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POSITION STATEMENT

Position statement: Recommendations on the diagnosis and treatment of *Malassezia* folliculitis

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Abstract

Malassezia is a lipophilic yeast that is a part of the human mycobiome. *Malassezia* folliculitis appears when the benign colonization of the hair follicles, by the *Malassezia* yeasts, becomes symptomatic with pruritic papules and pustules. Although *Malassezia* folliculitis is common in hospital departments, diagnosing and treating it varies among dermatologists and countries. The European Academy of Dermatology and Venereology Mycology Task Force *Malassezia* folliculitis working group has, therefore, sought to develop these recommendations for the

[†]European Academy of Dermatology and Venereology (EADV) Mycology Task Force working group on *Malassezia* folliculitis.

diagnosis and management of *Malassezia* folliculitis. Recommendations comprise methods for diagnosing *Malassezia* folliculitis, required positive findings before starting therapies and specific treatment algorithms for individuals who are immunocompetent, immunocompromised or who have compromised liver function. In conclusion, this study provides a clinical strategy for diagnosing and managing *Malassezia* folliculitis.

INTRODUCTION

Malassezia (previously *Pityrosporum)* is a lipophilic yeast that is a part of the human mycobiome.[1] Research has identified 18 different species of *Malassezia*,[1–3] among which *M. furfur, M. globosa, M. restricta, M. sympodialis* and *M. pachydermatis* have most frequently been isolated from *Malassezia* folliculitis (MF) lesions.[1,2,4,5] MF results when the normally benign colonization of the hair follicles, by *Malassezia* yeasts, becomes symptomatic with the appearance of pruritic papules and pustules on seborrhoeic skin areas and is often accompanied by excoriations and hyperpigmentation.[6–10] Commonly reported predisposing factors include sweating, hot climate, exercise, high sebum production, occlusion from sunscreens and emollients, recent antibiotic or corticosteroid use or immunosuppression.[7–10] Comprehensive epidemiological data describing the prevalence of MF in the general population are lacking. Studies from hospital departments have, however, reported that the prevalence of MF was 1%–2% in China, 3% in Saudi Arabia, 4% in Turkey and 16% in the Philippines.[7,8,10,11] The principal differential diagnoses of MF include acne vulgaris, acneiform eruptions, bacterial folliculitis and eosinophilic folliculitis. Acne vulgaris is usually not pruritic and also affects, in addition to the trunk, the face and is characterized by pathognomonic comedones and papules/pustules (nodules).[6,12] Acneiform eruptions present, similar to MF, with erythematous pustules and papules on the trunk, shoulders and face and often a punch biopsy is necessary to differentiate it from MF.[13] Bacterial folliculitis often affects the deeper portions of the hair follicle and can lead to purulent secretion or even fever.[14] Eosinophilic folliculitis can have accompanying elevated eosinophil counts in the blood, and it may be associated with haematologic cancers and human immunodeficiency virus infections.[15]

As MF is common in hospital departments, diagnosing and then adequately treating it should be uniform for healthcare professionals. However, numerous diagnostic tools and treatments exist, and their use varies among dermatological experts and countries.[16] Therefore, the European Academy of Dermatology and Venereology (EADV) Mycology Task Force working group on MF developed the present position statement for the diagnosis and treatment of MF. The method and recommendations are based on the opinions of a team of experts.

MATERIALS AND METHODS

The expert committee

The expert committee comprised dermatologists of the EADV Mycology Task Force working group on MF with expertize in mycology and MF. Conflict of interest forms were collected during the process of writing the study.

Aim of the position statement and target audience

The aim was to develop recommendations for the diagnosis and management of MF. The target audience is healthcare professionals who treat MF. The results are communicated through the diagnostic and therapeutic algorithms presented in this study.

Literature review

A systematic review was conducted, which is presented in the supplementary information.

