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Chapter 8

Fungal Infections in Neonatal Intensive Care

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Abstract

Neonates represent a unique and highly vulnerable patient population. Advances in medical technology have improved the survival and quality of life of newborns, particularly those with extreme prematurity or with congenital defects. Furthermore, immunologic immaturity and altered cutaneous barriers play some role in the vulnerability of neonates to nosocomial infections. In this context, the incidence of invasive fungal infections has increased significantly worldwide, representing an important infective complication in patients hospitalized in intensive care units. Invasive fungal infections in Neonatal Intensive Care Unit (NICUs) show high mortality; being species of *Candida,* the most isolates etiologic agents. The better prognosis of the patient is associated with the early diagnosis and fast treatment. However, guidelines to facilitate the optimal therapy choice for the treatment of neonatal fungal disease do not exist. The current antifungal agents that are available to treat fungemia among newborns and children are based on clinical trials in adults, since there are few comparative studies of antifungal agents in infants. The most commonly used drugs for the treatment of invasive fungal infections in neonates are classified in four different classes: polyene, azoles, analogs of pyrimidines and echinocandins.

Keywords: antifungal therapy, fungal infections, intensive care, neonates, sepsis

1. Introduction

During the last two decades, invasive fungal infections in preterm infants have become an increasing problem, mainly when hospitalized in a Neonatal Intensive Care Unit (NICU). Thus, for the last years, 6.3 million children under the age of 5 died each year are estimated,

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and more than 40% of these deaths occur in the neonatal period [1, 2]. These data have several causes and particularly the neonates are at high risk due to fungal infections, mainly by yeasts of the genus *Candida* [3, 4].

In addition, species of the genus *Candida* have the capacity to inhabit several niches, thus, as part of the skin, mucosa and gastrointestinal tract [5]. Therefore, is considered that there is an association between colonization and systemic candidiasis mainly in seriously ill patients [6].

Although *Candida albicans* are more frequent, species of *Candida* non-*albicans* are also cause of diverse clinical pictures important in neonates, especially those that are in NICUs. The main Candida non-albicans species included are *Candida parapsilosis* complex, *Candida glabrata* and *Candida krusei*. However, uncommon species as *Pichia fabianii* and *Kodamaea ohmeri* may occur [7–10].

The newborns clinical course in the Intensive Care Units usually complicates after the onset of fungal infections [11]. In this hospital environment, adverse events may occur due to the complexity of the patients [12]. In this sense, the treatments and procedures instituted for primary disease may be an important factor for the onset of fungal infections; birth weight between 1000 and 1500 g is also a predictive factor and a way for the clinical worsening [13].

The predisposing factors to fungal infections include prolonged use of antibacterial and use of medical devices, among other conditions that lead to fungal disease. In addition, biofilms are frequent on the surface of medical devices, being consider a negative event, since it characterizes greater pathogenicity and antifungal resistance of fungi.

Commonly, amphotericin B, azoles and echinocandins are used for the treatment of various invasive fungal infections. However, antifungal therapeutic failures contribute to a higher mortality rate and may occur due to intrinsic resistance, so it is important to perform antifungal sensitivity tests. These tests can predict the ideal antifungal or contribute in the choice according to the use of other medicines and the condition of the neonate [9].

2. Epidemiology and incidence of neonatal invasive fungal infections

Neonates represent a unique and highly vulnerable patient population. Advances in medical technology have improved the survival and quality of life of newborns, particularly those with extreme prematurity or with congenital defects. Immunologic immaturity and altered cutaneous barriers play some role in increasing the vulnerability of neonates to infections. In this context, neonatal infection is a major cause of mortality and morbidity in newborns. Estimates suggest that >1.4 million neonatal deaths worldwide annually are due to invasive infections [14, 15].

The occurrence of invasive fungal infections has increased significantly worldwide, representing an important infective complication in patients hospitalized in intensive care units. Premature infants in NICUs are at particular risk of these invasive fungal infections, and unfortunately, the incidence of fungal septicemia appears to be increasing [16, 17]. In this

context, *Candida* and *Malassezia* species are the most prevalent pathogen involved in fungal infections in NICU [18].

