Malassezia spp. Yeasts of Emerging Concern in Fungemia

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Malassezia spp. are lipid-dependent yeasts, inhabiting the skin and mucosa of humans and animals. They are involved in a variety of skin disorders in humans and animals and may cause bloodstream infections in severely immunocompromised patients. Despite a tremendous increase in scientific knowledge of these yeasts during the last two decades, the epidemiology of Malassezia spp. related to fungemia remains largely underestimated most likely due to the difficulty in the isolation of these yeasts species due to their lipid-dependence. This review summarizes and discusses the most recent literature on Malassezia spp. infection and fungemia, its occurrence, pathogenicity mechanisms, diagnostic methods, in vitro susceptibility testing and therapeutic approaches.

Keywords: Malassezia spp., epidemiology, pathogenesis, fungemia, diagnosis, therapy, antifungal profile

INTRODUCTION

Malassezia are lipid-dependent yeasts inhabiting the skin of healthy humans and other warm blooded animals. However, these yeasts may also act as opportunistic pathogens, causing dermatitis and otitis in animals, and dermatitis with (i.e., atopic dermatitis, folliculitis, and psoriasis) and without inflammation (Pityriasis versicolor) in humans (Guillot and Bond, 2020; Saunte et al., 2020). Besides their involvement in skin diseases, Malassezia spp. have increasingly been reported to cause severe systemic infections, especially among premature neonates and immunocompromised patients receiving parenteral nutrition (Miceli et al., 2011; Iatta et al., 2014a, 2018; Ilahi et al., 2017; Pedrosa et al., 2018). While fungemia caused by Candida species has been recognized as a cause of morbidity and mortality in hospitalized patients worldwide (Mellinghoff et al., 2018), the epidemiology of Malassezia-related fungemia remains largely underestimated most likely due to the difficulties in the isolation of these yeasts species due to their lipid-dependent growth (Iatta et al., 2018). Currently, the genus comprises 18 lipid-dependent species with a variable distribution on different hosts and pathologies (reviewed in Lorch et al., 2018; Guillot and Bond, 2020). Additionally, by using both fingerprinting methods and multigene sequence analysis, different Malassezia genotypes were identified as strictly related to the host, geographical origin, and/or clinical manifestations (Cafarchia et al., 2008, 2011b; Theelen et al., 2018). Several hypotheses have been proposed to explain the pathogenic mechanisms of these fungi, but the role of single species and genotypes in clinical manifestations remains to be elucidated (Theelen et al., 2018). In addition, scientific data suggest that Malassezia antifungal susceptibility profiles against
azole, amphotericin B (AmB) and terbinafine (TER) largely vary between Malassezia species or genotypes, thus influencing clinical management of patients (Theelen et al., 2018). This review summarizes and discusses the most recent literature on Malassezia fungemia, its occurrence, pathogenic mechanisms of the involved species, diagnostic methods, in vitro susceptibility testing and therapeutic approaches.

THE MALASSEZIA GENUS AND ETIOLOGY OF MALASSEZIA FUNGEMIA

Since the designation of the genus Malassezia by Baillon in 1889, the taxonomy has been updated and currently the genus comprises 18 lipid-dependent species with different genotypes showing variable pathology and distribution on different hosts (reviewed in Lorch et al., 2018; Guillot and Bond, 2020). All Malassezia species are lipid-dependent and, with the exception of Malassezia pachydermatis, do not grow on Sabouraud Dextrose Agar (SDA), which is most commonly used for culturing fungi in clinical labs. The genus Malassezia occurs on the skin of humans and animals but some species have only been observed on either humans or animals (reviewed in Guillot and Bond, 2020). Interestingly, Malassezia yeasts are the major component of the healthy human skin mycobiome (Findley et al., 2013; Oh et al., 2014; Wu et al., 2015). A recent phylogenetic study evaluating six genes suggested that the genus is deeply rooted in the Ustilaginomycotina and has a sister relationship with the Ustilaginomycetes and Exobasidiomycetes, assigning the genus its own class, Malasseziomycetes (Wang et al., 2014). Based on a phylogenomics study using 164 core eukaryotic genes, three main clusters were identified: Cluster A consisting of M. furfur, M. japonica, M. obtusa, and M. yamatoensis; Sub-cluster B1, with the most abundant human skin inhabitants M. globosa and M. restricta; Sub-cluster B2 consisting of M. sympodialis, M. dermatis, M. caprae, M. equina, M. nana, and M. pachydermatis; and Cluster C forming a basal lineage with M. cuniculi and M. slooffiae (Wu et al., 2015). Four more species have been described since then: M. brasiliensis and M. psittaci from parrot (Cabañes et al., 2016), M. arunalokei from human scalp (Honnavar et al., 2017), and M. vespertilionis from bat (Lorch et al., 2018). Multiple genotypes of a species can colonize the same patient (Cafarchia et al., 2008; Machado et al., 2010; Ilahi et al., 2017) but some genetic types might be linked to a particular body site or pathology thus indicating an affiliation of Malassezia genotypes with host, geographical origin and/or clinical manifestations (Cafarchia et al., 2008, 2011a;b; Ilahi et al., 2017). In particular, amplified fragment length polymorphism (AFLP) patterns of M. furfur skin isolates from Ontario, Canada clustered separately from mainly European references from other body sites, suggesting geographical or ecological/clinical variability in the species (Gupta et al., 2004). Sequence analysis of the intergenic spacer (IGS1) distinguished specific M. globosa, M. restricta, and M. pachydermatis variants in seborrheic dermatitis, atopic eczema, and on healthy skin of humans and animals (Sugita et al., 2003, 2004; Kobayashi et al., 2011). Moreover, sequence analyses of the LSU rDNA showed distinct Malassezia spp. subtypes on different host species (Gaitanis et al., 2012). Multilocus sequence analysis that included the D1/D2 domains of LSU rDNA, the chs2 gene, and the ITS1 region grouped M. pachydermatis strains from skin of healthy dogs and from skin lesions in three main genotypes (A, B, and C) with eight ITS1 subtypes. Genotype B included isolates from dogs of European origin and appeared to be present on healthy dog skin, without producing phospholipase. The A and C genotypes and their subtypes seemed to be predominantly associated with skin lesions and their isolates showed high phospholipase production (Cafarchia et al., 2008; Machado et al., 2010). Similarly, IGS1 subtypes 3C and 3D displayed high phospholipase production and were more frequently isolated from skin lesions of dogs with atopic dermatitis (Kobayashi et al., 2011). Only three Malassezia species have been described to cause bloodstream infections: M. furfur, M. pachydermatis, and M. sympodialis. Interestingly, AFLP analysis or ITS sequences showed that only one main M. furfur or M. pachydermatis genotype seems to be involved in blood stream infections in immunocompromised hosts (Theelen et al., 2001; Kaneko et al., 2012; Ilahi et al., 2017). All these Malassezia genotypes might also colonize the skin of patients or of hospital staff which might represent the driver for these systemic infections (Theelen et al., 2001; Gupta et al., 2004; Kaneko et al., 2012). With respect to the assessment of antifungal microbiological profiles, a reference method has not yet been developed for these yeasts and the culture media, inoculum sizes, incubation times, and the criteria used to determine MIC endpoints differ among studies. However, evidence suggested that Malassezia antifungal susceptibility profiles against azoles, AmB and TER vary according to the Malassezia species, regardless of culture medium or other conditions employed. M. sympodialis and M. pachydermatis are the most susceptible and M. furfur and M. globsa the least susceptible species to azoles, AmB and TER (Rojas et al., 2014; Cafarchia et al., 2015; Pedrosa et al., 2019b). Itraconazole (ITZ) and ketoconazole (KZT) were the most active drugs for all Malassezia species, and fluconazole (FLZ), voriconazole (VOR) and AmB the least active (Rojas et al., 2014; Cafarchia et al., 2015; Pedrosa et al., 2019b). Interestingly, antifungal profiles may also vary in relation to genotype (Sugita et al., 2005; Cafarchia et al., 2012). In particular, isolates derived from animal skin lesions and belonging to a unique genotype, showed reduced susceptibility to azoles when compared to genotypes associated with healthy skin (Cafarchia et al., 2008).

