

REVIEW

***Malassezia* infections: A medical conundrum**

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Malassezia yeasts have long been considered commensal fungi, unable to elicit significant damage. However, they have been associated with a diversity of cutaneous diseases, namely pityriasis versicolor, *Malassezia* folliculitis, seborrheic dermatitis, atopic dermatitis, psoriasis, and confluent and reticulate papillomatosis. Several hypotheses have been proposed to explain the pathogenic mechanisms of these fungi, but none have been confirmed. More recently, such organisms have been increasingly isolated from bloodstream infections raising serious concern about these fungi. Given the difficulty to culture these yeasts to proceed with speciation and antimicrobial susceptibility tests, such procedures are most often not performed and the cutaneous infections are treated empirically. The recurring nature of superficial skin infections and the potential threat of systemic infections raise the need of faster and more sensitive techniques to achieve isolation, identification, and antimicrobial susceptibility profile. This article reviews and discusses the latest available data concerning *Malassezia* infections and recent developments about diagnostic methods, virulence mechanisms, and susceptibility testing. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2013.12.022>.)

Key words: antifungal agents; dermatomycoses; fungemia; *Malassezia*; pityriasis versicolor; seborrheic dermatitis.

Formerly called *Pityrosporum* with only 3 species recognized for a long time (*P orbiculare*, *P ovale*, and *P pachydermatis*), this genus was further revised under the name *Malassezia*.^{1,2} In 1995, the 7 species were included in *Malassezia* genus based on molecular analysis (*M furfur*, *M obtusa*, *M globosa*, *M slooffiae*, *M sympodialis*, *M pachydermatis*, and *M restricta*).³ Currently, 14 species have been isolated from human beings and animals. *Malassezia* organisms are lipid-dependent yeasts, with the exception of *M pachydermatis*.^{2,4}

Malassezia are opportunistic yeasts of increasing medical importance, causing dermatologic and systemic diseases in human beings, despite being members of the indigenous cutaneous microbial population.⁵

Classic skin diseases caused by *Malassezia* yeasts include pityriasis versicolor (PV) and *Malassezia* folliculitis. Although *Malassezia* is considered to be involved in seborrheic dermatitis and dandruff, antifungals are effective in the treatment of both conditions, and improvement of such diseases is

associated with a reduction in *Malassezia* levels^{5,6}; many aspects of the physiopathology of such diseases and the role of specific species remain yet to be elucidated. Yet unexplained remains the high frequency of seborrheic dermatitis among patients with AIDS^{1,6} and among patients with Parkinson disease.⁷

Malassezia yeasts have also been associated with psoriasis, confluent and reticulated papillomatosis,^{2,8} and atopic dermatitis.^{9,10}

Medical concern about bloodstream infections caused by emergent *Malassezia* species, notably among immunocompromised hosts, has increased.¹¹

RESULTS**Epidemiology**

The proportion of *Malassezia* species isolated from the skin varies considerably among different medical conditions and in healthy skin. Table I displays an overview of the distinct *Malassezia* species isolated in distinct conditions. Its relative prevalence also varies with age, body site, and

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geographic location. In healthy subjects from Canada, *M globosa* was the most common isolate in individuals younger than 14 years, whereas *M sympodialis* was predominant in older subjects,¹² similarly to what was found in Korea.¹³ Although the former study detected more often *M globosa* in the head and *M sympodialis* in the trunk,¹² the latter recovered *M restricta* more frequently from the head and *M globosa* from the chest.¹³

M sympodialis was reported to be the most common isolate from healthy skin in Spain,¹⁴ and in Sweden¹⁵; conversely, among healthy Japanese, *M restricta* predominated.¹⁶ Recently in the United States, sequencing of the fungal inhabitants of 10 healthy volunteers demonstrated that the *Malassezia* genus predominated in 11 distinct skin sites; *M restricta*

predominated in external ear canal, retroauricular crease, and glabella, whereas *M globosa* predominated on the back, occiput, and inguinal crease.¹⁷

Specifically related to PV, *M globosa* was the most frequent isolate in a variety of studies from distant geographic locations, including Greece,¹⁸ Spain,¹⁴ and Iran.¹⁹ Conversely, *M sympodialis* was the most common isolate in a Canadian study.²⁰

Earlier studies,^{14,15,21} using cultural and phenotypic typing methods, resulted in contradictory data about the proportion of *Malassezia* species in seborrheic dermatitis cases. Molecular quantitative techniques demonstrated that *M restricta* was persistently the most common.²²⁻²⁴ In a recent study, the majority of seborrheic dermatitis lesions showed co-colonization with 2 or more *Malassezia* species, mainly *M globosa* and *M restricta*.²⁵

