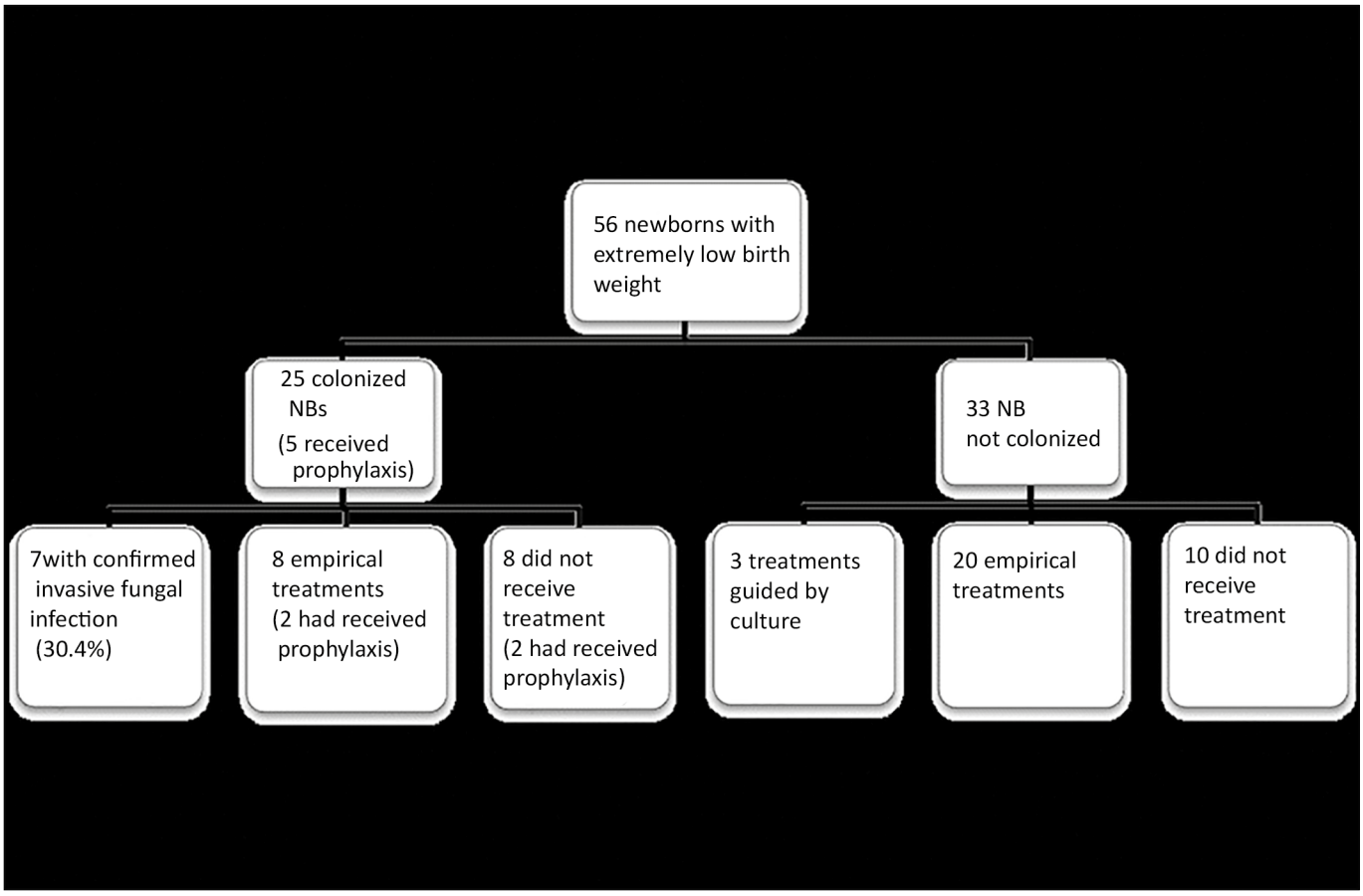

Figure 4. Antifungal treatment of extremely low birth weight newborns.

in the neonatal period. Another factor to be studied is the phenomenon *of replacement*, with the exchange of prevalence of classical strains for non-*albicans Candida* species such as *C. krusei* and *C. glabrata* that are more resistant to antifungal agents[25].

Based on literature review, the general recommendation is to not routinely start prophylactic fluconazole in the neonatal ICU for all ELBWNs. Since 2009, the *Infectious Diseases Society of America has* recommended that prophylactic antifungals in ELBWNs should be used in services with a high incidence of IC (between 5% and 10%), after all other non-pharmacological preventive measures have already been fully implemented[26].