EPIDEMIOLOGY OF MALASSEZIA YEASTS AND FUNGEMIA

The epidemiology of Malassezia fungemia has not been well-investigated until now due to the scant surveillance studies with this focus (see Table 1). Malassezia furfur, M. sympodialis, and M. pachydermatis are the only Malassezia species isolated from bloodstream infections to date (Table 1). Some authors propose that the fungal density on the skin as well the host immunological competence might be driving factors influencing their pathogenic role (Wheeler et al., 2017; partially reviewed in Theelen et al., 2018).
<table>
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<tr>
<th>References</th>
<th>Yeast species</th>
<th>Hosts and number</th>
<th>Cause of admission</th>
<th>Risk factors</th>
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<th>Treatment protocol</th>
<th>Length of treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Redline and Dahms (1981)</td>
<td>M. furfur</td>
<td>Preterm neonate/1</td>
<td>Respiratory distress syndrome</td>
<td>CVC, Preterm neonates, TPN</td>
<td>Histology/cytology</td>
<td>AmB + Flucytosine</td>
<td>NR</td>
<td>Dead</td>
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<td>Hassall et al. (1983)</td>
<td>M. furfur</td>
<td>Children/1</td>
<td>Fever, vomiting</td>
<td>CVC, bowel syndrome, urokinase therapy</td>
<td>Counter current immune-electrophoresis</td>
<td>CVC removal, AmB</td>
<td>42 days</td>
<td>Alive</td>
</tr>
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<td>Powell et al. (1984)</td>
<td>M. furfur</td>
<td>Preterm neonate/4</td>
<td>Fever, SEPSIS interstitial pneumonia, elevated neutrophil band counts, and thrombocytopenia</td>
<td>CVC, TPN, preterm neonates, prolonged hospitalization, pneumonia</td>
<td>CCVC tip culture on lipid media</td>
<td>CVC removal</td>
<td>NR</td>
<td>Alive</td>
</tr>
<tr>
<td>Redline et al. (1985)</td>
<td>M. furfur</td>
<td>Preterm neonate/3</td>
<td>Fever, thrombocytopenia in neonates, respiratory distress</td>
<td>CVC, TPN, preterm neonates, severe gastrointestinal disease and immunosuppression</td>
<td>Histology/cytology/blood and CVC tip cultures on lipid media</td>
<td>Discontinuation of the lipid administration, AmB (0.5–1 mg/kg/d), or AmB (40 mg/day), Flucytosine every 6–8 h</td>
<td>30–35 days</td>
<td>Dead (preterm neonates) Alive (children and adults)</td>
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<tr>
<td>Alpert et al. (1987)</td>
<td>M. furfur</td>
<td>Preterm neonate/6</td>
<td>Fever, respiratory distress asymptomatic (2 infants)</td>
<td>CVC, TPN, multiple potential causes for immunosuppression</td>
<td>Blood culture on lipid media</td>
<td>CVC, AmB alone or with flucytosine</td>
<td>5–42 days</td>
<td>2 Dead due to unrelated causes and 5 alive</td>
</tr>
<tr>
<td>Aschner et al. (1987)</td>
<td>M. furfur</td>
<td>Children/2</td>
<td>Fever, pulmonary diseases, thrombocytopenia</td>
<td>Apnea, bradycardia, pulmonary deterioration, thrombocytopenia</td>
<td>CVC tip on lipid media</td>
<td>CVC removal</td>
<td>NR</td>
<td>1 Dead</td>
</tr>
<tr>
<td>Dankner et al. (1987)</td>
<td>M. furfur</td>
<td>Preterm neonate/5</td>
<td>Fever, thrombocytopenia, hyperbilirubinemia</td>
<td>CVC, Premature neonates, prolonged hospitalization, tpn, broad-spectrum antibiotics, multiple potential causes for immunosuppression</td>
<td>Blood culture bottles on lipid media</td>
<td>AmB alone or AmB and flucytosine</td>
<td>4 days–6 weeks</td>
<td>Alive</td>
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<td>Garcia et al. (1987)</td>
<td>M. furfur</td>
<td>Adult/2</td>
<td>Fever and leukocytosis</td>
<td>CVC, TPN, Broad-spectrum antibiotics, multiple potential causes for immunosuppression</td>
<td>Blood culture on lipid media</td>
<td>Discontinuation of the lipid administration AmB (total dose 665 mg)</td>
<td>28 days</td>
<td>Dead</td>
</tr>
<tr>
<td>Wurtz and Knospe (1988)</td>
<td>M. furfur</td>
<td>Adult/1</td>
<td>Fever</td>
<td>Multiple potential causes for immunosuppression</td>
<td>Blood culture on lipid media</td>
<td>AmB followed by cephaexin and KTZ</td>
<td>18–25 days</td>
<td>Alive</td>
</tr>
<tr>
<td>Shek et al. (1989)</td>
<td>M. furfur</td>
<td>Preterm neonates/3</td>
<td>NR</td>
<td>NR</td>
<td>History</td>
<td>NR</td>
<td>NR</td>
<td>Dead due to Malassezia septicemia</td>
</tr>
<tr>
<td>Surmont et al. (1989)</td>
<td>M. furfur</td>
<td>Preterm neonates/6</td>
<td>Fever, pulmonary diseases, leukocytosis, thrombocytopenia</td>
<td>CVC, total parenteral nutrition, preterm neonates, broad-spectrum antibiotics, multiple potential causes for immunosuppression</td>
<td>CVC culture on lipid media</td>
<td>CVC removal, discontinuation of the lipid administration miconazole (13–30 mg/kg per d) alone or in combination with or cloxacillin and netilmicin</td>
<td>10–15 days</td>
<td>1 Dead 5 Alive</td>
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<tr>
<td>Masure et al. (1991)</td>
<td>M. furfur</td>
<td>Preterm neonates/1</td>
<td>Leukemia</td>
<td>CVC</td>
<td>Blood culture on lipid media</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weiss et al. (1991)</td>
<td>M. furfur</td>
<td>Preterm neonates/1</td>
<td>CVC</td>
<td>Blood culture on lipid media</td>
<td>Discontinuation of the lipid emulsion without CVC Removal</td>
<td>–</td>
<td>Alive</td>
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(Continued)
<table>
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<tr>
<th>References</th>
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<tr>
<td>Weibel et al. (1994)</td>
<td>M. pachydermatis</td>
<td>Preterm neonates /5</td>
<td>Thrombocytopenia</td>
<td>CVC, TPN, interavenous lipid, preterm neonates (interveuticular hemorrhage, sepsis, respiratory distress syndrome), prolonged hospitalization</td>
<td>Blood culture</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Barber et al. (1993)</td>
<td>M. furfur</td>
<td>Adults /4 children/3</td>
<td>Fever, leukocytosis, cough, apnea, myalgia, nausea/vomiting</td>
<td>CVC, Multiple potential causes for immunocompromise</td>
<td>CVC culture on lipid media</td>
<td>AmB (1 mg/kg/d)</td>
<td>NR</td>
<td>2 Dead due to unrelated causes 5 Alive</td>
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<tr>
<td>Shparago et al. (1995)</td>
<td>M. furfur</td>
<td>Adult /1</td>
<td>Fever, chills, dyspnea, pleuritic chest pain, and multiple bilateral pulmonary nodular infiltrates</td>
<td>CVC, TPN</td>
<td>Lysis-centrifugation fungal blood cultures on lipid media</td>
<td>CVC removal discontinuation of the lipid emulsion, and AmB (300-mg total cumulative dose)</td>
<td>&gt;2 weeks</td>
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<td>Chang et al. (1998)</td>
<td>M. pachydermatis</td>
<td>Preterm neonates/8</td>
<td>Fever intubation or reintubation and tachycardia</td>
<td>CVC, TPN with Lipids</td>
<td>Blood cultures</td>
<td>AmB for at least 10 days</td>
<td>NR</td>
<td>1 dead 7 alive</td>
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<tr>
