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Review article

Minireview: *Malassezia* infections in immunocompromised patients

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Summary

Malassezia spp. form part of the normal human cutaneous flora and are implicated in several mild, but recurrent cutaneous diseases, such as pityriasis versicolor, *Malassezia* folliculitis, seborrhoeic dermatitis, and, with lesser frequency, a range of other dermatological disorders. *Malassezia* spp. have also been associated with cutaneous and systemic diseases in immunocompromised patients including folliculitis, seborrhoeic dermatitis, catheter-related fungaemia and a variety of deeply invasive infections. In this review, we provide an overview of the epidemiology, risk factors, pathogenesis, clinical manifestations, diagnosis, treatment and outcome of cutaneous and invasive *Malassezia* infections in immunocompromised patients.

Key words: *Malassezia*, infection, sepsis, cancer, transplantation, HIV.

Introduction

Members of the genus *Malassezia* are opportunistic yeasts that belong to the basidiomycetous yeasts and are classified as the Malasseziales (Ustilaginomycetes, Basidiomycota). In 1996, the revision of the *Malassezia* genus classified the genus into seven species on the basis of morphology, ultrastructure, physiology and molecular biology: *M. globosa*; *M. restricta*; *M. obtusa*; *M. slooffiae*; *M. sympodialis; M. furfur* and the non-lipid dependent *M. pachydermatis*.[1] Since then, however, further six new *Malassezia* spp. have been identified including *M. dermatis*, *M. japonica*, *M. yamotoensis*, *M. caprae*, *M. nana and M. equina*.[2–5] *Malassezia* spp. form part of the normal human cutaneous flora and are implicated in mild, but often recurrent cutaneous diseases such as pityriasis versicolor, *Malassezia* folliculitis, seborrhoeic dermatitis, and, with lesser frequency, a range of other dermatological disorders.

In immunocompromised patients, *Malassezia* spp. may be associated with several skin conditions and systemic diseases, including folliculitis, seborrhoeic dermatitis, catheter-related fungaemia and sepsis and a variety of deeply invasive infections.[1,6–12] *Malassezia* folliculitis usually develops in patients with underlying immunosuppression resulting from diabetes, haematological malignancies, bone marrow transplantation, AIDS and solid organ transplantation.[11,13–19] Seborrhoeic dermatitis is a frequently relapsing skin disorder characterised by greasy scaly reddish patches with predilection of sebum-rich areas that occurs in around 2–5% of the healthy population; however, its incidence is much higher in immunocompromised individuals, especially those with AIDS, ranging from 30% to 80%.[11,20] However, infrequently, *Malassezia* species may also cause invasive infections in critically ill low-birth-weight infants and in immunocompromised children and adults. The clinical spectrum ranges from asymptomatic infection to life-threatening sepsis and disseminated disease, with intravascular catheters and administration of lipid supplemented parenteral nutrition acting as the main risk factors.[12,21–24]

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Malassezia folliculitis

Malassezia furfur folliculitis (MF) represents a benign and common cutaneous infection that often is misdiagnosed as acne. *Malassezia pachydermatis*, *M. globosa* and *M. furfur* are the predominant causative agents. It was first reported by Weary *et al.* in the setting of antibiotic therapy with tetracyclines and described in clinical detail by Potter *et al.* in 1973.[25,26] MF may develop in patients with immunosuppression resulting from diabetes, leukaemia, Hodgkin's disease, steroid treatment, bone marrow transplantation, AIDS and heart and renal transplantation.[11,13,15,18,18,26–28] MF has also been described in association with pregnancy, *Down*'s syndrome, multiple trauma and broad spectrum antibacterial therapy.[18,29–31]

Malassezia folliculitis lesions are distributed most commonly over the back, chest and upper arms and consist of small, scattered and erythematous papules that occasionally can enlarge and become pustular. In immunocompromised patients, lesions may spread rapidly and be accompanied by fever exceeding 39 °C. Folliculitis appears to be more frequent in tropical countries, probably because of the heat and humidity, but it has been also reported during the summer in countries with temperate climate.[1] In some geographical regions, particularly humid and tropical areas, the face and predominantly the cheeks are commonly involved in addition to other body areas.