The above-mentioned differences in the epidemiology of these yeasts have yet to be explained. Some authors propose that the composition of *Malassezia* microbiota is under the influence of age-related changes in sebaceous gland activity and in the fatty-acid composition of sebum.^{13,26} However, it should be taken into account that these studies used distinct methods to achieve speciation, which certainly has considerable impact in the species found. Furthermore, the variable pathogenic potential exhibited by the same species isolated from normal-appearing and diseased skin remains yet to be explained, although fungal density may interfere. Recent studies highlighted the genetic variability among implicated *Malassezia* strains.^{18,22}

In systemic infections and unlike the cutaneous disorders, the most common isolates were invariably *M furfur*,²⁷⁻²⁹ *M sympodialis*,²⁹ and *M pachydermatis*,³⁰ which may be related to a distinct pathogenic potential displayed by such species.

CAPSULE SUMMARY

- *Malassezia* interest re-emerged given its potential association with various skin diseases and bloodstream infections.
- No standardized methods for isolation, speciation, and susceptibility testing that could support therapeutic decisions are yet available.
- *Malassezia* pathogenicity mechanisms and their relation to disease and clinical manifestations remain to be elucidated.

Pathogenesis

Malassezia in the skin microflora is generally permitted to grow asymptotically, because of the leniency of the immune system. The yeasts become pathogenic when the immune balance is disturbed.³¹ The pathogen-associated molecular patterns that would otherwise induce an inflammatory response from the immune system are masked or not generated. The high lipid content of

the *Malassezia* cell wall, which provides mechanical stability and promotes osmoresistance, may favor its adhesion to host cells, protect the yeast from phagocytosis, and promote a down-regulation of the inflammatory response.⁴

PV represents one of the most common human skin diseases and the one wherein the causative relationship with *Malassezia* appears more consistent. Nevertheless, its pathogenic role does not appear to be related with the total number of organisms.²¹ Hyphae are observed in vivo in skin with excess of sebum, which seems to induce hyphae formation; such phenotype confers yeasts the ability to penetrate the host tissues.^{4,32}

Malassezia yeasts density in lesional versus non-lesional skin in patients with seborrheic dermatitis is controversial,^{21,33} suggesting that the disease may be related to an impaired immune response to the organism rather than its overgrowth.⁵ Faergemann et al³⁴ characterized the cellular profile in biopsy specimens of seborrheic dermatitis and *Malassezia* folliculitis lesions and speculated that an irritant nonimmunogenic stimulation of the immune system was involved in both conditions, evoked by products released by *Malassezia*. Yeast lipases break down sebaceous triglycerides, producing abundant unsaturated free fatty acids, which may act as irritant and immunostimulatory molecules.³² Recently, the role of *Malassezia* lipases and phospholipases as pathogenicity mechanisms in seborrheic dermatitis was enhanced by the demonstration of significant increased expression of lipase genes,²³ a finding

Table 1. Most frequent *Malassezia* species recovered from healthy skin, cutaneous and systemic conditions, according to different studies

Condition	<i>Malassezia</i> species
Healthy skin*	<i>M sympodialis</i> ¹²⁻¹⁵
	<i>M globosa</i> ^{12,13,17}
	<i>M restricta</i> ^{13,15-17}
Pityriasis versicolor*	<i>M globosa</i> ^{14,18,19}
	<i>M sympodialis</i> ²⁰
Seborrheic dermatitis*	<i>M restricta</i> ²²⁻²⁴
	<i>M globosa</i> ²⁵
Atopic dermatitis	<i>M sympodialis</i> ^{15,22}
	<i>M globosa</i> ^{15,22}
	<i>M restricta</i> ^{15,22}
	<i>M furfur</i> ^{15,22}
	<i>M obtusa</i> ^{15,22}
	<i>M slooffiae</i> ^{15,22}
	<i>M dermatitis</i> ²²
Bloodstream infections*	<i>M furfur</i> ²⁷⁻²⁹
	<i>M pachydermatis</i> ²⁹
	<i>M sympodialis</i> ³⁰

*Consensual rank between different available studies.

further supported by the in vitro induction of phospholipase activity of *Malassezia* seborrheic dermatitis isolates by β -endorphin, another putative virulence factor increased in inflammatory skin conditions.³⁵ As mentioned above, seborrheic dermatitis is more prevalent in patients with HIV/AIDS, which may be related to the CD4 T-cell lymphopenia allowing proliferation of *Malassezia* organisms, as suggested from a T-cell receptor transgenic animal model of seborrheic dermatitis—like disease.³⁶ The possibility of a distinct cutaneous lipid profile in individuals with HIV that could provide a better support for *Malassezia* growth has also been addressed, with conflicting results.³⁷⁻³⁹