<td>Morrison and Weisdorf (2000)</td>
<td>M. furfur</td>
<td>Children /1 Adult /1</td>
<td>Fever, Hurier’s alogeneica transplant</td>
<td>CVC, TPN with Lipids</td>
<td>Histology, dupont isolator system on lipid media</td>
<td>CVC removal discontinuation of the lipid emulsion</td>
<td>NR</td>
<td>1 dead due to unrelated causes 1 alive</td>
</tr>
<tr>
<td>Schleman et al. (2000)</td>
<td>M. pachydermatis</td>
<td>Adult /1</td>
<td>Fever</td>
<td>CVC, TPN with lipids, multiple abdomanual surgeries</td>
<td>Blood culture bottles</td>
<td>CVC Removal AmB</td>
<td>NR</td>
<td>Alive</td>
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<tr>
<td>Chryssanthou et al. (2001)</td>
<td>M. pachydermatis</td>
<td>Preterm neonates/8</td>
<td>Fever, respiratory distress syndrome</td>
<td>Preterm neonates, TPN</td>
<td>BACTEC blood culture bottles</td>
<td>L-AmB (1 mg/Kg/d), flucytosine (8 mg/Kg/d PO or EV), FLZ (50–150 mg kg/d)</td>
<td>21–35 days</td>
<td>Alive</td>
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<td>Kikuchi et al. (2001)</td>
<td>M. sympodialis</td>
<td>Adult /1</td>
<td>Gastric cancer</td>
<td>Fever elevated leukocyte counts and C-reactive protein</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Chu and Lai (2002)</td>
<td>M. furfur</td>
<td>Adult /1</td>
<td>Fever</td>
<td>Broad-spectrum antibiotic corticosteroid treatment,</td>
<td>Blood culture bottles</td>
<td>AmB (0.7 mg/kg/d for 10 days), FLZ (200 mg daily for 14 days)</td>
<td>24 days</td>
<td>Alive</td>
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<td>Rosales et al. (2004)</td>
<td>M. furfur</td>
<td>Preterm neonate /1</td>
<td>Hypotension, Thrombocytopenia, High level C-reactive protein apnea, temperature instability, Bilious residual</td>
<td>CVC, Parenteral nutrition, preterm neonate (low birth-weight), chronic lung disease, necrotizing, enterocolitis intraventricular</td>
<td>Histology, radiographically/ photomicrogram</td>
<td>AmB</td>
<td>26 days and 2 days</td>
<td>Died</td>
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<td>Giusiano et al. (2006)</td>
<td>M. furfur / M. sympodialis</td>
<td>Adult /2</td>
<td>Oncology</td>
<td>NR</td>
<td>CVC tips cultures</td>
<td>Nr</td>
<td>NR</td>
<td>NR</td>
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<td>Oliveri et al. (2011)</td>
<td>M. furfur</td>
<td>Preterm neonate /1</td>
<td>Fever, gastrointestinal disturbs, cyanosis</td>
<td>CVC, Parenteral nutrition, prolonged hospitalization, antibiotic treatment, ileostomy surgery</td>
<td>Lysis-centrifugation blood culture on Dixon</td>
<td>CVC removal L-AmB (4 mg/Kg/d)</td>
<td>45 days</td>
<td>Alive</td>
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<tr>
<td>Iatta et al. (2014a)</td>
<td><em>M. furfur</em></td>
<td>Preterm neonates/6 (3 with FLZ prophylaxis) and children/2</td>
<td>Fever, apnea, high level c-reactive protein, abdominal distension, thrombocytopenia</td>
<td>CVC, Parenteral nutrition, Preterm neonates, Prolonged hospitalization, Neonatal asphyxia, Abdominal surgery (infants)</td>
<td>Lysis-centrifugation blood culture on Dixon</td>
<td>CVC removal L-AmB (2.5–5 mg/Kg)</td>
<td>6–20 days</td>
<td>Alive</td>
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<td>Al-Sweih et al. (2014)</td>
<td><em>M. pachydermatis</em></td>
<td>Preterm neonate/1</td>
<td>Fever, respiratory distress syndrome</td>
<td>CVC, Preterm neonates TPN, necrotizing enterocolitis</td>
<td>BACTEC blood culture bottles</td>
<td>L-AmB</td>
<td>7 days</td>
<td>Alive</td>
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<tr>
<td>Choudhury and Marte (2014)</td>
<td><em>M. pachydermatis</em></td>
<td>Adult with posaconazole prophylaxis/1</td>
<td>Fever</td>
<td>CVC, acute myeloid leukemia, chemotherapy</td>
<td>BACTEC blood culture bottles</td>
<td>CVC removal L-AmB (1 mg/Kg/d)</td>
<td>NR</td>
<td>Alive</td>
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<td>Aguirre et al. (2015)</td>
<td><em>M. sympodialis</em></td>
<td>Children /1</td>
<td>Fever, respiratory distress with hypoxemia</td>
<td>CVC, History of prolonged hospitalization, broad-spectrum antibiotic treatment Abdominal surgeries, viral infections</td>
<td>Lysis-centrifugation blood culture on Dixon</td>
<td>CVC removal, L-AmB (1 mg/Kg/d)</td>
<td>21 days</td>
<td>Alive</td>
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<td>Roman et al. (2016)</td>
<td><em>M. pachydermatis</em> + mycobacteria</td>
<td>Adult/1</td>
<td>Fever, pneumonia, dyspnea</td>
<td>CVC, Bacteremia, Leprosis</td>
<td>BACTEC blood culture bottles</td>
<td>CVC removal, AmB (5 mg/Kg/d) and nafcillin (400 mg IV d)</td>
<td>7 days</td>
<td>Alive</td>
</tr>
<tr>
<td>Iatta et al. (2018)</td>
<td><em>M. furfur</em></td>
<td>Preterm neonates/9</td>
<td>Fever, respiratory distress, elevated or depressed leukocyte count, increased C-reactive protein levels, thrombocytopenia</td>
<td>CVC, Preterm neonates TPN</td>
<td>CVC tips cultures on lipid media</td>
<td>NR</td>
<td>NR</td>
<td>1 Died and 8 Alive</td>
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<td>Pedrosa et al. (2018)</td>
<td><em>M. furfur</em></td>
<td>Preterm neonates/1 and Adult /2 with fluconazole prophylaxis</td>
<td>Fever</td>
<td>CVC, Broad-spectrum antibiotic and glucocorticoid therapies, Auto-immune diseases, Carcinoma</td>
<td>BACTEC blood culture bottles and (MALDI-TOF-MS)</td>
<td>CVC removal, FLZ (10 mg/kg/d) and/or L-AmB (3 mg/kg/d) or (5 mg/kg/d) for Adults</td>
<td>50 days</td>
<td>2 Dead (adults) 1 Alive</td>
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<td>Chen et al. (2019)</td>
<td><em>M. furfur</em></td>
<td>Preterm neonates with fluconazole prophylaxis/1</td>
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<td>CVC, TPN with Lipids Premature infant (Low birth-weight).</td>
<td>Blood culture in media with lipid</td>
<td>CVC removal, AmB (1 mg/kg/d)</td>
<td>NR</td>
<td>Alive</td>
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<td>Lee et al. (2019)</td>
<td><em>M. pachydermatis</em></td>
<td>Adult/1</td>
<td>Intraabdominal abscess</td>
<td>CVC, TPN with Lipids, Multiple potential causes for immunocompromised, Gastric cancer, Chemotherapy</td>
<td>Blood culture on 5% on Sabouraud dextrose agar.</td>
<td>AmB</td>
<td>2 days</td>
<td>Dead due to unrelated causes</td>
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<td>Huang et al. (2020)</td>
<td><em>M. pachydermatis</em></td>
<td>Preterm neonates with fluconazole prophylaxis/4</td>
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<td>BACTEC blood culture bottles</td>
<td>CVC removal (2/4), AmB</td>
<td>14–21 days</td>
<td>Alive</td>
</tr>
<tr>
<td>Chow et al. (2020)</td>
<td><em>M. pachydermatis</em></td>
<td>Preterm neonates with fluconazole/3</td>
<td>CLABSI, necrotizing enterocolitis, peritonitis, infected urinoma</td>
<td>CVC, Broad-spectrum antibiotics, TPN with Lipids, Preterm neonate (low birth-weight)</td>
<td>CVC culture</td>
<td>NR</td>
<td>NR</td>
<td>Alive</td>
</tr>
</tbody>
</table>