There are three main clinical subforms of the disorder.[32] The first form, which is more common in young adults, is characterised by the development of small erythematosus follicular papules with a central 'dell' representing the follicle mainly localised on the back, chest or upper arms. Sometimes, papules slowly enlarge and become pustular or nodular. Lesions may be asymptomatic or pruritic. In the second form of the disease, there are numerous small follicular papules in the chest and back. The third form, eosinophilic folliculitis (EF), is mainly seen in patients with advanced HIV-infection and consists of pustules on the trunk and face.[27,32]

Eosinophilic folliculitis in HIV infected patients has an occurrence of 9% as recently reported by Uthayakumar *et al.* [33]. Affected individuals with EF complain of a chronic intense intractable pruritus. Clinically, the skin eruption is characterised by erythematosus perifollicular papules with occasional pustules and is often heavily excoriated. Confluent erythematous plaques and urticarial lesions have also been reported. In most cases, the distribution is truncal. A peripheral eosinophilia has been reported in 25–50% of patients with HIV related EF.[34–36] Moreover, elevated serum IgE levels have been found in a high proportion of patients.[34,37]

Malassezia folliculitis has also been described in postallogeneic marrow transplant, kidney and heart transplant recipients.[14,19,28] Skin eruptions as a result of MF in these patients can easily be confused with other conditions, such as acne vulgaris, *Candida* folliculitis, chronic urticaria and other forms of folliculitis that are commonly seen in immunocompromised patients (Fig. 1). Rhie *et al.* [14] reported a series of 11 heart transplant patients who were on a standard immunosuppressive regimen with cyclosporine, prednisolone and azathioprine that developed MF. Diagnosis was confirmed microscopically in all 11 cases with culture confirmation in six cases (*M. pachydermatis* and *M. furfur* in three cases each). Recently, a minor outbreak has been reported in an intensive care unit

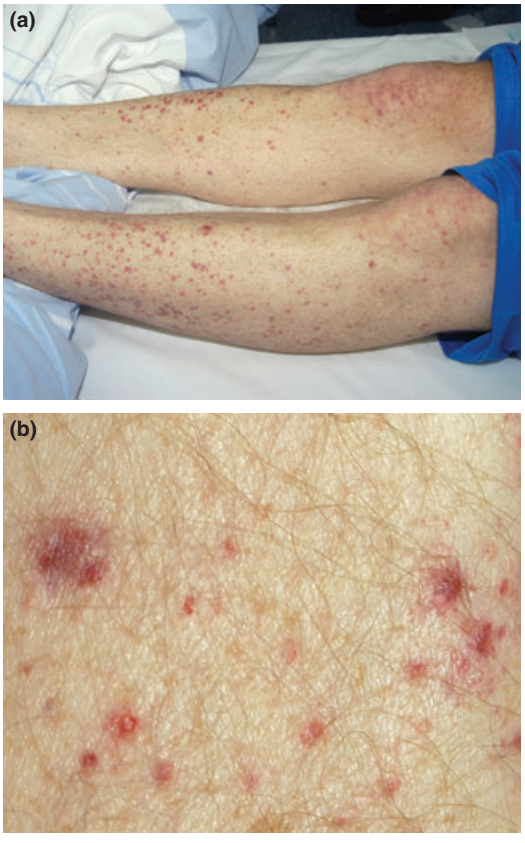

Figure 1 *Malassezia* folliculitis in a granulocytopenic patients 12 days posthematopoietic stem cell transplantation. (a) Disseminated macular-papular skin eruption. (b) The higher magnification reveals a scattered follicular lesions with minor inflammatory infiltrate. The diagnosis was confirmed by biopsy with demonstration of the organism within the follicular lesions.

in three adult patients with predisposing factors such as immunosuppression and/or antibiotic treatment.[18] In this report, *Malassezia furfur* folliculitis was related to the high temperatures and humidity in association with the lack of optimum patient skin hygiene that resulted in sebum accumulation. Another important characteristic of this mini-outbreak was the fact that it occurred simultaneously in the three patients and that they were cared in the ICU in neighbouring beds.

