

SPECIAL REPORT

Evidence-based Danish Guidelines for the Treatment of *Malassezia*-related Skin Diseases

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Internationally approved guidelines for the diagnosis and management of *Malassezia*-related skin diseases are lacking. Therefore, a panel of experts consisting of dermatologists and a microbiologist under the auspices of the Danish Society of Dermatology undertook a data review and compiled guidelines for the diagnostic procedures and management of pityriasis versicolor, seborrhoeic dermatitis and *Malassezia* folliculitis. Main recommendations in most cases of pityriasis versicolor and seborrhoeic dermatitis include topical treatment which has been shown to be sufficient. As first choice, treatment should be based on topical antifungal medication. A short course of topical corticosteroid or topical calcineurin inhibitors has an anti-inflammatory effect in seborrhoeic dermatitis. Systemic antifungal therapy may be indicated for widespread lesions or lesions refractory to topical treatment. Maintenance therapy is often necessary to prevent relapses. In the treatment of *Malassezia* folliculitis systemic antifungal treatment is probably more effective than topical treatment but a combination may be favourable. Key words: *malassezia*; *seborrhoeic dermatitis*; *pityriasis versicolor*; *malassezia folliculitis*; *guidelines*.

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The lipophilic yeast *Malassezia* is a common commensal of adult human skin particularly in the lipid-rich skin areas, such as the face, scalp, chest and back. The genus *Malassezia* comprise at least 14 different species: *M. furfur*, *M. sympodialis*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffiae*, *M. dermatis*, *M. japonica*, *M. nana*, *M. yamatoensis*, *M. equina*, *M. caprae*, *M. cuniculi* and *M. pachydermatis* (1). *Malassezia* can cause various skin diseases, including pityriasis versicolor (PV), *Malassezia* folliculitis and seborrhoeic dermatitis (SD), which are all common skin diseases.

Although European guidelines exist for the diagnosis and treatment of rare invasive yeast infections

including those involving *Malassezia* (2), guidelines concerning the far more common skin diseases are lacking. Therefore, a panel of experts consisting of dermatologists and a microbiologist appointed by the Danish Society of Dermatology undertook a data review and compiled guidelines on the diagnostic procedures and management of *Malassezia*-related skin diseases. The 'head and neck dermatitis', in which hypersensitivity to *Malassezia* is considered to be of pathogenic importance, is not included in this review as it is restricted to a small group of patients with atopic dermatitis.

METHODS USED TO CONSTRUCT THE GUIDELINES

Literature review and grading of evidence

A MEDLINE (PubMed) search from 1950–September 2012 was performed using the MeSH terms; *Malassezia*, *Pityrosporum*, seborrhoeic dermatitis, seborrhoeic eczema, seborrheic dermatitis, seborrheic eczema, pityriasis versicolor, tinea versicolor *Malassezia* folliculitis and *Pityrosporum* folliculitis and publications in English were reviewed irrespective of their nature (e.g. case reports, clinical trials, original research, and review articles). Additionally, cited references in these papers were retrieved. Only medications commonly available in Denmark were included. The quality of evidence (see below) was graded in each of the topics; PV, SD and *Malassezia* folliculitis. Ratings for the strength of recommendation was discussed in the panel and evidence-based treatment algorithms were developed for consensus recommendations for the management of *Malassezia*-related skin diseases. The final guideline proposal was circulated for comments among members of the DDS and members of the Danish Society for Clinical Microbiology and revised accordingly where appropriate.

Evidence- and recommendation level

The grading system for the strength of recommendation and its quality of evidence used throughout this guideline is displayed in Table I. Evidence was graded using levels of evidence developed by Shekelle et al. (3). A grading system for the strength of recommendation was based on the nomenclature used by European Society for Clinical Microbiology and Infectious Diseases (ESCMID) (4).