The incidence of bloodstream infections due to *Candida* species in the overall population ranges from 1.7 to 10 episodes per 100,000 inhabitants. An estimated 33–55% of all episodes of candidemia occur in intensive care units and are associated with mortality rates ranging from 5 to 71% [16].

Invasive candidiasis is an important cause of sepsis in the NICU. Candida infections in infants are associated with significant mortality and morbidity, including neurodevelopmental impairment. The incidence of invasive candidiasis in NICU ranges from 2.6 to 13.2% in very low birth weight infants (1500–1000 g) and from 6.6 to 26.0% in extremely low birth weight infants (<1000 g) [19].

C. albicans has been the most frequently isolated species; however, infections caused by others species have been diagnosed with increased frequency. In the NICU in the 1990s, the overall incidence of candidemia increased because of the increased survival and intensive care of extremely preterm infants. During that time period, the proportion of candidemia decreased because of *C. albicans*, whereas increased because of *C. parapsilosis* [20, 21].

Invasive infections associated with *C. parapsilosis* cause fewer acute lethal events in premature newborns than systemic infections with *C. albicans*; nevertheless, *C. parapsilosis* fungemia significantly increases the morbidity and mortality of severely ill infants who require care in a NICU [22].

Laboratory studies have documented that *C. parapsilosis* is less virulent than *C. albicans*. However, the capability to adhere tenaciously to prosthetic materials forming biofilm and to proliferate rapidly in high concentrations of glucose are factors that facilitate the infection in the hospital environment. This trait may contribute to its ability to adhere to plastic catheters and cause systemic infections in premature newborns receiving total parenteral nutrition, blood pressure transducers or other invasive devices. Such a route of transmission may account for the occurrence of epidemic outbreaks of *C. parapsilosis* bloodstream infections [21].

Other emerging *Candida* species such as *C. haemuloniii*, *C. pelliculosa* and *C. tropicalis* have also been associated with infections in NICU. *C. pelliculosa* and *C. haemuloniii* caused clonal infection in NICU [11]. An outbreak of *C. tropicalis* fungemia in a NICU was traced to receipt of total parenteral nutrition and antimicrobial agents [23].

Malassezia species in immunocompromised patients may be associated with several skin conditions and systemic diseases, including folliculitis, seborrhoeic dermatitis, catheter-related fungemia and sepsis. However, this yeast may also cause invasive infections in critically ill low birth weight infants. *Malassezia* fungemia is predominantly caused by *Malassezia furfur* and *Malassezia pachydermatis*. *M. furfur* has been described predominantly in conjunction with nosocomial outbreaks in NICU, particularly in neonates and infants receiving intravenous lipids solution. Additionally, *M. pachydermatis* has been associated with bloodstream infection in preterm with very low birth weight and the prolonged use of indwelling catheters and parenteral lipid formulations [18, 24].

3. Neonatal *Candida* infections

Candida species are correlated to invasive fungal infections among at-risk groups as neonatal patients admitted NICU in and have been ranked third to seventh as a cause of nosocomial bloodstream infection, defined as candidemia, depending on geographical patterns [25–28]. Studies on invasive candidiasis infections and candidemia are frequently focused on specific diagnoses and/or specific populations. In all published studies, ICU was the most frequent localization of the patients, even with different frequencies [29].

Candidemia is associated with high rates of illness and death and has an attributable mortality rate that varies widely in the literature, ranging from 29 to 76%, both in adult and pediatric patients [30, 31]. Furthermore, *Candida* species are common gastrointestinal flora that causes a wide range of severe manifestations when disseminated into the bloodstream. Thus, candidemia has been described as the most common manifestation of invasive candidiasis [32].

These yeasts are less frequent than those infections caused by Gram-positive or Gram-negative bacteria; nonetheless, they are higher rates of morbidity and mortality. Particularly, among newborn with extremely low weight, 10% may to develop candidemia that has until 30% mortality in this patient group. Among infants who survive these infections, several long-term neurological impairments such as cerebral palsy, blindness, hearing and cognitive deficits and periventricular leukomalacia may occur [9, 27].