Histological examination of skin biopsies in patients with *Malassezia* folliculitis shows, as the name suggests, invasion and dilatation of follicles with large number of *Malassezia* yeast and rare hyphae, an inflammatory infiltrate consisting of lymphocytes, histiocytes, neutrophils and focal rupture of the follicular epithelium.[38,39] Diagnosis of MF is mainly accomplished by microscopic examination of skin scrapings of affected areas stained with 10–15% potassium hydroxide or *Albert's* solution to dissolve the keratin and debris. As *Malassezia* spp. are part of the normal cutaneous flora, their isolation in culture does not contribute to the diagnosis.

Treatment with topical application of imidazole or selenium sulphide is usually effective in the immunocompetent host. However, in cases with extensive or recalcitrant lesions and in immunocompromised individuals, systemic antifungal treatment with fluconazole or itraconazole is recommended.[32]

Seborrhoeic dermatitis

Next to pityriasis versicolor, seborrhoeic dermatitis (SD) is the second most common condition associated with *Malassezia* yeast. *Malassezia furfur*, *M. globosa*, *M. sympodialis* and *M. slooffiae* are the main causative agents associated with the development of SD. It is observed in 3–5% of the general population and is more frequent in men than in women.[11] The incidence of SD, however, is much higher in immunocompromised individuals, especially in those with AIDS, ranging from 30% to 80% in different series.[20,40–43] In a retrospective and a prospective study conducted simultaneously in the same department in 147 patients with HIV, an incidence for SD of 4.7% and 16.7% respectively was reported.[44] A similar high prevalence of SD has been observed in patients under treatment for carcinomas of the upper respiratory and digestive tracts.[45]

Seborrhoeic dermatitis represents a chronic, frequently relapsing skin disorder characterised by greasy scaly reddish patches with predilection of sebum-rich areas.[32] Lesions of SD occur primarily on the eyebrows, nasolabial folds, cheeks and interscapular region. In immunocompetent individuals, SD generally begins after puberty and becomes chronic with frequent flares, often relapsing or exacerbated in stress. In AIDS patients, the condition may be much more severe and refractory to topic therapy than in non-immunocompromised patients (Fig. 2).[46,47] The increased incidence of SD in immunosuppressed hosts, such as HIV infected patients, suggests that altered immune response plays an important role in the pathogenesis of the disease. Both cellular immunity and humoral immunity have been investigated with conflicting results. Recent reports suggest that in HIV-infected patients, the onset of seborrhoeic dermatitis is often an early sign of CD4 T-lymphocyte cell suppression.[48–50]

Topical treatment with imidazoles and low dose corticosteroids is usually effective in the treatment of SD. Oral treatment with fluconazole or itraconazole may be indicated in immunocompromised patients and are appropriate in those not responding to topical treatments.[32]

Invasive *Malassezia* infections

Epidemiology and risk factors

Information about *Malassezia* fungaemia and invasive disease is limited. A overwhelming majority of invasive infections reported in the literature have been associated with *M. furfur* and *M. pachydermatis*. *Malassezia furfur*, an obligatory lipophilic yeast and a common saprophyte in humans, has been described predominantly in conjunction with nosocomial outbreaks in neonatal intensive care units (NICU) and sporadically in severely

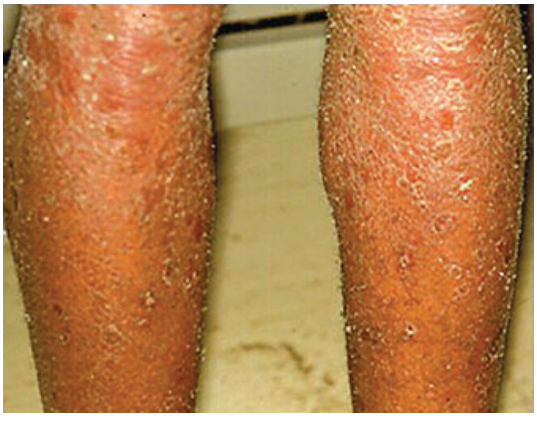

Figure 2 Generalised seborrhoeic dermatitis-like eruption in a patient with AIDS. Note the extensive greasy scaly reddish patches at a localisation atypical for seborrhoeic dermatitis in immunocompetent hosts (from Schwartz R *et al.* Seborrhoeic dermatitis: an overview. *Am Fam Physician* 2006; **74**: 125–130, with permission).