Limitations of the guideline

Data are based upon the publications which were available at the time when the document was prepared. Future studies may necessitate a revision of the recommendations. It is recognised that under certain conditions it may be necessary to deviate from

Table I. *Quality of evidence and strength of recommendation*

Level of evidence	Type of evidence
I-i	Evidence from meta analyses of RCT.
I-ii	Evidence from at least one RCT.
II-i	Evidence from at least one controlled study without randomisation.
II-ii	Evidence from at least one type of quasi-experimental study.
III	Evidence from descriptive studies, such as comparative, correlation, or case-control.
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.
Strength of recommendation	
Grade A	DDS strongly supports a recommendation for use.
Grade B	DDS moderately supports a recommendation for use.
Grade C	DDS marginally supports a recommendation for use.
Grade D	DDS supports a recommendation against use.

RCT: randomised controlled trial; DDS: Danish Society of Dermatology.

the guidelines. On the other hand adherence to the guideline should not constitute a defence against a claim of negligence.

PITYRIASIS VERSICOLOR

Definition

PV is a superficial fungal infection of the skin caused by *Malassezia* yeasts that under certain conditions may transform from the commensal yeast phase to a pathological mycelia phase which invades the stratum corneum. In the entire stratum corneum numerous budding yeast cells and short hyphae are found. The invasion causes a disruption of the structure of the stratum corneum which leads to an increased fragility of the affected skin areas (5).

Background and epidemiology

The prevalence of PV varies by geography and age. Thus, the prevalence is low (1–4%) in Scandinavia with the highest number in the summer season but more frequent among people living in a hot and humid climate in tropical parts of the world. The prevalence was for example reported to be 49% in Western Samoa (6–8). The disease is rare before puberty and in the elderly population. The aetiology is multifactorial and genetic susceptibility seems to play a role. Other recognised risk factors are malnutrition, oral contraceptives, immune suppression, hyperhidrosis and use of oil or greasy skincare products as well as topical corticosteroid (9–11).

Clinical presentation

PV is primarily localised to the chest, back and upper arms. Lesions of the face, skinfolds or widespread skin involvement may also occur, particularly among inhabitants in the tropics. The disease is characterised by flaky round or oval macular elements. In larger lesions flaking is often only apparent at the outer border

of the macule. Lesions are light pink, hypopigmented (a common finding in dark skin individuals) or hyperpigmented. Mild itching may accompany the visible changes (10, 12, 13).

Diagnosis

The diagnosis is made on the basis of the clinical findings and fungal microscopy. Skin scraping should be taken with curette or scalpel and examined by light microscopy. *Malassezia* cells reproducing by unipolar budding and hyphae in a meatballs and spaghetti pattern, are typical when *Malassezia* is more than just a coloniser. Wood's light (filtered UV light with a peak of 365 nm) can be used as a diagnostic tool. In Wood's light a bright yellow colour may be emitted from the lesions and thus visualise the extent of the affected skin areas. Notably, however, a negative Wood's light examination does not exclude PV as not all *Malassezia* species fluoresce.

Treatment

Several topical- and systemic medications are available for the treatment of PV (Table II). Topical agents are based on an antifungal and/or a keratinolytic effect and will usually be sufficient, whereas systemic treatment alone or in combination with topical treatment should be reserved for severe cases or infections refractory to topical treatment (14). Confirmation of the clinical diagnosis by a microscopic examination should be performed (14) prior to initiation of systemic antifungal therapy. Finally, it should be noticed that it may take several months to regain a normal skin appearance despite successful treatment, especially for hypopigmented lesions and therefore mycological cure rate is the primary treatment objective. It should be emphasised that relapses are common (15).

Topical treatment. Ketoconazole is the most extensively studied treatment approach. In a meta analysis, topical ketoconazole was associated with a mycological eradication rate of 65% compared to 45% for terbinafine (15). Based on limited data, zinc pyrithione shampoo (clinical response and mycological cure rate of 100%) (16), selenium disulphide shampoo (clinical cure rate of 76–97%) (6, 17, 18), and propylene glycol in aqueous solution (clinical response rate of 100%) (19) are all effective alternatives (Table II).