NR, not reported; CVC, central venous catheter; TPN, total parenteral nutrition; AmB, Amphotericin b; L-AmB, Liposomal Amphotericin b; FLZ, fluconazole; CLABSI, central line-associated bloodstream infection.
Malassezia bloodstream infections have been described in adult and child immunocompromised patients, and neonates (Table 1). According to general knowledge, the main ecological niche of Malassezia yeasts is human and animal skin, and they represent 50 to 80% of the total human skin mycobiome (Nagata et al., 2012; Findley et al., 2013; Gupta et al., 2014). Therefore, it would make sense to consider the skin mycobiome as a potential reservoir and point d’entrée for bloodstream infections. More is currently known about the adult human skin mycobiome but little information is available about the child and neonatal skin mycobiome. Even if Malassezia skin colonization may be the result of both maternal and environmental sources, data suggests that colonization of human skin begins immediately after birth and Malassezia species distribution varies with age (Jo et al., 2016; Ward et al., 2018). The limited data currently available about the cutaneous mycobiomes in preterm and term neonates shows that Malassezia species distribution on skin of neonates and children varies between studies, but M. globosa, M. furfur, M. sympodialis, and M. restricta seem to be the most prevalent species described (Bernier et al., 2002; Zomorodain et al., 2008; Jang et al., 2009; Gupta et al., 2014; Prohic et al., 2014; Jo et al., 2016; Paul et al., 2019). Variation between studies could be the result of methodological differences such as number of subjects studied, DNA extraction, target region selection and PCR-conditions, and data processing and interpretation; but also geographical and host-specific differences may explain study discrepancies. The study of Paul et al. determined M. restricta to be the most abundant Malassezia species in both term and preterm neonates (n = 30), similar to adult skin (Paul et al., 2019). Interestingly, this species has thus far not been linked to bloodstream infections. Malassezia colonization increases quickly after birth but a very important shift, making Malassezia the most predominant genus of the human skin mycobiome, takes place during adolescence and has been linked to lipid composition shifts of the skin (Grice and Segre, 2011; Findley et al., 2013; Jo et al., 2016). In adults, M. restricta and M. globosa seem to be the dominating Malassezia species on the skin, followed by M. sympodialis, depending on body site (Findley et al., 2013; Wu et al., 2015). Geographical factors may influence Malassezia species distribution on healthy human skin (Leong et al., 2019; Saunte et al., 2020). In addition, the proportion of Malassezia species isolated from the skin varies considerably among different medical conditions (Saunte et al., 2020). As the two most abundant Malassezia species on healthy human adult skin have not been linked to Malassezia bloodstream infections, studies focusing on genetic and functional differences between cells of Malassezia species involved in bloodstream infections and ones that are not, in addition to potentially selective host parameters, could help explain this. Recent molecular studies highlighted the genetic variability among single species implicated in both skin and systemic infections (Theelen et al., 2001; Kaneko et al., 2012; Gupta et al., 2014), suggesting pathogenicity variation at species and sub-species levels. Malassezia pachydermatis is mainly known from animals and is not commonly associated with human skin colonization yet in multiple cases it was linked to Malassezia bloodstream infections (Table 1). A study evaluating cats and dogs (107 healthy and 123 with chronic otitis externa), showed that occurrence and population size of M. pachydermatis increased according to the presence in skin lesions, not only in affected areas of the skin but also at other sites without detectable skin lesions, suggesting that the yeasts could be easily transmitted from site to site because of scratching induced by pruritus (Cafarchia et al., 2005). This finding is also relevant from a zoonotic point of view since the yeasts may be mechanically transmitted from dogs to their owners (Morris et al., 2005) and subsequently can cause health problems as previously reported from an intensive care nursery (Chang et al., 1998). A similar transmission route—animal to human or human to human—from health care worker or family member for M. furfur or M. sympodialis may also occur and should be further explored in future studies. Even when these species are part of the stable mycobiomes of Malassezia bloodstream infection patients, isolates causing the infection could belong to different genotypes, transmitted from external sources. The first case of Malassezia spp. as a pathogen in bloodstream infection and sepsis was reported in 1981 by Redline and colleagues (Table 1). Until now, a total of 118 cases were published, but only three surveillance studies (Table 1). Malassezia furfur was the most encountered species with 82 cases, followed by M. pachydermatis (33 cases), and only three cases of M. sympodialis fungemia have been described. To date, Malassezia fungemia cases were observed with highest incidence in neonates (82 cases), followed by 23 in adults and 17 in children. Numerous cases were reported in the past two decades, particularly in neonates and infants receiving intravenous lipids. In our 1-year survey on yeast fungemia involving 290 neonatal and 17 pediatric patients with intravascular catheters, lipid parenteral nutrition, prolonged ward stay, and surgery, were evaluated. This diagnostic survey on bloodstream infections (BSIs) resulted in a higher prevalence of M. furfur (2.1%) than Candida spp. (1.4%) and suggested that Malassezia BSIs might be underestimated, due to improper diagnosis (Iatta et al., 2014a). The surveillance study was repeated 4 years later, and a total of 202 neonatal patients with intravascular catheters were enrolled (Iatta et al., 2017). A total of 10 cases of BSIs were registered, thus suggesting the relevance of these yeasts in catheter mediated fungemia (Iatta et al., 2018). Incubator, sheets and the skin of patient or hospital staff may represent potential sources of Malassezia infection. Recently, lipid infusion type, phototherapy light sources, central venous catheter placement, and prophylactic fluconazole were proposed as risk factors affecting Malassezia colonization and /or fungemia more than candidemia (Chen et al., 2019).