A strategy to avoid administering antifungal prophylaxis in all ELBWNs is to assess those at higher risk for invasive fungal disease by conducting surveillance cultures of *Candida* spp. In a retrospective study of 51 ELBWNs, 16 of the colonized NBs developed fungal infection between 24 and 72 h after detection of the colonization: 12 cases of candidemia, two cases of mucocutaneous candidiasis, and two cases of *Candida* pneumonia. Among the 35 non-colonized NBs, none had invasive candidiasis or received fluconazole[27].

In the present study, although most ELBWNs with cutaneous candidiasis (75%) and with IC (70%) were previously colonized by *Candida* spp., it was not possible to previously isolate the *Candida* species in 30% of those with systemic infection, which can be explained by a lower inoculum of *Candida* spp. in these patients.

A study conducted in São Paulo, Brazil, with weekly surveillance culture medium for fungi of the gastrointestinal and respiratory tract of ELBWNs, demonstrated a 72% reduction in the incidence of neonatal invasive candidiasis when compared with the pre-intervention period. The incidence of colonization of the studied newborns was 27%, which avoided the unnecessary use of fluconazole in many non-colonized ELBWN. Fluconazole was well tolerated and was not associated with adverse effects. There was no change in the species *Candida* that colonized or infected the NBs[25].

As in the present study, *C. albicans* is the most frequently isolated species; however, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, *C. famata*, *C. glabrata*, *C. guilliermondii*, *C. lusitaniae,* and other species of *Candida* have also been described as causing infections. In the past 10 years, an exponential increase of *C. parapsilosis* and *C. glabrata* has been observed[5,6,28,29].

The main risk factors for systemic candidiasis are associated with extreme prematurity, ELBW, and the use of broad-spectrum antimicrobials. *Candida* spp. are found

on the normal flora of the gastrointestinal tract, skin, and genitourinary tract; however, their growth may be favored with the suppression of bacterial microflora after antibiotic use. Another risk factor is the use of central venous catheters, which provides a gateway by breaking the previously intact skin barrier; venous catheters also function as a site for *Candida* spp. biofilm formation.

The use of parenteral nutrition and lipid solutions are risk factors for invasive candidemia possibly favoring the growth and multiplication of the fungus. The use of endotracheal intubation with mechanical ventilation is also associated with invasive fungal infections. Likewise, abdominal surgical procedures and necrotizing enterocolitis can facilitate the invasion of the intestinal mucosa by fungi, as well as secondary infection. Other drug therapies, such as the use of H_2 blockers and systemic corticosteroids, are associated with fungal infections[1,3,7,8,30].

In the present study, there was no correlation between the presence of PN, central venous catheters, and mechanical ventilation with IC, which can be explained by the small number of IC cases. The use of broad-spectrum antibiotic was high in both groups of patients (colonized and non-colonized); once again, no association with IC was observed.

Remington et al. observed cutaneous candidiasis in 28% of preterm NBs and the association of cutaneous candidiasis with IC in 32% of preterm NBs; only 2.1% did not present invasive disease[3]. A previous study indicated that the most common ICs in the neonatal period are bloodstream infections (70%), urinary tract infections (15%), and central nervous system infections (10%)[8]. Mucocutaneous candidiasis, urinary tract infection, and meningitis were also the most frequent *Candida* spp. infections in the present study. Sepsis was less frequent, as in these patients CSF alterations were a common finding, which explains the importance of CSF collection in patients with sepsis.

The small number of patients who received fluconazole prophylaxis was one of the limitations of the present study. This occurred due to a delay in receiving the reports of surveillance cultures in ELBWNs, a fact that hindered the early initiation of prophylaxis before the infants were symptomatic.

Regarding the only ELBWN with IC who received prior fluconazole prophylaxis, there was a delay of 7 days between the first positive swabs and the start of prophylaxis. Therefore, the delay of this approach may prevent prophylaxis in a timely manner in many neonatal units at risk.

CONCLUSION

In the present study, the incidence of ELBWNs colonized by *Candida* spp. was high. Most NBs with IC were previously colonized by *Candida* spp.; *C. albicans* was the species most associated with colonization and infection. Therefore, the establishment of preventive measures is necessary to reduce colonization by *Candida* in ELBWNs. The prophylactic use of fluconazole in colonized ELBWNs may minimize the number of cases of IC and consequently reduce the lethality of this agent in this population.

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