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# INTEGRATIVE REVIEW ARTICLE

# FUNGAL INFECTIONS IN PRETERM INFANTS BY YEASTS OF THE GENUS MALASSEZIA

INFECÇÕES FÚNGICAS EM PREMATUROS POR LEVEDURAS DO GÊNERO MALASSEZIA INFECCIONES POR HONGOS EN LOS RECIÉN NACIDOS PREMATUROS POR LEVADURAS DEL GÉNERO MALASSEZIA

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#### **ABSTRACT**

Objective: to analyze in newborn infants hospitalized in Neonatal Intensive Care Units for fungal infections caused by yeasts of the genus Malassezia. Method: this is a bibliographical study, descriptive of integrative review, developed in six stages, with search of articles between December 2017 and January 2018, LILACS, BDENF, Science Direct, Medline and Portal of Journals CAPES. The results were interpreted and synthesized the knowledge critically and descriptive. Results: we included 12 studies published in English (84.61%), Spanish (7.69%) and French (7.69%). Conclusion: it was considered that the Malassezia spp. may be responsible for the colonization and infection, skin and blood, in hospitalized premature neonates, highlighting the species M. fufur and M. pachydermatis. It is recommended the need for further studies.

Descriptors: Malassezia; Microbiota; Fungemia, Neonatal Intensive Care Units; Premature Infant; Parenteral Nutrition.

#### RESUMO

Objetivo: analisar em recém-nascidos prematuros internados em Unidades de Terapia Intensiva Neonatal por infecções fúngicas causadas por leveduras do gênero Malassezia. Método: trata-se de estudo bibliográfico, descritivo, tipo revisão integrativa, desenvolvido em seis etapas, com busca de artigos entre dezembro de 2017 e janeiro de 2018, nas bases de dados LILACS, BDENF, Science Direct, Medline e no Portal de Periódicos CAPES. Interpretaram-se os resultados e se sintetizou o conhecimento de forma crítica e descritiva. Resultados: incluíram-se 12 estudos publicados em inglês (84,61%), espanhol (7,69%) e francês (7,69%). Conclusão: considerou-se que o Malassezia spp. pode ser responsável pela colonização e infecção, cutânea e sanguínea, em neonatos prematuros hospitalizados, destacando-se as espécies M. fufur e M. pachydermatis. Recomenda-se a necessidade de mais estudos. Descritores: Malassezia; Microbiota Fungemia; Unidades de Terapia Intensiva Neonatal; Recém-Nascido Prematuro; Nutrição Parenteral.

#### **RESUMEN**

Objetivo: analizar en neonatos hospitalizados en Unidades de Cuidados Intensivos Neonatales infecciones fúngicas causadas por levaduras del género Malassezia. Método: este es un estudio bibliográfico, descriptivo, examen integrador, desarrollado en seis etapas, con búsqueda de artículos entre diciembre de 2017 y enero de 2018 BDENF, Lilacs, Medline, Science Direct, Portal de Periódicos y CAPES. Los resultados son interpretados y sintetizan el conocimiento crítico y descriptivo. Resultados: se incluyeron 12 estudios publicados en inglés (84,61%), español (7,69%) y francés (7,69%). Conclusión: se consideró que la Malassezia spp. puede ser responsable de la colonización e infección, la piel y la sangre, en neonatos prematuros hospitalizados, destacando las especies M. fufur y M. pachydermatis. Se recomienda la necesidad de más estudios. Descriptores: Malassezia; Microbiota; Fungemia; Unidades de Cuidado Intensivo Neonatal; Recien Nacido Prematuro; Nutrición Parenteral.

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#### **INTRODUCTION**

It explains that the species of the genus Malassezia are lipophilic yeasts present in the normal microbiota of the skin and mucosa of a variety of homeothermic animals. 1-2 This genus includes 18 species that can colonize or infect humans and animals. 1,3 These yeasts belong to Malasseziomycetes, class subphylum Ustilaginomycotina, phylum Basidiomycota, the species are anthropophilic M. furfur, M. sympodialis, M. globosa, M. obtusa, M. restricta, M. slooffiae, M. dermatis, M. japonica, M. arunalokei. Since the species zoophilic, reported in the literature are M. yamatoensis, M. pachydermatis, M. equina, M nana, M. capre, M. cuniculi, M. brasiliensis, M. psittaci and M. vespertilionis. It notes that M. Pachydermatis is monotypic not lipiddependent.3-4