immunocompromised patients. *Malassezia pachydermatis*, in contrast, a zoophilic yeast associated with otitis externa and seborrhoic dermatitis in dogs, is only occasionally isolated from human skin, but has been implicated in nosocomial infections in hospitalised severely ill neonates.[21,22]

The first case of *Malassezia* spp. as a pathogen in bloodstream infection and sepsis was reported in 1981 by Redline *et al.*; these authors reported a case of *Malassezia* pulmonary vasculitis in an infant receiving total parenteral nutrition via an indwelling central venous catheter.[51] Until 1987, only few further reports of *Malassezia* fungaemia in infants and adults emerged.[10,52–55] During the past two decades, however, there have been numerous reports of outbreaks of invasive *Malassezia* infections in NICUs, particularly in neonates and infants receiving intravenous lipids.[21,56–59] Cases have also been described in immuno-compromised children and adults with central venous catheters and, more rarely, in patients with preceding abdominal surgery and other significant underlying conditions.[59–63]

Little systematic data exist on the frequency of invasive *Malassezia* infections in immunocompromised patients that provide information on the overall clinical relevance of this opportunistic infection. Studies investigating the colonisation of central venous lines specifically by *Malassezia* spp. have demonstrated colonisation rates of 2.4–32% in critically ill neonates and of 0.7% in unselected hospitalised adults.[52,64–66] Among 3044 bone marrow transplant patients, six (0.2%) developed *Malassezia* infections, two of which with involvement of the blood stream.[59] In a study in critically ill neonates, eight of 25 consecutive explanted central venous catheters grew *M. furfur*, and one of these infants (4%) had evidence of systemic infection.[52] While only routine blood cultures were utilised in the transplant patients, the study in neonates used media supplemented with olive oil, emphasising the importance of methodological aspects in culture-based systematic epidemiological investigations.

Whereas *Malassezia* spp. may be isolated from the skin of 3% of healthy newborn infants, 30–64% of hospitalised premature infants become colonised by the second week of life.[24,52,58] Bell *et al.* [67] reported isolation of *M. furfur* from 41% of critically ill newborns in the NICU, while less than 10% of hospitalised newborns in a non-intensive care setting were colonised. Aschner *et al.* [52] reported that 28% of infants in an NICU were colonised in the first week of life, whereas 84% of older infants in the NICU were skin culture positive for *M. furfur*. These and other data indicate that colonisation in neonates and infants is associated with low gestational age, admission to the NICU and length of hospitalisation.[68–71]

Risk factors for invasive *Malassezia* infections in neonates and infants include prematurity, the presence of a central venous catheter, use of broad-spectrum antibacterial treatment, multiple underlying complications and prolonged parenteral nutrition with administration of parenteral lipids.[58,71] While invasive infections may occur sporadically, in the last decade, nosocomial outbreaks of neonatal *M. furfur* and *M. pachydermatis* infection have been widely reported. As revealed by molecular typing methods, infants become colonised by skin contact with parents or healthcare workers, which may further transmit the organism from an infected or colonised infant to others via their hands.[21,56,58] This is well illustrated by the investigation of an outbreak of *Malassezia* pachydermatis infection in an intensive care nursery that suggested that the organism was introduced into nursery on health care workers' hands after being colonised from pet dogs at home. The organism persisted in the nursery through patient-to-patient transmission and was interrupted by improving hand-washing practices.[56] Other outbreak investigations have shown that *Malassezia* can also persist for prolonged time on incubator surfaces, providing an additional source for continued transmission.[72]

No systematic data exist on risk factors of invasive *Malassezia* infections in immunocompromised patients beyond the neonatal age. While colonisation and the presence of a central line appear to be obligatory prerequisites for fungaemia, administration of parenteral lipids may act as facilitating factor.[12,22,59]

Pathogenesis and immunology

Little is known about virulence factors and host immune responses in invasive *Malassezia* infections. *Malassezia* is able to exist in both yeast and mycelial forms, can grow under microaerophilic and anaerobic conditions and can adhere to and form biofilms on the surfaces of different materials.[73–75] It has an exceptionally thick cell wall in comparison with other yeast with an additional layer on the outside. This layer appears to be important for the organism's ability to suppress cytokine release and downregulate phagocytic uptake and killing, and elaborates a range of enzymes and metabolites including acelaic acid, which has been shown to decrease the production of reactive oxygen species in neutrophils.[73] While these factors are in support of the general ability of the organism to cause invasive disease, their biological relevance *in vivo* remains to be elucidated.