Level of recommendation

The level of recommendation by the EADV Mycology Task Force working group on MF was determined using a grading system ranging from A to D, employed by the European Society for Clinical Microbiology and Infectious Diseases.[17,18] The recommendations are as follows:

- Grade A: The EADV Mycology Task Force working group on MF strongly supports a recommendation for use.
- Grade B: The EADV Mycology Task Force working group on MF moderately supports a recommendation for use.
- Grade C: The EADV Mycology Task Force working group on MF marginally supports a recommendation for use.
- Grade D: EADV Mycology Task Force working group on MF supports a recommendation against use.

Expert opinion

The expert panel comprised 19 members of the EADV Mycology Task Force working group on MF. Consensus on diagnostic methods and treatments was reached by mailing questions, followed by two discussions via video. At the first video conference, a summary of the responses from the questionnaire was discussed and compared with the results of the systematic review. A draft including a summary of the discussion and suggestions for a consensus was circulated among the Task Force members before the second video conference was conducted. At the second video conference, a consensus on recommendations on diagnostics and treatments was reached.

Consensus

Consensus on all recommendations was defined as an agreement by at least 80% of the members of the EADV Mycology Task Force working group on MF.

RESULTS

Diagnosing *Malassezia* folliculitis

The methods for confirming the diagnosis of MF are divided into 'recommended' and 'supplementary'. The former is applied to confirm or reject the clinical suspicion of MF while the supplementary is to be considered as adjuvant means of diagnosis in cases of ambivalent results from the recommended methods.

Clinical presentation

MF presents with 2–4 mm pruritic papules and pustules on erythematous skin, often located on seborrheic skin areas, such as the upper arms and chest, back, face, neck and shoulders.[7–10,19] Excoriations and hyperpigmentation can accompany the MF lesions.[7,8] MF has also been described as presenting with cysts.[8] The absence of comedones can differentiate MF from acne vulgaris. Other clinical manifestations such as abscesses are not considered typical MF signs.

Direct microscopic examination

Direct microscopy is performed on the content of pustules, which is transferred onto a glass slide and dissolved in 10–20% potassium hydroxide (KOH).[6,8] Positive diagnostic microscopy findings include unipolar budding yeasts (blastoconidia), conidia and rarely hyphae.[6,17] Examples of staining techniques used in the literature for diagnosing MF include Parker blue, Gram staining, Methylene blue, May–Grünwald–Giemsa (MGG) and Chicago sky blue. Also, Calcofluor white/Blancophor has been used, which requires fluorescence microscopy. The diagnostic properties of Gram staining were investigated in 26 individuals with MF diagnosed as having at least two of the following criteria: (a) typical clinical presentation, (b) histopathological examination showing *Malassezia* in an inflamed hair follicle or (c) clinical response to antifungal treatment.[20] Gram staining correctly identified 22 of 26 patients with MF, with a sensitivity of 84.6%. In the same study, six patients without MF were correctly diagnosed (i.e. negative), resulting in a specificity of 100%.[20] The diagnostic properties of KOH and MGG were assessed in 49 patients with MF diagnosed by cytological examination, fungal culture and molecular analysis.[7] KOH correctly identified 40 of these patients and MGG all of them, generating a sensitivity of 81.6% and 100% respectively. As all the included patients in this study had MF, the specificity of KOH or MGG was not reported.[7]

Histopathological examination

In histopathology, a punch biopsy is taken from the central part of the hair follicle and stained with for example, haematoxylin–eosin (HE) or periodic acid–Schiff (PAS). Findings include plugged and dilated hair follicles with surrounding inflammatory eosinophils, lymphocytes, neutrophilic granulocytes and plasma cells.[6,21]

Molecular-based detection

Polymerase chain reaction (PCR) and matrix-assisted laser desorption ionization time-flight mass spectrometry (MALDI-TOF MS) can identify specific strains and genotypes of *Malassezia* and thereby support an MF diagnosis.[6,19,22–24] As *Malassezia*, however, is part of the normal skin flora, molecular diagnosis cannot, on its own, confirm a pathogenic transformation.[6,22] PCR modalities include real-time PCR, end-point PCR, restriction fragment length polymorphism (RFLP)-PCR, terminal RFLP-PCR (tRFLP) and PCR sequencing.[6,22] Neither PCR nor MALDI–TOF MS is performed routinely in most countries.