It knows that Malassezia species are associated with pityriasis versicolor, dermatitis, folliculitis, atopic seborrheic dermatitis and psoriasis. 1,2,5 Furthermore, it has been hypothesized a connection between these yeasts and carcinogenesis of the skin, particularly in the case of Carcinoma. However, it is unknown whether, in large part, its pathophysiology. It is known that, in healthy skin, the Malassezia yeast extract essential nutrients for its growth without causing disease. When this process is adapt, changed, they modifying expression of enzymes involved in acquisition of energy and synthesize a series of bioactive.<sup>5</sup> It is noteworthy that skin disorders may be exacerbated by interactions between Malassezia sp. and the immune system of the host.1

Facilitate the establishment of infections by invasive procedures and the use of broad spectrum antibiotics.<sup>5</sup> Patients with total parenteral nutrition, immunocompromised patients, in the long period of hospitalization, in particular, in intensive care units, and premature babies with very low birth weight (<1500 g) have a higher risk of developing infections caused by *Malassezia*, where the dissemination and the prognosis is influenced by the immune status of the host.<sup>5-6</sup>

It is the transmission of *Malassezia* for baby vertically or horizontally, where the degree of prematurity, the condition of the skin, the endotracheal intubation, the central vascular access, diseases such as necrotizing enterocolitis or intestinal perforation and focal abdominal surgery can contribute heavily to the colonization. This process is reinforced by the pathogen virulence factors

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such as the adhesion and the formation of biofilms on central venous catheters.<sup>5</sup>

#### **OBJECTIVE**

• To analyze in newborn infants hospitalized in Neonatal Intensive Care Units fungal infections caused by yeasts of the genus Malassezia.

### **METHOD**

It is a bibliographical study, descriptive, integrative review.<sup>8,9,10</sup> Type for both considered the steps: (1) identification of the theme and selection of research question; (2) establishment of the inclusion/exclusion criteria; (3) definition of the information to be collected, categorization and evaluation of selected studies (4) and (5) of the included; (6) interpretation of the results and synthesis of knowledge.<sup>11</sup>

This study was guided by the following question: What is the panorama, reported by world scientific literature about fungal infections caused by *Malassezia* spp. in newborn infants hospitalized in Neonatal Intensive Care Units?

The articles were sought between the months of December 2017 and January 2018. Consult the databases MEDLINE (Medical Literature Analysis and Retrievel System Online), Lilacs (Latin American and Caribbean Literature in Health Sciences), ScieceDirect, BEDENF (Bibliographic Database Specialized in the area of Nursing) and the Portal of Journals CAPES.

We used a combination of Descriptors in Health Sciences (DeCS), in English, the Premature Infant, Neonatal Intensive Care Units, and Parenteral Nutrition, Catheters, malassezia and the keyword neonates, separated by the Boolean operator AND. Settled, as inclusion criteria, scientific articles available in the databases mentioned above, in its entirety, which submit familiarity and relevance with the object of study and the guiding question. There was no temporal clipping. It excluded preliminary notes, editorials, letters to the editor, reflective studies, experience reports and duplicate publications. 12

It rescued 304 articles. After reading titles and abstracts, we selected 13. After the complete reading, with the intent to confirm their inclusion, the remaining 12 studies. These publications were forwarded to the insightful analytics of their references in an attempt to identify other studies that have not been redeemed from the search strategy above and adding to the inclusion of a publication, as the image 1.