At present, it remains unclear which components of the immune system are most important in the host's defence against invasive infections. Studies examining cellular and humoral immune responses specific to *Malassezia* species in patients with superficial *Malassezia*-associated diseases and healthy controls have generally been unable to define significant differences in their immune response. *Malassezia* may not only stimulate the reticuloendothelial system and activate the complement cascade but also suppress cytokine release and downregulate phagocytic uptake and killing, and it appears that the lipid-rich external layer of the organism is pivotal in this alteration of phenotype. Thus, elucidating the non-specific immune response to *Malassezia* species may be key to understand better how these organisms live as commensals and so rarely cause invasive disease.[73]

Probably because of the sporadic nature of invasive infections, no clinical studies have addressed the immunological predisposition and responses to *Malassezia* in critically ill neonates or in immunocompromised children and adults.[73] Most patients had a serious underlying disease affecting overlapping components of host responses, had an indwelling vascular access, and had received parenteral nutrition containing lipid emulsions. As evidenced by outbreak investigations, the cutaneous commensal flora of the patient or health care workers is the usual source of the infecting organism.[1,11,56,58] Apart from contamination during insertion or following administration of a contaminated parenteral solution, catheters may become infected by migration of organism from the exit site along the outer catheter wall or from the hub through the lumen of the catheter, adherence of the organism to the catheter material with biofilm production, resulting in local replication and shedding of the organism in the blood.[71,73–77] Microbial and host factors may play a role in localising the organisms to the catheter or in progression to fungaemia and clinical sepsis.[62,78] However, even if host defences are able to clear the organism from the blood, the infection may not be resolved until the catheter is removed.

Similar to catheter-related candidaemia, catheter-related *Malassezia* fungaemia has been associated with administration of parenteral lipid emulsions. While the exact mechanisms of this association remain unclear, it is conceivable that lipids administered through the catheter may provide a growth advantage for *Malassezia*.[56,58,76,79] On the other hand, parenterally administered lipids may negatively affect host immunity by blocking the reticuloendothelial system, reducing the generation of reactive oxygen species and decreasing phagocytosis by neutrophils *in vitro* and thereby contribute to clinical disease.[73]

Clinical manifestations

The clinical signs and symptoms of *Malassezia* fungaemia and sepsis are generally non-specific. Depending on the severity of the infection, the most commonly reported symptoms in critically ill, premature infants have been fever and respiratory distress; other less frequent symptoms include lethargy, bradycardia, hepatomegaly, splenomegaly, seizures and cyanosis.[22,58,80] Respiratory distress may result in pneumonia or bronchopneumonia with an interstitial appearance on radiography. The main laboratory findings in this setting are leucocytosis or leucopenia, and thrombocytopenia. Affected patients usually are premature, low birth weight infants with multiple co-morbidities, extended hospitalisation, central venous catheters and parenteral nutrition including lipid emulsions.[10,21,54,56,81,82]

Catheter-associated *Malassezia* fungaemia is sporadic in immunocompromised children and in adults and therefore clinical manifestations are not as well described as in infants. Fever appears to be universal;[71] other symptoms and findings may include chills and rigours, myalgia, nausea and vomiting, respiratory distress with or without apnea, pneumonia, leucopenia, thrombocytosisis and less frequently, leucocytosis; signs of exit site inflammation are uncommon.[2,12,59,71] Similar to the neonatal setting, the most common patient profile includes prolonged hospitalisation, the presence of central venous catheters and the use of

Table 1 Topical and systemic agents for *Malassezia* infections in immunocompromised patients.