A further health threat by these pathogens is their propensity to develop biofilm on skin and at the surface of indwelling medical devices. Biofilm represents a serious medical problem because it promotes resistance to antifungal drugs and acts as a reservoir for the seeding of infectious organisms at distant places.⁴⁰ Specific strains of *M pachydermatis* were able to form a 3-dimensional biofilm on plastic catheters commonly used in clinical practice.⁴¹ More recently, this finding was confirmed and expanded using *M pachydermatis* isolates from dogs; the authors unveiled that the quantity of biofilm production was directly proportional to the phospholipase activity and suggested that both could act synergistically, exacerbating lesions at topical and/or systemic level.⁴²

Particular features of *Malassezia* organisms such as its nonautoaggregation behavior and a very high

lipolytic enzyme activity may play an important role in the pathogenicity of parenteral lipid emulsion *Malassezia*-related sepsis.⁴³

Clinical presentations

PV is a chronic superficial fungal disease caused by *Malassezia* yeasts and characterized by hyperpigmented or hypopigmented, round to oval, flaking lesions, most commonly found on the trunk and upper aspects of the arms. Most patients are asymptomatic, but these lesions can be pruritic. It is most commonly found in adolescents and young adults in whom sebaceous gland activity is maximal.^{5,6}

Malassezia folliculitis, presenting as erythematous, asymptomatic, or pruritic papules and pustules on the torso, neck, and arms, is clearly associated with *Malassezia*, revealing on biopsy specimen large numbers of yeasts inside dilated hair follicles.^{6,44}

Dandruff and seborrheic dermatitis are common chronic relapsing skin diseases causing flaking and itching, considered by some authors as differing severity manifestations of a common cause.^{6,45} The former is restricted to the scalp, displaying loosely adherent oily flakes, generally not associated with overt inflammation. In the latter condition, inflammation is observed with superimposed greasy and yellowish flakes, affecting predominantly the scalp, nasolabial folds, ears, eyebrows, and the chest; it commonly affects male adolescents and young adults.^{5,6}

Atopic dermatitis is a chronic dermatitis with frequent exacerbations; high levels of specific IgE antibodies against *Malassezia* have been correlated with a particular subtype, the head and neck dermatitis.⁹ In addition, it has also been shown that a subset of these patients, recalcitrant to conventional therapy, responds to systemic antifungal agents.^{46,47} A review by Darabi et al⁴⁸ concluded that *Malassezia* allergy may contribute to some cases of refractory head and neck dermatitis.

Isolation and identification methods

Whenever the diagnosis of *Malassezia* infection is suspected and the clinical situation requires speciation, which generally has been only considered in systemic infections,²⁷ the yeast can be characterized by cultural or noncultural methods. None of the reviewed studies used skin samplings for diagnosis of infection, but as an effort to identify the implicated *Malassezia* species and to assess the epidemiology of *Malassezia* yeasts in relevant diseases.

The sampling procedures to recover *Malassezia* from clinical specimens vary among studies; there are reports about the use of contact plates,^{12,15} skin scrapings,^{49,50} tape samples,^{22,25,51} swabs,³³ and

detergent scrub techniques.²⁴ Contact plates filled with culture media enable quantitative culturing.^{12,15}

Sabouraud agar covered with sterile olive oil was initially used, but it did not allow enumeration of colonies because they coalesced.¹ Alternative media such as Leeming-Notman and modified Dixon agar are frequently used; however, the newly discovered species cannot be reliably recovered and maintained in such media.¹ More recently, efforts were made to develop a selective and differential medium, easy to prepare, that allows recovery of clinically relevant *Malassezia* species⁵¹⁻⁵³; following the modification of the chromogenic *Candida* medium with some lipid components (CHROMagar *Malassezia*, Paris, France), the authors were able to support the growth of up to 9 distinct *Malassezia* species.⁵¹

The development of molecular methods provided the possibility to identify yeasts directly from skin samples without the need to cultivate.^{22,50} The performance of such methods is mostly dependent on the sensitivity of the nucleic acid extraction procedure.⁵⁰

Phenotypical yeast identification systems such as API ID32C (BioMérieux, Marcy l'Etoile, France), Auxacolor (Bio-Rad, Hercules, CA), and Vitek 2 (BioMérieux) were compared with sequencing.⁵⁴ The authors found a correct identification of all 8 strains of *M. furfur* by Vitek 2, but misidentifications with other species, namely with *M. pachydermatis*.

Antimicrobial susceptibility profile

Antifungal susceptibility tests have been developed for these fungi to provide insights regarding the usefulness of the usually prescribed compounds.

The variety of susceptibility tests includes urea broth microdilution methods,^{55,56} a liquid medium using a colorimetric indicator for metabolic activity,⁵⁷ and a modified broth and solid Roswell Park Memorial Institute 1640 (Sigma, St Louis, MO) media.⁵⁸ All of them seem too cumbersome to be used in routine clinical testing.