Fungal culture

Fungal culture can be conducted on various culture media, including Dixon's, Leeming–Notman agar and Ushijima's.[19,25] The results of a fungal culture can support an MF diagnosis and provide information on the susceptibility of antimycotics, but the clinician should be aware of the risk of non-pathogenic *Malassezia* growth collected from adjacent skin during sampling.[6,26] Additionally, different *Malassezia* species grow at different rates, which may bias the interpretation and, additionally, cultures may not be routinely available.[6,12]

Wood's light

In Wood's light examination, UV light (wavelength 320–400 nm) is directed towards the MF lesions, which emit a green-yellow light.[7,12,27] In 49 patients with MF diagnosed by cytological examination, fungal culture and molecular analysis, the sensitivity of Wood's light was 65.3%.[7] It is important to notice that Wood's light examination can support the clinical diagnosis but is neither genus- nor species-specific (see Table 1).

Comments on the diagnosis of *Malassezia* folliculitis

Direct microscopic examination is a non-invasive technique with high diagnostic accuracy, which is recommended when confirming the clinical suspicion of MF. Nevertheless, it is not included among the recommended diagnostic tools before starting topical antifungals. While this may introduce uncertainty about the MF diagnosis, microscopic examination is not available at all healthcare facilities, which may delay the initiation of treatment. Additionally, topical antifungals have a cure rate of 100% in some studies with mild and few adverse events (Table S5).[28,29] Therefore, we argue that the advantage of basing the diagnosis of MF on clinical examination alone outweighs the need for microscopic confirmation in this situation. It should, however, be noted that microscopic examination is included in the supplementary diagnostics, which may prove valuable in the treatment of refractory cases.

Treatments against *Malassezia* folliculitis

The evidence for treating MF is based on one randomized controlled trial that examined the effect of oral itraconazole, several comparative and non-comparative non-randomized interventional trials, observational studies and case reports. The treatment recommendations are presented in Table 2 and the evidence in Tables S5 and S6. Prophylaxis recommendations are presented below. The epidemiology of the included studies is presented in Table S7.

Topical azole and non-azole treatments

For topical regimens, the availability of medications and formulations varies between countries. Therefore, the recommendations on topical azole-containing treatments (e.g. ketoconazole or econazole) are restricted to formulations containing the active ingredient without reference to additives. Topical azole treatments identified in the literature include clotrimazole, econazole, ketoconazole, miconazole and sertaconazole. Topical non-azole treatments include propylene glycol, selenium sulfide and sulphur soap. See Table S5 for a summary of topical regimens. Side effects remain generally poorly reported for topical MF treatments with only one study reporting a burning sensation from the use of topical azoles.[30]

Oral azole treatment

Oral treatments identified in the literature for MF include fluconazole and itraconazole. There are, however, many other systemic azoles (e.g. voriconazole or posaconazole) used primarily against invasive fungal infections. In Table S6, the oral regimens reported in the literature are summarized.

Treatment of immunocompetent individuals

Altogether eight studies have assessed the effect of oral azole monotherapy or topical azole or non-azole treatment

TABLE 1 Recommendations for methods used for diagnosing *Malassezia* folliculitis and excluding differential diagnoses.