PATHOGENESIS

Almost all-available research to date focuses on Malassezia virulence factors linked to skin and pathogenesis for Malassezia BSIs has hardly been studied, likely due to the relatively low number of cases when compared to skin diseases. With an increasing number of cases in recent years and the likely underestimation of Malassezia BSIs as a result of the use of standard culture media without lipid supplementation in
the clinic, future studies will hopefully address some of the missing knowledge. Here, we focus on known virulence factors of the three fungemia causing *Malassezia* species (i.e., *M. pachydermatis*, *M. furfur*, and *M. sympodialis*) and discuss findings, even if they were derived from skin. Virulence factors, to some extent, may be of a more general nature and could potentially also be relevant for bloodstream infections. Several hypotheses have been proposed to explain the pathogenic behavior of these fungi. The relationship between host and *Malassezia* metabolism seems to be key for the understanding the pathogenesis of infection (Cafarchia and Otranto, 2004; Velegraki et al., 2015; Theelen et al., 2018).

Various *Malassezia* cell characteristics may be involved in BSI pathogenesis. *Malassezia* spp. have cell walls with a very thick multi-layered structure that may protect them from different environmental stresses and have been described to help evade phagocytosis (Celis et al., 2017a). Biofilm formation has been linked to increased drug resistance and virulence. *M. furfur*, *M. sympodialis*, and *M. pachydermatis* are able to form biofilms, a process that seems to be strain dependent (Figueredo et al., 2013; Angiolella et al., 2017; Pedrosa et al., 2019a). In particular, *M. pachydermatis* strains isolated from dogs with and without skin lesions were able to form biofilms with variable extracellular matrix (ECM) quantity and structure depending on the sources (Figueredo et al., 2013). Accordingly, a structural heterogeneity of biofilm was found between those formed by *M. furfur* and *M. sympodialis* isolates, with both species exhibiting yeast aggregates in multilayer clusters but with a denser entrapment by a more gelatinous ECM in case of *M. furfur* biofilms (Pedrosa et al., 2019a). Biofilm formation and the extracellular matrix generation were responsible for the emergence of antifungal resistance (Figueredo et al., 2013; Angiolella et al., 2017). The biofilm formation was well-correlated with hydrophobicity, adherence, and phospholipase production of pathogenic *M. pachydermatis* and *M. furfur* cells, which may help explaining the change from a commensal to a pathogenic phenotype of these organisms (Figueredo et al., 2013; Angiolella et al., 2017). *Malassezia furfur* colonization of central venous catheters was already observed in 1994 (Sizun et al., 1994) and the ability *M. pachydermatis* to form biofilms on catheter surfaces in the laboratory was confirmed in another study (Cannizzo et al., 2007). Though not observed frequently, *Malassezia* yeasts are able to produce mycelium, a feature first suggested from an observation of hyphae in the scales of PV. Later, researchers managed to also obtain a mycelial phase for *M. furfur in vitro* (Saadatzadeh et al., 2001). In a recent review, the importance of morphological switching for fungal pathogens was highlighted: shape-shifting between different morphologies allows fungi to adapt to different host environments. The authors suggest that to understand pathogenesis mechanisms, it is crucial to establish how fungal morphology impacts virulence strategies (Min et al., 2020). It would be useful to further investigate *Malassezia* morphology switching and its potential relevance in bloodstream infections.

It has been shown that µ-opioid receptors (MORs) are present on *M. pachydermatis* cell membranes, having a role in modulating the phospholipase activities (Cafarchia et al., 2010). In animals without lesion MORs were expressed as dimers with other opioids thus resulting in an inactive form (Cafarchia et al., 2010). The high concentration of beta-endorphin normally present on lesioned skin of hosts (Pan, 2005; Honnavar et al., 2017) influenced the expression of MOR in their active form, thus favoring phospholipase production (Cafarchia et al., 2010). Increased phospholipase activity may be linked to the appearance of skin lesions and in some cases septicemia (Cafarchia and Otranto, 2004; Vlachos et al., 2013).