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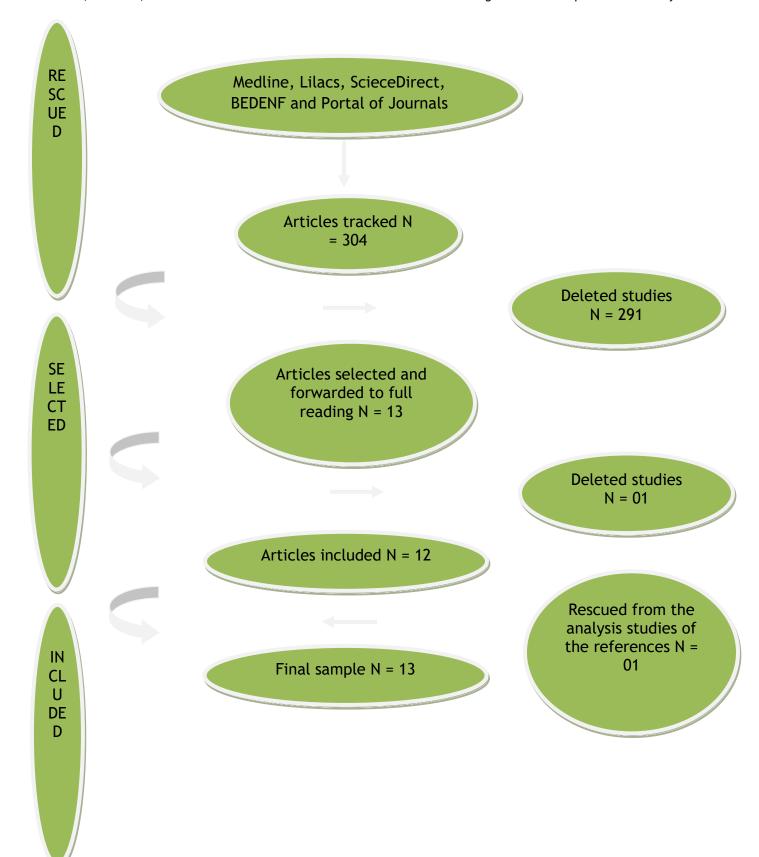


Figure 1. Flowchart for search, selection of the surveys. Maceió (AL), Brazil, 2018.

Information of the studies selected and included in this review got from Microsoft Word®, which included title, year of publication, country of origin of the studies, objective and main results.

The results were interpreted and synthesized the knowledge critically and descriptive. The studies included were classified in levels of evidence, namely: level 1 - meta-analysis of multiple controlled studies; level 2 - individual study with experimental design; level 3 - study with quasi-experimental design as study without randomization with single group pre and posttest, temporal series or case-control; level 4 -

non-experimental survey as descriptive correlational and qualitative research or case studies; level 5 - report of cases or data obtained in a systematic manner, of verifiable quality or program evaluation data; level 6 - opinion of reputable authorities based on clinical competence or opinion of the expert committees including interpretations of information not based research.<sup>11</sup>

#### **RESULTS**

We included 13 studies published in English (84.61%), Spanish (7.69%) and French (7.69%), in international journals, between the years of 2001 and 2017, being one article per year

in 2001, 2002, 2008, 2009, 2011, 2012, 2015, 2016 and 2017 and four studies in the year 2014. The characterization of the studies is

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shown in Figure 2 and includes title, journal, year, objective and methodological design and level of evidence.

Title	Journal/Year	Objective	Delineation	Level of evidence
Malassezia pachydermatis fungaemia in a neonatal intensive care unit	Acta Pediatric, 2001	Investigating eight cases of colonization and infection by M. pachydermatis in a neonatal intensive care unit for six months.	Prospective study	IV
Skin colonization by Malassezia in neonates and infants	Infection Control & Hospital Epidemiology, 2002	Identify the time, the pattern and determinants of neonatal colonization by Malassezia.	Prospective observational study	IV
Molecular analysis of Malassezia species isolated from hospitalized neonates	Pediatric Dermatology, 2008	Determine the distribution of Malassezia spp. in newborns hospitalized.	Prospective observational study	IV
Colonización por levaduras en piel sana de recien nacidos	Kasmer, 2009	Determine colonization by species of yeast on the skin of newborns in order to establish prevalence in the early hours of your life.	Analytical study, transversal	IV
Malassezia furfur fungaemia in a neonatal patient detected by lysis-centrifugation blood culture method: first case reported in Italy	Mycoses, 2011	Documenting the first case of Italy of fungemia by Malassezia furfur in a newborn.	Case report	V
Transmission of the major skin microbiota, Malassezia, from mother to neonate	Pediatrics International, 2012	Investigate the possible cutaneous transmission of Malassezia from a mother to her newborn.	Prospective observational study	IV
Fungal prophylaxis in neonates: a review article	Advances in Neonatal Care, 2014	Review the scientific literature	Revisão da literatura	V
Skin Colonization by Malassezia spp. in hospitalized neonates and infants in a tertiary care centre in North India	Mycopathology, 2014	Determine the rate of colonization of Malassezia species and associated factors in newborns and hospitalized infants	Cohort study	IV
Bloodstream infections by Malassezia and Candida species in critical care patients	Medical Mycology, 2014	Report the results of research of Malassezia spp. and Candida spp. in a neonatal intensive care unit (NICU) and in a Pediatric Surgical ward of a hospital in southern Italy	Prospective observational study	IV
Malassezia pachydermatis fungemia in a preterm neonate resistant to fluconazole and flucytosine	Medical Mycology Case Reports, 2014	Describe a case of fungemia caused by M. pachydermatis in a preterm newborn.	Case report	V
Malassezia - Can it be ignored?	Indian Journal of Dermatology, 2015	Review the scientific literature	Literature review	V
Colonisation à levures chez les prématurés de moins de 1500g hospitalisés em réanimation néonatale	Archives de Pédiatrie, 2016	Describe the profile and characteristics of fungal colonization on premature infants admitted to Neonatal Intensive Care Unit	Prospective cohort study	IV
Molecular epidemiology of a Malassezia pachydermatis neonatal unit outbreak	Medical Mycology, 2017	Describe the epidemiology of the outbreak of M. pachydermatis in a Neonatal Intensive Care Unit (NICU).	Prospective epidemiological study	IV