	Topical treatment	Systemic treatment
Malassezia folliculitis	Antidandruff shampoo, topical azoles	Oral triazoles (fluconazole, itraconazole)
Seborrhoiec dermatitis	Topical azoles, hydroxypyridones; adjuvant: tacrolimus, pimecrolimus, selenium sulphide, zinc pyrithione, coal tar, salicylic acid, steroids	Oral triazoles (fluconazole, itraconazole)
Invasive *Malassezia* infections		Intravenous triazoles (fluconazole or voriconazole), amphotericin B

intravenous fat emulsions.[12,22,59,61] Patients reported in literature presented with a variety of underlying diseases such as bowel surgery, Crohn's disease, haemorrhagic pancreatitis, cancer and bone marrow transplantation.[12,59,60,62,64,80] However, individual cases without the typical risk factors have been reported.[83,84]

Catheter-associated *Malassezia* fungaemia may result in embolic-metastatic infection of the heart and the lungs and less frequently, dissemination to other organs such as the skin, the kidneys, the pancreas, the liver, the spleen and the brain.[76,83,84] Histopathological changes include mycotic thrombi around the tips of catheters, vegetations on the endocardium, septic inflammatory lesions in the heart and the lungs.[76,80,85] Reported invasive *Malassezia* infections other than fungaemia include individual cases of *Malassezia* mastitis, thrombophlebitis, sinusitis, malignant otitis externa, meningitis, septic arthritis, soft tissue abscesses and catheter-associated peritonitis in continuous ambulatory peritoneal dialysis patients.[73,85–87]

Laboratory diagnosis

As *Malassezia* represent an uncommon cause of fungaemia and sepsis, a high index of suspicion is needed to diagnose the infection. However, while *Malassezia* fungaemia has been increasingly recognised over the past two decades, its frequency may, in fact, be higher as the current clinical data suggest. Detection is complicated by the organism's lipid-dependent nature as most routinely used media do not support its growth.[11,71] Use of lipid supplemented media may be warranted in certain specimens, especially if cultures appear sterile on routine media and yeasts have been observed on microscopy; the patients in whom this may be most appropriate are critically ill premature neonates receiving parenteral lipid emulsions through central venous lines. Supplementation of blood culture bottles with palmitic acid has been shown to improve recovery of *Malassezia* in this patient group.[11]

Malassezia spp. can be detected in blood and other specimens by direct microscopic examination, by culture and by molecular methods.[56] Examining Giemsa- or Gram-stained smears of blood or buffy coat of blood specimens obtained through the catheter is helpful and may provide the clue to culture the specimen on Sabouraud's agar overlaid with sterile olive oil or another lipid-enriched fungal medium that support growth of *Malazzesia*.[11,70,77] However, because of the time it takes to culture *Malassezia* (5 days and longer, dependent on the species) and the realisation that no single medium can reliably recover all species, the use of non-culture-based molecular diagnostic methods is appealing, but not yet ready for routine clinical use. In a small sample of four patients, the sensitivity of PCR for detecting blood culture-proven *M. furfur* fungaemia was only 25%.[88,89]

Clinical management and outcome

As invasive *Malassezia* infections are rare and larger patient series are lacking, evidence-based treatment recommendations cannot be made. However, based on the association of the disease with central venous catheters and the ability of the organism to produce biofilms, there is general consensus that the management of *Malassezia*-related fungaemia and sepsis requires the prompt removal of any indwelling catheter in addition to intravenous antifungal therapy and the temporary discontinuation of parenteral nutritional lipid solutions.[74,75,77] *In vitro* studies of superficial and invasive clinical *Malassezia* isolates consistently demonstrate susceptibility to amphotericin B and antifungal triazoles, whereas flucytosine and echinocandins appear to be inactive.[11,65,71,90–92] Thus, in the absence of experimental and comparative clinical data and the large clinical experience with invasive *Candida* infections, fluconazole or voriconazole may be rational first-line options for antifungal chemotherapy with an amphotericin B product as back-up for refractory or life-threatening infections (Table 1). While the duration of treatment has not been defined, we would advocate a course of 14 days of effective antifungal therapy after the last positive blood culture and catheter removal as recommended for invasive *Candida* infections and optional switch from initial intravenous to oral therapy depending on the individual patient's clinical response.[79]

Very little is known about the detailed morbidity and mortality of invasive *Malassezia* infections. While *Malassezia* can cause severe disease and fatal cases have been reported in untreated patients, available series of catheter-associated fungaemia in premature neonates and in immunocompromised non-neonatal patients suggest low attributable mortality with appropriate management.[12,21,56,80,93,94]

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