Neonatal candidemia during the first week of life is less common and less well described than the later onset of this group of infections. According to Barton et al. [33], risk factors for candidemia among neonates had not been studied before their research, in early onset disease (EOD, ≤7 days) or compared to late onset disease (LOD, >7 days). After a 2-year study, the authors concluded that risk factors such as birthweight <750 g, gestation <25 weeks, chorioamnionitis and vaginal delivery were strongly associated with EOD. Infection with *Candida albicans*, disseminated disease, pneumonia and cardiovascular disease were significantly more common in EOD than in LOD. Also, neurodevelopmental impairment and mortality were also higher than controls.

Extremely low birth weight is considered a risk factor related to a poor prognosis in EOD. Also, the role of perinatal transmission is supported by its association with chorioamnionitis, vaginal delivery and pneumonia. Dissemination and cardiovascular involvement are common, and affected infants often die. Empiric treatment should be considered in these risk situations [33, 34].

Pereira et al. [34] developed a retrospective observational study to investigate the risks for sepsis in neonates, including *Candida* infections, and verified an association between healthcare-associated sepsis, antibiotic therapy in day 1, the duration of parenteral nutrition and the use of central vascular catheter. For each extra week on gestational age, the risks declined in 20%, and for each day of parenteral nutrition, the risk increased 22%.

Kung et al. [35] affirm that infants in NICU have a higher incidence of *Candida* infections than any other pediatric or adult population. The predisposing factors were evaluated in Taiwan

using a retrospective matched case-control study conducted in the NICUs of a teaching hospital from July 2003 to June 2006. A total of 164 infants with culture-proven bloodstream infections were identified and the common etiologic pathogens included coagulase-negative staphylococci (28.7%), *Staphylococcus aureus* (16.5%), *Klebsiella pneumoniae* (14.6%) and *Candida* species accounting for 11 (6.7%) episodes. According to these authors, parenteral nutrition was a significant and independent risk of late-onset neonatal sepsis, including those caused by *Candida* species. This risk should be considered when implementing early parenteral nutrition in NICUs.

The collected potential risk factors consisted of: (1) prenatal and maternal history such as toxemia, multiple gestation, intra-uterine growth retardation and perinatal infections; (2) perinatal history such as premature rupture of membrane greater than 18 hours and delay in initial crying; (3) invasive procedures such as instrument insertion and its duration (e.g., placement of nasogastric tubes, endotracheal tubes, mechanical ventilation, peripherally inserted central catheters, chest tubes, blood transfusion or exchanged blood transfusion and lumbar puncture); (4) the concomitant use of medications such as parenteral nutrition and intravenous lipid, antibiotics and steroids and (5) comorbidities such as meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), inborn error of metabolism and cardiac anomalies (except for patent ductus arteriosus and secundum type of atrial septal defect). However, transfusion, antimicrobial treatment, use of steroids and the presence of other comorbidities were not associated with *Candida* infections in neonates [35].

Invasive neonatal candidiasis presented an overall mortality rate of 35% during a study in Los Angeles (USA) in a neonatal intensive care unit. In general, every infant used a central venous catheter (CVC), required mechanical ventilation and previous administration of antibacterial agents. According to the authors, delayed institution of antifungal therapy was associated with increased mortality as well as length of hospitalization and the duration of prior antibacterial therapy [36].

Frequently, *C. albicans* is the most fungal clinical isolate; however, the incidence of bloodstream infections caused by *Candida* non-*albicans*, mainly *C. parapsilosis* complex and *C. glabrata*, has increased over the past 15 years. The current high rate of *Candida parapsilosis* infections may be attributed the capacity of this isolate to form biofilms and contaminate solutions, as those used in parenteral nutrition [8].

In recent Italian study, *C. albicans* was the most frequently identified strain, but nearly 20% of infections were due to *Candida* non-*albicans*, mainly *C. krusei* and *C. glabrata* [10]. Since both these strains can be resistant to fluconazole, that is the antifungal drug with the best urinary penetration [37], treatment of these patients could be challenging, despite a recent report that showed effective concentrations of micafungin in the urinary tract [38]. In these search, fungemia was the second most frequent diagnosis and was more frequent in children with malignancy/hematopoietic stem cell transplantation, those undergoing abdominal surgery and in low birth weight neonates, also in this case, confirming other recent pediatric data such as Ota et al. [39] and Steinbach et al. [40].