*M. furfur* yeasts also produce esterases, lipases, and proteases, of which the latter have a crucial role in interactions with the host and microbial community such as *Staphylococcus aureus* thus making it unfavorable for colonization (Chen and Hill, 2005; Li et al., 2018; Tee et al., 2019). Additionally, *M. furfur* secretes aspartyl proteases, capable of degrading a wide range of human skin associated extracellular matrix (ECM) protein, and might also be able to modify the skin environment potentially interfering with wound re-epithelialization (Poh et al., 2020). These enzymes could on one hand contribute to pathogenesis but on the other hand have a protective function, leading to a potentially very complex role for *Malassezia* on and in the human host. Lipases particularly have been considered virulence factors of *Malassezia* yeasts since they may be involved in the invasion, colonization, persistence and proliferation within host tissues (Petrokilidou et al., 2019). The first *Malassezia* gene encoding an extracellular lipase was identified in *M. furfur* and was designated as LIP1. Subsequently, orthologs were identified in *M. pachydermatis*, *M. globosa*, and *M. restricta*. *Malassezia* species possess multiple genes encoding putative lipases (from 9 to 14 depending on the species) that are differently involved in various skin disorders (Park et al., 2017; Tee et al., 2019). Interestingly, the lipase and phospholipase activities of *Malassezia* yeasts vary according to the species and they are implicated in both skin diseases and fungemia. In particular, *M. furfur* strains causing fungemia showed very high lipolytic enzyme activity thus suggesting that parenteral lipid emulsions may play an important role in modulating the growth and pathogenicity of *Malassezia*-yeasts in sepsis (Kaneko et al., 2012). *Malassezia* strains from skin disorders produce metabolites, such as indirubin and indolo[3,2-b] carbazole (ICZ) which are associated with carcinogenesis, immune regulation and mediation of ultraviolet radiation (UVR) damage (Gaitanis et al., 2011; Theelen et al., 2018). Recently, it has been shown that both *M. furfur* and *M. sympodialis* are able to produce nanovesicles enriched with allergens and/or proteins that interact with keratinocytes and monocytes, thus causing and maintaining the inflammation (Johansson et al., 2018; Zhang et al., 2019). In particular, nanovesicles produced by *M. sympodialis* (MalaEx) are also able to activate human keratinocytes causing an enhanced intercellular adhesion molecule-1 (ICAM-1) expression, which can cause an attraction of immune competent cells, thus causing host cutaneous defense to *M. sympodialis* (Vallhov et al., 2020). So far, the function of these extracellular vesicles for *Malassezia* spp. has only been studied in relation to skin but various studies in other fields related to similar kinds of nanovesicles show that their function in cell-to-cell communication may be much broader than that. For example, a study on human pathogen *Cryptococcus gattii*, showed that vesicles were taken...
up by macrophages of the infected host, allowing long distance pathogen-to-pathogen communication resulting in virulence enhancement (Bielaska et al., 2018). It would be interesting to explore whether extracellular vesicles might also play a role in Malassezia BSIs.

In order to gain better understanding of Malassezia pathogenesis in general, and in BSIs in particular, it is important to assess known Malassezia virulence factors, as well as investigate potentially unknown factors, and perform comparative studies between BSI-derived isolates and skin isolates. In recent years, many useful new tools have been developed for this purpose. Although to date, no model systems for studying systemic Malassezia infections have been described, recent advances for other Malassezia-affected areas of the human body may offer useful insights for future application to studying host-pathogen interactions in BSIs. Sparber et al., reported of a murine epicutaneous infection model that allowed studying the interaction of Malassezia with mammalian skin in vivo (Sparber and LeibundGut-Landmann, 2019; Sparber et al., 2019) and in the same year the association of Malassezia with Crohn’s disease was reported using mouse models (Limon et al., 2019). Performing Malassezia host-pathogen interaction studies in model systems such as the mouse may sometimes be difficult, but with the recent establishment of an in vivo infection model using Galleria mellonella, host-pathogen interaction studies are becoming more accessible. The G. mellonella model has multiple advantages, such as the absence of ethical hurdles, low cost, ease of use, yet the immune response has similarities with the human system (Torres et al., 2020). In addition, recently developed Malassezia transformation systems can aid in studying the role of specific genes and virulence factors in Malassezia pathogenicity. Agrobacterium tumefaciens mediated transformation systems for the BSI-relevant Malassezia species were developed, allowing direct gene manipulation to better understand gene function (Ianiri et al., 2016; Celis et al., 2017b). With the recent improvements to the CRISPR/Cas9 strategy, this gene editing system has already contributed to various fungal virulence studies (Malavia et al., 2020), and also its first application for research in functional Malassezia genetics has recently been reported (Ianiri et al., 2019).

### DIAGNOSIS

Since multiple Malassezia species and/or genotypes with varying antifungal susceptibility profiles may cause unique or similar pathologies, serious concern about the diagnostic procedures and antifungal treatment has been raised. Isolation and enumeration of Malassezia cells from clinical specimens remain a challenge because of their lipid dependency. Although microscopy of swab specimens is useful for diagnosing animal and human dermatitis, a more accurate etiological diagnosis is needed in high-risk patients (Iatta et al., 2018). Clinical features, laboratory markers, strategies of patient management, and outcomes of Candida and Malassezia fungemia do not differ. In some studies, M. furfur fungemia appeared earlier than candidaemia (average day 26 vs. day 42), most likely due to its exogenous origin. In addition, duration of Malassezia fungemia is longer than candidaemia, most likely due to the late removal of the central venous catheters (CVC) and also as a result of the lower efficacy of the antifungal therapy (Iatta et al., 2014a, 2018). The first signs causing suspicion of Malassezia fungemia usually are bloodstream infections manifested in fever of unknown origin in hospitalized and severely immunocompromised patients with CVC (i.e., preterm neonates or cancer patients) or in patients with pulmonary distress (Table 1) (Morrison and Weisdorf, 2000; Iatta et al., 2015, 2018). Malassezia fungemia should however be confirmed with the laboratory isolation of the responsible agent and identification by molecular means (Morrison and Weisdorf, 2000; Iatta et al., 2015, 2018; Pedrosa et al., 2018). In literature Malassezia yeasts were mainly isolated by culturing blood or CVC-tip directly on specific media and mainly by using the Isolator system (Table 1). It has been shown that the automated blood culture system BacT/Alert is not suitable for detecting M. furfur fungemia (Campigotto et al., 2016; Iatta et al., 2018). Out of 9 M. furfur fungemia cases reported by using BacT/Alert bottles only 1 case of M. furfur fungemia was detected whereas all the M. pachydermatis cases were easily detected using the above mentioned method, since this species grows on the media included in the bottles (Iatta et al., 2018, Table 1). Interestingly, it has been shown that human blood has a toxic effect on yeast growth and the addition of 3% of palmitic acid in the bottle might be able to overcome the inhibitory effect of both small (0.5 ml) and larger (3 ml) volumes of blood, thus favoring Malassezia growth (Nelson et al., 1995). Finally, although molecular tools have been used to detect Malassezia yeasts from biological samples no studies were performed to molecularly diagnose Malassezia directly from blood, thus culture remains the gold standard to isolate and identify the yeasts. This method is also suitable for yeast quantification, viability assessment, and genotyping and eventually to test the antifungal susceptibility profile of the isolated species (Peker et al., 2018). Generally, clinics use standard culture media without lipid supplementation, likely leading to underdiagnosis of both M. furfur and M. sympodialis in BSIs. It is recommended to carefully assess Malassezia BSI risk factors and apply the use of lipid-rich culture media when Malassezia spp. may be the causative agent.

