RESUMO
Objetivo: analisar em recém-nascidos prematuros internados em Unidades de Terapia Intensiva Neonatal por infecções fúngicas causadas por levaduras do gênero Malassezia. Método: trata-se de estudo bibliográfico, descriptivo, 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 descriptiva. 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.

Descriptors: Malassezia; Microbiota; Fungemia; Unidades de Cuidados Intensivos Neonatal; Recém-Nascido Prematuro; Parenteral Nutrition.

RESUMEN
Objetivo: analizar en neonatos hospitalizados en Unidades de Cuidados Intensivos Neonatales por infecciones fúngicas causadas por levaduras del género Malassezia. Método: se trata de 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.

Descriptors: Malassezia; Microbiota; Fungemia; Unidades de Cuidado Intensivo Neonatal; Recién Nacido Prematuro; Nutrición Parenteral.

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.
Fungal infections in preterm infants by...

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.\textsuperscript{1,2} This genus includes 18 species that can colonize or infect humans and animals.\textsuperscript{1,3} These yeasts belong to the class Malasseziomycetes, subphylum Ustilaginomycotina, phylum Basidiomycota, the species are anthropophilic \textit{M. furfur}, \textit{M. sympodialis}, \textit{M. globosa}, \textit{M. obtusa}, \textit{M. restricta}, \textit{M. slooffiae}, \textit{M. dermatis}, \textit{M. japonica}, \textit{M. arunalokei}. Since the species zoophilic, reported in the literature are \textit{M. yamatoensis}, \textit{M. pachydermatis}, \textit{M. equina}, \textit{M. nana}, \textit{M. capre}, \textit{M. cuniculi}, \textit{M. brasiliensis}, \textit{M. psittaci} and \textit{M. vespertilionis}. It notes that \textit{M. Pachydermatis} is monotypic not lipid-dependent.\textsuperscript{4,4}

It knows that \textit{Malassezia} species are associated with pityriasis versicolor, seborrheic dermatitis, folliculitis, atopic dermatitis and psoriasis.\textsuperscript{1,2,5} Furthermore, it has been hypothesized a connection between these yeasts and carcinogenesis of the skin, particularly in the case of Squamous Carcinoma.\textsuperscript{6} However, it is unknown whether, in large part, its pathophysiology. It is known that, in healthy skin, the \textit{Malassezia} yeast extract essential nutrients for its growth without causing disease. When this process is changed, they adapt, modifying the expression of enzymes involved in the acquisition of energy and synthesize a series of bioactive.\textsuperscript{5} It is noteworthy that skin disorders may be exacerbated by interactions between \textit{Malassezia} sp. and the immune system of the host.\textsuperscript{1}

Facilitate the establishment of infections by invasive procedures and the use of broad spectrum antibiotics.\textsuperscript{3} 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 \textit{Malassezia}, where the dissemination and the prognosis is influenced by the immune status of the host.\textsuperscript{5-6}

It is the transmission of \textit{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 such as the adhesion and the formation of biofilms on central venous catheters.\textsuperscript{9}

OBJECTIVE

- To analyze in newborn infants hospitalized in Neonatal Intensive Care Units fungal infections caused by yeasts of the genus \textit{Malassezia}.

METHOD

It is a bibliographical study, descriptive, integrative review.\textsuperscript{9,10} 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.\textsuperscript{11}

This study was guided by the following question: What is the panorama, reported by world scientific literature about fungal infections caused by \textit{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 Retrieval 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.\textsuperscript{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.
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 post-test, 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.¹¹

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

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

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 lipid-dependent, but which is becoming increasingly common in the microbiota of humans.\(^\text{13}\)

Become increasingly present reports that the genus Malassezia is the etiologic agent of Fungaemia. Two studies reported blood infection caused by *M. furfur*,\(^\text{14,15}\) being that, in one of the studies, there were six episodes of fungemia, caused by this species, among the ten recorded in the NICU.\(^\text{13}\) 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,\(^\text{16}\) being the *M. furfur* the most applicant of the genus.\(^\text{17,18}\) The period in which the colonized patients remained receiving parenteral nutrition and antibiotic therapy was the longest of those who were not colonized.\(^\text{16}\)

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.\(^\text{17,19}\) 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.\(^\text{20}\)

It should be stressed that, although the primary concern is fungus *Candida albicans*, Malassezia, Aspergillus and Zygomycetes are considered less prevalent and should receive greater importance when the signs and symptoms of sepsis could arise in the newborn.\(^\text{4}\)

#### 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,\(^\text{16}\) who demonstrated that increase the likelihood of colonization by presenting the habitat of favorable growth of fungi.\(^\text{16}\)

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 other drugs, prolonged total parenteral nutrition, intravenous fat emulsions, 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.\(^\text{4,18}\)

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*.\(^\text{21}\)

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.\(^\text{17}\) *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.\(^\text{4}\)

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 of 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.\(^\text{4}\)
Flucytosine; however, a case of fungemia by M. pachydermatis showed reduced susceptibility to fluconazole.\textsuperscript{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. furfur 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 severity of the infections caused by Malassezia spp. in newborn infants, especially by impairment of their immune system, and for the long period of hospitalization 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.

**REFERENCES**


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Submission: 2018/05/03
Accepted: 2018/08/19
Publishing: 2018/10/01

Corresponding Address
Davi Porfirio da Silva
Rua das Chagas, 134
Bairro Clima Bom
CEP: 57071-419 – Maceió (AL), Brazil