Gupta et al⁵⁹ evaluated the in vitro susceptibility of *Malassezia* isolates from skin and blood to different azoles and terbinafine, unveiling that *Malassezia* species were susceptible to voriconazole, ketoconazole, and itraconazole, but showed variable susceptibility to terbinafine, namely in case of *M. furfur*, *M. globosa*, and *M. obtusa*. Conversely, Velegraki et al,⁵⁸ using the modified Roswell Park Memorial Institute media, reported a low minimal inhibitory concentration of azoles and terbinafine for all *Malassezia* species tested, but high minimal inhibitory concentration values of amphotericin B against *M. furfur*, *M. globosa*, *M. restricta*, and *M. slooffiae*. Widespread susceptibility to azoles was not

confirmed by Miranda et al⁶⁰; fluconazole minimal inhibitory concentration values were somewhat higher in comparison with the other azoles. Recently, Cafarchia et al⁶¹ described a few *M. pachydermatis* strains resistant in vitro to fluconazole. Tacrolimus exhibited antifungal effect against approximately 50% of *Malassezia* isolates, as reported by Sugita et al.²⁶

The discrepancy between in vitro susceptibility testing results and the clinical outcome, a common finding with other yeasts, eg, such as *Candida*,⁶² should also be addressed in the future with respect to *Malassezia*.

Treatment

As mentioned above, *Malassezia* yeasts could be susceptible to a wide variety of antifungal agents. Despite the attempt to control such yeasts with topical and systemic antifungals, a trend toward the recurrence of clinical signs of infection is often noticed, especially concerning PV and seborrheic dermatitis.⁶ The beneficial effects of antifungals, especially azoles, attending also to its intrinsic anti-inflammatory properties still remain to be elucidated.^{6,63,64}

Topical compounds such as tea tree oil (*Melaleuca alternifolia*),⁶⁵ tacrolimus,²⁶ honey,⁶⁶ and cinnamic acid⁶⁷ have demonstrated activity both in vitro and in vivo against *Malassezia* species, displaying simultaneously anti-inflammatory properties.⁶⁸ In the case of widespread lesions or refractory to topical treatments, oral antifungal therapy may be indicated; especially fluconazole or itraconazole have been reported to be effective in PV and seborrheic dermatitis.^{6,7} The European Medicines Agency recommendation to suspend the marketing authorizations for oral ketoconazole relegated this drug for topical use.⁶⁹

Oral terbinafine is not effective in PV,^{6,7} possibly because of a more uneven distribution at the skin surface⁶ and also considering its variable in vitro activity against *Malassezia*.⁵⁹ However, oral terbinafine efficacy in moderate to severe seborrheic dermatitis cases was demonstrated in a randomized trial using a dose of 250 mg/d for 4 weeks, an effect maintained 8 weeks after the end of treatment.⁷⁰ Oral itraconazole (200 mg/d for a week, followed by a maintenance single dose of 200 mg every 2 weeks) in cases of facial seborrheic dermatitis resulted in significant clinical improvement and a decrease of *Malassezia* organisms,⁷¹ confirming the findings of Kose et al.⁷² Nevertheless, data about oral therapy for seborrheic dermatitis are sparse, as recently reported by Gupta et al⁷³ in a systematic review.

Malassezia folliculitis is usually treated with topical antifungal agents. In more severe or refractory cases, systemic antifungals should be used to eradicate *Malassezia* organisms located deep inside the hair follicle⁷¹; oral itraconazole, 200 mg/d for 7 days, produced a significant improvement over placebo.⁷⁴

Systemic, catheter-related *Malassezia* infections are usually treated with catheter removal, discontinuation of the lipid infusion, and administration of systemic antifungal therapy.⁷⁵ Intravenous amphotericin B is the most commonly prescribed antifungal agent in such instances. Therapy with an azole may represent an alternative option, based on in vitro susceptibility results rather than clinical studies.¹¹ There are no reports yet about treatment of *Malassezia* infections, of any kind, with echinocandins.

The whole-genome sequencing of *M globosa* and *M restricta* has paved the way to a more detailed understanding of *Malassezia* biochemical adaptation to the sebum-rich skin, notably secreted proteins such as lipases, phospholipases, and oxidoreductases, which may allow the future design of therapeutic regimens specifically directed to these targets.⁴⁵

Concluding remarks

In summary, we reviewed the available data concerning *Malassezia* infections, especially its implication in frequent cutaneous diseases, such as PV and seborrheic dermatitis. Such skin disorders, often neglected or empirically medicated with topical agents labeled as antifungal and/or anti-inflammatory compounds, represent a considerable source of concern for afflicted patients. The common recurrence may seriously disturb patients' quality of life and self-esteem.

In addition to papillary skin diseases, *Malassezia* species have been increasingly reported as emergent yeasts involved in severe systemic infections, namely in newborns and immunosuppressed patients.

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