### THERAPY, ANTIFUNGAL PROFILE, AND PROBABLE RESISTANCE PHENOMENA

For treatment of Malassezia-related infections, azoles, and the polyene AmB are frequently employed, both in humans and animals. Topical antifungal agents (mainly azoles) are adequate for the management of localized skin lesions, while systemic ITZ or FLZ for severe skin diseases (Bond et al., 2020; Saunte et al., 2020). For catheter-related Malassezia infections, there are only recommendations, and patients were usually treated with catheter removal, discontinuation of lipid infusion and administration of antifungal drugs such as FLZ, AmB, and or VOR (Arendrup et al., 2014; Table 1). Amphotericin B is...
effective in the treatment of Malassezia systemic infections, both in preterm infants and adults, but both FLZ and posaconazole (POS) fail to prevent Malassezia fungemia (Table 1). Usually, about 24 days of AmB treatment might be useful for a positive outcome of Malassezia fungemia but the length of the treatment might be different depending on the Malassezia species (Table 1). M. pachydermatis fungemia resolve more quickly than M. furfur fungemia (about 14 vs. 24 days, Table 1).

Despite attempts to treat these fungal infections, a trend toward recurrence is often observed in humans and animals with dermatitis (Negre et al., 2009; Bond et al., 2010, 2020; Saunte et al., 2020). Moreover, the induction of in vitro FLZ resistance in M. pachydermatis as well as the clinical evidence of treatment failure with TER in patients with pityriasis versicolor and, with KTZ in dogs with otitis (Kim and Pandya, 1998; Gupta et al., 2014; Kim et al., 2018) or with FLZ or POS in preventing M. furfur fungemia in humans, suggested the occurrence of drug resistance phenomena in these yeast species (Choudhury and Marte, 2014; Iatta et al., 2014a; Pedrosa et al., 2018; Chen et al., 2019). Antifungal susceptibility test methods have not yet been standardized, neither by the Clinical and Laboratory Standards Institute (CLSI) nor by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Arendrup et al., 2014), resulting in the absence of clinical breakpoints for these yeast species. A recent study showed that drug efflux pumps (EPMs) are involved as defense mechanisms to azole drugs in Malassezia yeasts (Iatta et al., 2017). By using a broth microdilution checkerboard analysis, the in vitro efficacy of azoles in combination with EPMs (i.e., haloperidol-HAL, promethazine-PTZ, and cyclosporine) was evaluated. The MICs of FLZ and VOR of Malassezia spp. decreased in presence of subinhibitory concentrations of HAL and/or PTZ, and a synergistic effect was observed only in strains with FLZ MIC ≥ 128 µg/mL for M. furfur, FLZ MIC ≥ 64 µg/mL for M. pachydermatis, and VOR MIC ≥ 4 µg/mL in both Malassezia spp., suggesting that the above FLZ and VOR MIC values might be considered the cut-off to discriminate susceptible and resistant strains (Iatta et al., 2017). Finally, the in vitro susceptibility of Malassezia for echinocandins suggests that this genus is intrinsically resistant to these drugs. Indeed, MIC ≥ 32 µg/mL were usually recorded for M. pachydermatis and M. furfur regardless of the employed CLSI protocol for testing drug efficacy (Prado et al., 2008; Yurayart et al., 2013; Al-Sweih et al., 2014; Leong et al., 2017).

DISCUSSION

Our knowledge on Malassezia yeasts has increased tremendously during the last two decades. Many questions remain ambiguous however, such as their role in pathology, diagnostic procedures,azole susceptibility profiles and clinical implications. Malassezia is the major component of the healthy human skin mycobiome but data on the constitution of the skin mycobiome and the abundance of Malassezia yeasts directly after birth and during the first years of life are highly inconclusive. Additional studies are needed as a better understanding of early (skin) mycobiome development may aid in understanding transmission routes, and may subsequently aid in infection containment. For example, in cases where M. pachydermatis was involved, transmission from pets via healthcare workers to patients was suggested which warrants better hygiene measures for hospital staff (Chang et al., 1998; Morris et al., 2005). Interpreting available literature on this topic should be done with caution as variation between studies may arise from methodological differences for factors such as study group size, identification methods and geography.

Concerning the causative species of bloodstream infection, epidemiological surveys suggest that M. furfur is the most common species involved. Although further studies are needed to understand the exact mechanisms of this finding: the colonization of skin of patients, as well as the higher virulence of Malassezia strains involved in fungemia, might be the driving factors influencing BSI epidemiology.

The occurrence of these infections seems lower among adult patients, and higher among neonatal patients, yet a slanted view exists as cases are likely underestimated, given the special lipid requirement of these yeast species (Iatta et al., 2018). Interestingly neonatal patients seem more frequently colonized with M. furfur strains than adults, but more data is needed to support this trend. Although lipid infusion and/or total parenteral nutrition seems to be one of the major risk factors in causing Malassezia fungemia due to the lipolytic properties of Malassezia yeasts, cases unrelated to intravenous nutrition were also observed (Table 1; Pedrosa et al., 2018; Chen et al., 2019). Interestingly, these infections are usually confined to severely immunocompromised hosts with CVCs, thus confirming the importance of this portal of entry (Iatta et al., 2018; Pedrosa et al., 2018; Chen et al., 2019). Several potential virulence factors have been described and may be involved in Malassezia pathogenesis of BSIs. In particular, the ability to produce enzymes such as lipases and/or phospholipases, production of various indolic compounds, the ability to form biofilms, and allergen enriched nanovesicle production were described for M. furfur and M. sympodialis which are frequently related to fungemia. The properties of these microorganisms to adhere to the skin and to medical indwelling devices by forming biofilms influence the antifungal profile of cells, which might represent another virulence factor in fungemia of severely immunocompromised hosts (Figueredo et al., 2013; Pedrosa et al., 2019a). Interestingly the structure of Malassezia biofilms is strain dependent and those of M. furfur and M. pachydermatis from skin lesions are composed of a more gelatinous extracellular matrix (Figueredo et al., 2013; Angiolella et al., 2018; Pedrosa et al., 2019a). Since the extracellular matrix is directly linked to the virulence of these yeasts, M. furfur and M. pachydermatis should be more virulent than M. sympodialis, which may explain the lower observed incidence of M. sympodialis fungemia (Figueredo et al., 2013; Angiolella et al., 2018; Pedrosa et al., 2019a). In recent years, useful new tools for studying virulence and host-pathogen interactions have been developed. Galleria mellonella has proven to be a promising in vivo infection model (Torres et al., 2020) and two studies showed the potential of a Agrobacterium tumefaciens mediated transformation system for studying the role of specific virulence related genes (Ianiri et al., 2016; Celis et al., 2017b). As the clinical outcome of Malassezia fungemia...
does not differ from that of *Candida* yeasts (Iatta et al., 2014a),
clinical guidelines need to be organized for an early diagnosis
of these yeasts infections. In particular, fever of unknown origin
and very high values of C-reactive protein (CRP) should alert
the clinicians to suspect *Malassezia* related systemic infections.
Diagnostic procedures to recover *Malassezia* organisms from
blood are not routinely available, and the most common system
used in many laboratories for the detection of bacterial and fungal pathogens (i.e., BaC/Alert system), is ineffective for
diagnosing *M. furfur* fungemia (Iatta et al., 2018). Recently, CVC
culturing on lipid-supplemented media, has been proposed as
a routine procedure to diagnose *M. furfur* fungemia in severely
immunocompromised patients (Iatta et al., 2018).