Figure 2. Characterization of the studies included as title, journal, year, purpose, outline of studies and level of evidence. Maceió, AL, Brazil, 2018.

There were characterized, concerning delineation, the productions as prospective studies, literature reviews and case reports. In relation to the goal, we realize that the researches are devoted to investigating, report and describe the epidemiology of colonization and infection of neonates in Neonatal Intensive Care Units (NICU) by species of *Malassezia*.

#### **DISCUSSION**

#### Incidence

Increases the importance of yeasts of the genus Malassezia from its recognition as important opportunistic pathogens. In relation to newborns, fungal infections are a serious risk to the immune system, especially those who were born prematurely, as observed in a study where 100% of hospitalized infants in a NICU were colonized by species of Malassezia and 75% of these had positive blood cultures for M. pachydermatis, zoophilic species and unique among those of the genus non lipiddependent, but which is becoming increasingly common in the microbiota of humans. 13

Become increasingly present reports that the genus Malassezia is the etiologic agent of Fungaemia. Two studies reported blood infection caused by M. furfur, 14-5 being that, in one of the studies, there were six episodes of fungemia, caused by this species, among the ten recorded in the NICU.<sup>15</sup> Furthermore, the colonization by Malassezia sp. in neonates hospitalized in intensive care units is not uncommon and can be a precursor to clinical infection, coming to represent 46% of the total of fungal colonizations, 16 being the M. furfur the most applicant of the genus. 17-8 The period in which the colonized patients remained receiving parenteral nutrition and antibiotic therapy was the longest of those who were not colonized.16

It is understood that the average time in which the colonization occurs in any anatomic site is 14 days, being rare in the first 10 days of birth. 17,19 All reports pointed out the relationship of colonization and infection with parenteral nutrition and the catheterization with lipid infusion due to the high content of dextrose and lipids, which provides its habitat of favorable growth. *M. pachydermatis* was isolated in 89% of the 61 infants with central venous catheter and in 86% from 57 children who were receiving parenteral nutrition. 20

It should be stressed that, although the primary concern is fungus *Candida albicans*, *Malassezia*, *Aspergilos and Zygomycetes* are considered less prevalent and should receive greater importance when the signs and

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symptoms of sepsis could arise in the newborn.<sup>4</sup>

#### Risk factors and transmission

Reported, among the premature neonates, each time more species of *Malassezia* as agents of fungemia related to central venous catheter, in those who received intravenous lipid emulsions, <sup>16</sup> who demonstrated that increase the likelihood of colonization by presenting the habitat of favorable growth of fungi. <sup>16</sup>

The newborns are put at increased risk of infection due to many conditions, treatments and procedures. The presence of central intravenous catheters, endotracheal tubes, exposure to more than two antibiotics and drugs, prolonged total parenteral intravenous fat emulsions, nutrition, surgeries, long hospital stay and early gestational age at which the child was born also influenced to a greater incidence of colonization and possible infection. 4,18