Invasive fungal infections in NICUs show high mortality. The better prognosis of the patient with invasive candidiasis/or candidemia admitted in NICU is associated with the early diagnosis and fast treatment. Evidence suggests an estimated mortality rate of 40% if therapy is not initiated early. Therefore, it is not a good practice to wait for cultures to become positive. This need for early therapy must be balanced against the need to use antifungal agents to avoid selection of resistant strains. Early empiric therapy guided by stratification systems for high-risk patients should help address these cases [41].

The score for exact risk measurement of invasive candidiasis has yet to be developed. The "Candida Score" presented by Spanish group in 2006 provides an easy-to-use tool to assist the health professionals with critically ill adults [42]. However, we believe that will should be adapted to pediatric patients, in the near future. In this stratification, the selected variables by logistic regression model with increasing weight are total parenteral nutrition, surgery, multifocal *Candida* species colonization and severe sepsis [42].

Recent Infectious Disease Society American guidelines suggest that "empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever." Risk factors for invasive candidiasis are well identified. When analyzing clinical data, surveillance culture and levels of anti-*Candida* antibodies plus β-D-glucan in the serum, the same Spanish researchers showed a positive correlation among increasing values of the "*Candida* score" and the rate of invasive *Candida* infections. Such a score was calculated by variables such as total parenteral nutrition, surgery, multifocal *Candida* colonization and severe sepsis. Thus, *Candida* score ≥3 suggest patients at high risk for invasive candidiasis and enable to differentiate patients who would benefit from early antifungal treatment from those for whom invasive candidiasis is highly improbable [43].

4. Other neonatal fungal infections

Despite *C. albicans* is known to be primarily responsible for most neonatal fungal diseases, the prevalence of infections caused by other fungi in neonates and young infants is not significant, except for *Malassezia* species, which may occur in epidemic outbreaks [44–46].

Since 1980, this genus has been recognized in sepsis and systemic infections involving neonates receiving lipidic parenteral nutrition using a central venous catheter. It is believed that lipid supplementation facilitates the colonization of the catheter that used to infuse the nutrients. In newborns, colonization by *Malassezia* can progress to fungemia. The removal of the infected catheter is sufficient to limit infection in most cases [46, 47].

The vast majority of cases of fungemia occur in children less than 12 months old. In this population, this *Malassezia* infection rarely remains asymptomatic. Interstitial pneumonia and thrombocytopenia are common clinical manifestations in this group of patients, and the most frequent symptoms in systemic infections are fever and respiratory dysfunction with or without apnea [46, 48].

Other less common symptoms include lethargy, malnutrition, bradycardia and hepatosplenomegaly. However, no signs of erythema, swelling or purulence appear at the catheter entry site. Signs of skin rash are also not evident in children with systemic infections. Interstitial bronchopneumonia can be found in 40% of children [44–46].

The diagnosis of fungal infection by *Malassezia* is made by isolating the microorganism from blood collected through the catheter or by culturing the catheter tip after its removal. In suspected sepsis by *Malassezia*, the tip of the catheter should be cultured in broth enriched with lipids [45, 46].

The standard therapeutic management for systemic infections by *Malassezia* is still not well defined, since the fungemia by this microorganism is relatively unusual. However, some authors recommend the use of amphotericin B to treat these infections [45, 46, 49]. Morrison and Weisdorf [50] found that all patients enrolled in their study were cured without the administration of systemic antifungal therapy.

Studies have indicated that the most important factor for therapeutic success against systemic infection is the removal of the infected catheter and the interruption of lipid infusion, with or without antifungals [18, 45, 46].