Guidelines for the treatment of *Malassezia* spp. skin disorders
of pet animals and humans have been assessed, but those related
to systemic infections still need to be addressed. Clinical evidence
indicated efficacy of azole drugs for the control of skin infections
and of AmB for systemic ones (*Table 1*). However, common recurrences of skin disorders (Negre et al., 2009; Theelen et al.,
2018; Bond et al., 2020) as well as the clinical evidence of
treatment failure with TER in patients with *pitryiasis versicolor*,
with KTZ in dogs with otitis (Kim and Pandya, 1998; Gupta et al.,
2014) or with FLZ or POS in preventing *M. furfur* fungemia in
humans, suggested the occurrence of drug resistance phenomena
in these yeast species.

Additionally, the high level of inter- and intraspecies differences of *Malassezia* antifungal profiles might explain the differences in mycological cure rates when an antifungal agent is used to treat what appears to be clinically the same
disease state. Different *Malassezia* species might be involved
in the same clinical diseases, and/or different genetic types
with different antifungal profiles might colonize the same host
(Prohic et al., 2015; Velegraki et al., 2015). However, even
if the MIC data of *Malassezia* species vary according to the
protocol used for susceptibility testing, there are evidences of
a very low susceptibility of these yeasts to FLZ, VOR and echinocandins (reviewed in Theelen et al., 2018; Bond et al.,
2020). Although *Malassezia* species show differences in their
antifungal susceptibility *in vitro*, the *in vivo* efficacy of antifungal agents needs to be further evaluated by comparing *in vitro* MICs and clinical outcomes. Correlation of high azole MIC
values for *Malassezia* spp. with unsuccessful treatment has been
reported in some studies (Velegraki et al., 2005; Iatta et al.,
2014a; Rojas et al., 2014). The above results need to be further
validated with multicentre studies in order to develop therapeutic
guidelines. For the moment, it is important to be aware that
the genus *Malassezia* comprises a heterogeneous group of
species and genotypes that may cause the same pathology, but
may vary in their susceptibility to different antifungal agents.
Species identification is of paramount importance not only
for epidemiological surveillance and outbreak investigation,
but also when therapy failure is registered. Interestingly, AmB
is among the preferred therapeutic options for the first-line
approach, mainly in patients under FLZ prophylaxis (Iatta et al.,
2014b). Liposomal-AmB seems to be the most active
drug due to the lipophilic nature of these yeasts even if *in vitro*
resistance phenomena were registered for L-AmB. The favorable
outcome of patients after therapy with micafungin and L-AmB
followed by FLZ, might suggest *in vivo* synergism between
these drugs as has been previously reported for *Candida* spp.
(Rosato et al., 2012; Iatta et al., 2015). Although the observed
frequency of systemic *Malassezia* infections is not very high,
this may in part be due to underdiagnosis. Use of FLZ prophylaxis
with reduced susceptibility for this drug, and the increase of
immunocompromised patients, may lead to a higher number of
observed *Malassezia* BSIs in the future. Regardless, emerging
infections need to be timely diagnosed to aid clinicians in
better patient management. The persistence of *Malassezia*
organisms on incubator surfaces and on the hands of health care
workers or parents suggested the need for punctilious hygienic
measures (Chang et al., 1998; Iatta et al., 2014a,b). The role
of lipid infusion in aiding the spread of different *Malassezia*
species infections should be also explored. The lack of sufficient
literature showing the prevalence of *Malassezia* fungemia, low
specificity and sensitivity of different blood culture systems used
for the diagnosis of this fungal sepsis, the lack of standardized
methods for *in vitro* antifungal susceptibility testing, as well
as the lack of studies investigating drug resistance phenomena
in these yeasts, call for further studies drafting guidelines for
the diagnosis and correct management of *Malassezia* related
diseases. Until specific guidelines for diagnosis and treatment
of *Malassezia* bloodstream infections are available, clinicians must
be aware of the patient population at risk for these infections and
they must communicate to the laboratory the need to include
special procedures to recover the organisms. Importantly,
commonly used culture media in the clinic do not include lipid
supplementation, which is needed for *Malassezia* yeasts to grow
due to their lipid dependence. Finally, the very low susceptibility
of some of these yeasts to azole drugs (i.e., FLZ and VOR)
and echinocandins should be considered when a long term or
prophylactic therapy is expected to be used. As stated before,
*Malassezia* are the major fungal component of the human skin
microbiome but for a long time the vast majority of scientific
research focused on the role of bacterial microbiota in health
and disease. In recent years, the role of fungi attracted more
attention regarding their interplay with the human host, but
also with other members of the microbiome. Any alteration
in either host or microbiota can result in infections and some
recent studies emphasized a role for *Malassezia* spp. in other
parts of the body, and linked to other diseases known until
then (Kong and Segre, 2020). One study reported a role for *M.
restricta* in Crohn’s disease, observing higher relative abundances
of intestinal *Malassezia* compared with healthy controls, evoking
inflammatory responses through CARD9 signaling (Limon et al.,
2019). Though a few recent studies reported dysbiosis signatures
of mycobiota in colorectal cancer (CRC) with enrichment of
*Malassezia* in CRC compared with controls (Gao et al., 2017;
Coker et al., 2019); a new study, for the first time, showed direct
proof for the involvement of *Malassezia* in the pathogenesis
of cancer. A much increased fungal community in pancreatic
ductal adenocarcinomas (PDAs) was significantly enriched for
*Malassezia*. Removal of the mycobiome reduced tumor growth,
and only repopulation with *Malassezia* accelerated oncogenesis.
PDA progression was dependent on mannose-binding lectin

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Iatta et al., 2014a; Rojas et al., 2014

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(MBL), which binds to glycans of the fungal cell wall to activate a part of the immune system called the complement cascade (Aykut et al., 2019). The relationship between Malassezia and the host is complex and more research is needed to understand the various roles that Malassezia may express in/on the human host, and the conditions that trigger them. However, the above-mentioned recent advancements have paved the way with new tools and insights that may also benefit a better understanding of Malassezia bloodstream infections.

REFERENCES


AUTHOR CONTRIBUTIONS

CC planned, wrote, and contributed to the critical review of the manuscript. WR and BT performed an initial electronic search and drafted and edited the manuscript. CC, BT, TB, and DO performed data cleaning and reviewed the manuscript. CC and BT approved the manuscript for submission. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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