	Recommended	Supplementary
Methods for diagnosing MF	• Clinical examination • Direct microscopic examination	• Histopathological examination • Fungal culture • Wood's light examination • Optical devices (e.g. Reflectance confocal microscopy and optical coherence)
Methods for assessing differential diagnoses	• Clinical examination • Direct microscopic examination • Bacterial culture	• Histopathological examination • Fungal culture • Molecular-based diagnostic methods (e.g. PCR) • Optical devices (e.g. reflectance confocal microscopy and optical coherence)
Positive findings before starting topical treatment against MF	• Clinical examination	• Direct microscopic examination • Wood's light
Positive findings before starting systemic treatment against MF	• Clinical examination • Direct microscopic examination	• Histopathological examination • Fungal culture • Wood's light • Molecular-based diagnostic methods (e.g. PCR) • Optical devices (e.g., reflectance confocal microscopy and optical coherence)

Note: *Recommended* is applied to confirm or reject the clinical suspicion of MF and *Supplementary* is to be considered as adjuvant means of diagnosis in cases of ambivalent results from the list of recommended methods.

Abbreviations: Methylene blue, May–Grunwald–Giemsa, MGG; Periodic acid–Schiff, PAS; Potassium hydroxide, KOH.

TABLE 2 *Malassezia* folliculitis treatments recommendation.

Immunocompetent	Immunocompromised	Concurrent liver disease
Grade A Recommendation; Evidence Level		
Azoles topical 1–2 daily for 2–4 weeks; IIb Selenium sulfide once daily for 3 days, then once weekly intermittently; IIb Ciclopirox gel 0.77% or cream 1.5% or shampoo 1.5% twice daily for 2–4 weeks; NA Propylene glycol 50% in water twice daily for 3 weeks; IIB Zinc pyrithione 1% 1–2 daily for 2–4 weeks; NA	Itraconazole 100–200 mg daily for 1–4 weeks; Ib–III Fluconazole 100–200 mg daily for 2–3 weeks or 300 mg weekly for 3 weeks; III	Azoles topical 1–2 daily for 2–4 weeks; IIb Selenium sulfide once daily for 3 days, then once weekly intermittently; IIb Ciclopirox gel 0.77% cream or 1.5% or shampoo 1.5% twice daily for 2–4 weeks; NA Propylene glycol 50% in water twice daily for 3 weeks; IIb Zinc pyrithione 1–2 daily for 2–4 weeks; NA
Grade B Recommendation; Evidence Level		
Fluconazole 200 mg daily for 1–2 weeks or 200–300 mg weekly for 3 weeks; III Itraconazole 200 mg daily for 1–2 weeks; Ib–IIb	Azoles topical 1–2 daily for 2–4 weeks; IIb Selenium sulfide once daily for 3 days, then once weekly intermittently; IIb Ciclopirox gel 0.77% cream 1.5% or shampoo 1.5% twice daily for 2–4 weeks; NA Propylene glycol 50% in water twice daily for 3 weeks; IIb Zinc pyrithione 1% 1–2 daily for 2–4 weeks; NA	Itraconazole 100–200 mg daily for 1–2 weeks; Ib–IIb Fluconazole 150–300 mg weekly for 2 weeks; III
Grade C Recommendation; Evidence Level		
Terbinafine spray twice daily for 2–4 weeks; NA Combinations with comedolytics or topical antifungals; IV Isotretinoin 0.65–1.00 mg/kg/day for 3–4 months; III MAL-PDT three sessions, every other week for 7.5 minutes; III	Combination of topical and oral treatments; NA	NA

Note: It should be noted that ciclopirox gel and selenium sulfide are not available as medications in the Russian Federation.The category of evidence was assessed using the clinical guidelines published by Shekelle et al., which ranges in descending order from level I to IV.[42] Category Ia is based on evidence from meta-analyses of randomized controlled trials (RCTs), category Ib on RCTs, category IIa on non-randomized controlled studies, category IIb on quasi-experimental studies, category III on descriptive non-experimental studies and category IV on expert opinion.