5. Treatment of neonatal fungal infections

The appropriate use of antifungals agents is of particular importance in the prevention and treatment of invasive fungal infection in neonates; however, guidelines to facilitate the optimal therapy choice do not exist. The current therapeutic options that are available to treat fungemia among newborns and children are based on clinical trials in adults, since there are few comparative studies of antifungal agents in infants. The optimal treatment of fungal infection in this special population requires detailed studies on pharmacokinetics, safety and efficacy of antifungal therapies [51–54].

Similar to neonatal invasive infections by species of *Candida*, the management of *Malassezia* sp. fungemia requires the removal of any catheter as soon as the first positive blood culture occurs and the temporary discontinuation of parenteral nutrition in combination with an intravenous antifungal therapy. The most commonly used agents for the treatment of invasive fungal infections in NICU are classified into four different classes: polyene, azoles, analogs of pyrimidines and echinocandins. Among many years, the drugs of choice in this group of patients were amphotericin B alone or in combination with fluocitosin, liposomal formulation of amphotericin B or fluconazole. However, the development of a new generation of azoles and echinocandins, such as micafungin, has increased the therapeutic options for the treatment [45, 54].

Amphotericin B deoxycholate and lipid preparations are traditional choices for invasive fungal infections being active against a majority of clinical important *Candida* species and with reported use for *Malassezia* [45, 55]. Amphotericin B deoxycholate is well tolerated

by neonates who do not exhibit many of the toxicities seen in older children and adults. However, liposomal amphotericin B has been found to be safe and efficacious in newborns with renal impairment. Another polyene agent, nystatin suspension, is administered orally to infants with gestational age ≤ 27 weeks or birth weight less than 750 g until removal of central venous catheters; this is shown to reduce colonization of the gastrointestinal tract and the rate of invasive candidiasis [55].

Among the azoles, fluconazole is more frequently used in NICUs for the treatment of oropharyngeal and systemic candidiasis, but has no inherent activity against the genus *Aspergillus*, which is rare pathogen in neonates. This antifungal agent is commonly recommended as prophylactic therapy in NICU with a high incidence in fungal infections. Fluconazole prophylaxis is effective in reducing the rate of colonization and progression to systemic infection in nursery; on the other hand, some studies have revealed that prophylactic or empiric therapy with antifungal agents may be associated with changes in *Candida* ecology and antifungal agent susceptibility. Actually, the fluconazole dose recommended for neonates is 6 mg/kg/day, and maintenance doses currently used in NICUs in Europe is often higher, between 6 and 12 mg/kg [53, 56–58].

New azoles such as voriconazole, posaconazole and ravuconazole have limited utility in the nursery and are rarely used to treat neonatal infections. Voriconazole is a second-generation triazole that has excellent activity against *Candida* and *Aspergillus* spp.; however, data on its use in neonates are limited. Posaconazole and ravuconazole are the newest agents of the triazole family with added action against zygomycetes, however there are scarces of survey involving these antifungal agents in infants and the use of ravuconazole is not already approved by the Food and Drug Administration (FDA) [59, 60].

The echinocandins (micafungin, caspofungin and anidulafungin) are increasingly used for treatment of *Candida* sp. infections. Their role in the nursery is not so clear, although accruing evidence suggests they may be safe and effective, especially for the treatment of invasive infections caused by *Candida* spp. Some point have to be taken under consideration before the use of echinocandins in NICUs: first, limited clinical data also suggest that these agents may be effective for the treatment of central nervous system infections. Second, a high incidence of *C. parapsilosis* in NICUs is usually reported and this species is related to higher minimum inhibitory concentration (MIC) front of echinocandins [56, 57].

Among the three representatives of the group, micafungin is the most recommended and its use is approved for adults, children and newborns, being considered the one with better description for neonatal population. The use of caspofungin is approved by the FDA, but only for adults and children over 3 months of age. There were no relevant clinical trials that support the administration of anidulafungin among neonates and children [56, 57].

Invasive fungal infections are devastating pathologies that still result in death or serious long-term morbidity in neonates; however, the management of this mycosis has progressed greatly, with the azole agents playing a significant role. Effective prophylactic strategies have recently become available; therefore, the choice and use of appropriate antifungal drugs need careful assessment of neonatal characteristics, the epidemiology and drug pharmacokinetics [53].

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