It adds that there are many ways of transmission to the yeast that can represent a significant problem in many neonatal intensive care units, among which the professionals themselves who assist the patient as well as other patients and mothers of these patients. In relation to maternal transmission, a study showed that the genotype that colonized the skin of the neonate resembled with which colonized the mother's skin noting also that, with time, the rates of colonization of neonates were similar to the mothers, with prevalence of *M. restricta*. <sup>21</sup>

Remember that there is evidence that suggest that the strains of *M. pachydermatis* may introduce themselves in the NICU through the hands of the professionals from the health team owners of dogs. <sup>17</sup> *M. pachydermatis* should be treated with caution, because it can persist on surfaces of the incubator for up to three months, in spite of the standard disinfection. <sup>4</sup>

It shows, by means of studies that, among the risk factors that increase the probability of mortality related to invasive fungal infection, there is the thrombocytopenia, the presence of central venous catheter, the prolonged total parenteral nutrition and intravenous fat emulsions, the presence of the endotracheal tube, the treatment with broad spectrum antibiotics, the use corticosteroids and third-generation cephalosporin or carbapenem in the last seven days. To meet more than two of these factors, it must start the treatment, as well as empirical antimicrobial agents.4

It can influence the excessive growth of *Malassezia* by geographical factors, in which a higher density of different species of *Malassezia* on skin is common in tropical and humid heat and in subtropical climates. In addition, there is the influence of hormonal factors and pathogenesis, when there are changes in the sebum secretion.<sup>4</sup>

# Disease, diagnosis and treatment

Stresses that M. furfur, M. sympodialis, M. globosa, M. obtusa, M. restricta, M. slooffiae, dermatis, М. umbrosum and yamatoensis constitute part of the microbiota of the skin and mucous membranes may, in some circumstances, act as pathogens, causing disturbances of the skin of the neonate, as cephalic pustulosis, pityriasis versicolor, seborrheic dermatitis in infants, causing the called Seborrheic Dermatitis (DSI), as well as it may be associated with infections related to the use of central venous catheter. 4,17,21-2

Warns that these yeasts colonize the seborrheic parts of the skin and they nourish using the fatty acids present in the normal sebum of the skin, lipid source for its growth, being the scalp, face and headscarf; the locations most colonized.<sup>4,17</sup>

It is evident that the fungal infections follow a staggered pattern of pathogenesis in First, the micro-organism humans. transmitted to the newborn, occurring the colonization, which can appear in various locations, including intravenous catheters and areas of degradation of the skin. Once the fungus has a region of the body that is suitable for its growth; occurs the infection of the blood or body fluid and, finally, it is disseminated throughout the body different organs, leading to failure of these.4

Warns that, although these fungi are recognized many years ago, its demanding nature and its culture and techniques of speciation restricted the research, which still needs to be improved for better results. Molecular techniques such as Polymerase Chain Reaction (PCR) and the genotyping were used to identify the studies analyzed.<sup>21</sup> The use of a location supplemented with lipids can optimize the growth of *Malassezia* in clinical specimens. A method of lysis centrifugation is used to increase the yield of blood cultures when suspected fungal infections.<sup>14</sup>

It is clarified that, in the population of preterm babies, amphotericin B was the antifungal that had the greatest success as prophylaxis and treatment, followed by fluconazole. The highest index of fungal resistance was before the administration of

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flucytosine; however, a case of fungemia by *M. pachydermatis* showed reduced susceptibility to fluconazole. 13,23

# CONCLUSION

It presents the scientific production on fungal infections caused by Malassezia spp. in premature newborns, especially in those hospitalized in Neonatal Intensive Care Units. Although scarce, it focuses on countries of the European continent and points to the species of the genus Malassezia as a potential agent of blood and skin infections, especially if there is use of central venous catheter and prolonged lipid parenteral nutrition. However, it has been observed that the Malassezia sp. is little reported as agent of fungaemia in premature neonates, being M. fufur and M. pachydermatis the species most identified in the studies analyzed. This fact can be coupled to the cultivation conditions, which are very demanding.

Considers, in this context, considering the of the infections caused severity Malassezia spp. in newborn infants, especially by impairment of their immune system, and long period of hospitalization for the observed, as well as the little knowledge about the pathophysiology of diseases caused by this pathogen, that there is a need for further studies on the subject, so that health professionals can understand and prevent infections related to health care (IRAS) and the phenomena involved.

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