Abbreviations: MAL-PDT, Methyl 5-amino-levulinic acid–Photodynamic therapy; NA, Not available.

in individuals with MF.[7,11,28,29,31–34] The treatment duration for all regimens was 2–4 weeks, and the effect was evaluated within 3 months after treatment initiation. In only two studies, the presented data confirm the exclusion of immunosuppressed individuals.[32,33]

Treatment of organ transplant recipients

Two studies have assessed the effect of oral azole or topical azole or non-azole treatments in organ transplant patients with MF, and only one of the two studies reported the treatment outcome.[35,36] Eleven heart transplant patients received topical clotrimazole 1% or selenium sulfide for 4 weeks. Those who were not cured, then received oral fluconazole 100–200 mg daily for 1–4 weeks (Tables S5 and S6).[36]

Treatment of children

While most of the previously referenced studies included both adult and paediatric patients, only two studies have presented separately the results of MF treatment in children (Tables S5 and S6).[34,37] Nine immunocompetent children received sertaconazole or clotrimazole twice daily for 2 weeks or oral itraconazole or oral ketoconazole 200 mg daily for 4 weeks.[34] In another study, five children and teenagers with treatment-resistant MF and acne vulgaris received a combination of oral and topical azoles.[37]

Oral isotretinoin

Two cases have reported the effect of oral isotretinoin 0.65 mg/kg/day for 20 weeks and 1.00 mg/kg/day for 3 months in adults with treatment-resistant MF (Table S6).[38,39]

Photodynamic therapy

A regimen of methyl 5-amino-levulinic acid (MAL) photodynamic therapy (PDT) (wavelength: 600 nm) for 7.5 min every other week for altogether three sessions was administered in six individuals. PDT was indicated because the participants either had MF refractory to oral azoles or could not receive oral therapies because of the potential hepatotoxicity owing to concurrent liver diseases (Table S6).[40]

Malassezia folliculitis prophylaxis recommendations

The prophylaxis recommendations are identical for individuals who are immunocompetent, immunocompromised or have concurrent liver disease. The recommendations are as follows:

Grade A recommendations:

- Topical azoles 1–3 times weekly
- Selenium sulfide for 3 days, then once weekly
- Ciclopirox gel 0.77% or cream 1.5% or shampoo 1.5%, once daily for 4 weeks
- Propylene glycol 50% in water twice daily for 3 weeks
- Zinc pyrithione 1% 1–3 times weekly

Grade B recommendations:

- Fluconazole 400 mg monthly
- Itraconazole 400 mg monthly

Biochemical screening before and during oral azole treatment

EADV Mycology Task Force working group on MF recommends that biochemical screening before and during systemic azole treatment should follow local or national guidelines.

Prognosis

According to published studies, up to 100% of individuals with MF relapse after the end of treatment.[29,32,41] Notably, only one study (n = 75) assessed the effect of prolonged antifungal treatment; all the patients were in remission for 2–3 months after the administration of topical ketoconazole cream or shampoo 3–4 times per week.[28] Therefore, a continued topical regimen may be useful to prevent symptomatic relapses of MF, especially in individuals with several risk factors.

Comments on treatments against *Malassezia* folliculitis

There is a high co-occurrence of MF and acne vulgaris, which are difficult to differentiate clinically, due to shared pathomechanism.[6] A study on 52 individuals compared clinical and histopathological characteristics of MF and acneiform eruption.[13] Only histopathological findings could differentiate between the two dermatoses. Fungal spores in the follicular lumen indicated MF ($p < 0.001$), while intrafollicular inflammation ($p = 0.009$), irregular keratin plugging ($p = 0.008$), and nuclear dust in the follicular lumen ($p < 0.001$) indicated acneiform eruption.[13] Individuals with concomitant MF and acne who receive antifungals may experience an improvement in MF but have a limited effect on acne. Therefore, in cases with suspected concomitant MF and acne, it may be advisable to supplement the azole treatment with anti-acne medications.

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DATA AVAILABILITY STATEMENT

Data sharing are not applicable to this article as no new data were created or analysed in this study.

ETHICAL APPROVAL

This is a position statement based on expert opinions. No ethical approval is required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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