Systemic treatment. In an open-label study where patients were randomised to 2 × 300 mg doses of fluconazole one week apart or itraconazole 200 mg once daily for 7 days, the mycological eradication rate at day 30 was 97% and 80%, respectively. Two months after treatment cessation mycological treatment failure- or relapse-rate was 23% for both agents (20). In an open study, mycological eradication was obtained by 92% of the patients after treatment with 200 mg of

Table II. Dosage regimens of topical and oral treatment for pityriasis versicolor^a

Compounds	Formulation	Dose regimen	Level of evidence and strength of recommendation	References
Topical treatments				
<i>Antifungals agents</i>				
Ketoconazole	2% shampoo	Once daily for 5 days. Prophylactic treatment once daily up to 3 days in the beginning of the summer season	A I-i	(15, 24, 25)
	2% cream	1–2 times daily	B I-i	(15)
Ciclopirox olamine	1.5% shampoo	2 times weekly for 2 weeks	B I-ii	(26)
Miconazole	Cream	Twice daily	B I-ii	(27)
Clotrimazole	Cream	Twice daily for 2 weeks	B I-ii	(22)
Terbinafine	Cream, gel	Twice daily for 1 week	C I-i	(15)
<i>Miscellaneous products</i>				
Selenium sulphide	2.5% shampoo	Once daily for 3 days followed by the same procedure one week later. Maintenance therapy once every 3 rd month	B I-ii	(25, 28)
Zinc pyrithione	1% shampoo	2–3 times weekly	B II-i	(16)
Propylene glycol	50% in water	Twice daily for 2 weeks	B II-ii	(19)
Systemic treatment				
Fluconazole		300 mg weekly for 2–3 weeks	A I-ii	(29, 30)
Fluconazole		Single dose of 400 mg	B I-ii	(20, 22, 23)
Itraconazole		200 mg daily for 1 week or 100 mg daily for 2 weeks.	B I-i	(15)
		Maintenance treatment with 200 mg twice daily once a month		
Itraconazole		Single dose of 400 mg	B I-ii	(31)

^aTreatment objectives were mycological and/ or clinical cure.

itraconazole for 7 days (21). Studies comparing single versus multiple dosing of fluconazole show conflicting results (15). Mycological – or clinical response rates in the range of 65–92% have been reported after a single dose of 400–450 mg of fluconazole (22, 23).

A systematic review and meta analysis of clinical studies indicated that itraconazole and fluconazole seemed equally effective for the treatment of PV (15). However, taking into account the broader spectrum of itraconazole (and hence greater potential for selection of resistance in various fungi), together with its more variable bioavailability and greater potential for drug interactions and side effects, it is the opinion of the panel that fluconazole should be the preferred agent when systemic treatment is required.

Maintenance treatment. Few studies have focused on maintenance therapy. In a randomised double-blind placebo-controlled trial 200 mg of itraconazole twice daily one day per month for 6 months resulted in mycological eradication in 88% compared to 57% in the placebo group (21). Topical treatment with selenium disulphide was shown to reduce the relapse rate from 82% to 20% after 2 years of treatment every third month (18). Prophylactic daily treatment with ketoconazole 2% shampoo for up to 3 days in the beginning of the summer season has been recommended (evidence-level IV) (24) (Table II).

SEBORRHOEIC DERMATITIS

Definition

Seborrhoeic dermatitis (SD) is an eczema localised to the seborrhoeic areas.

Background and epidemiology

SD is a multifactorial disease where interactions between endogenous (genetic) and exogenous factors, as well as colonisation of the skin with the lipophilic yeast *Malassezia* play an aetiological role. Colonisation with *Malassezia* is rare in childhood, but increases considerably during puberty. *Malassezia* is regarded an essential player in the pathogenesis of SD. Supporting this theory, treatment with antifungals decreases the number of *Malassezia* yeasts in parallel with a clinical improvement, whilst recolonisation precedes a clinical relapse (10, 13, 32, 33). However, a clear correlation between the degree of yeast carriage and symptoms in SD patients versus healthy controls has not been found. Hence it has been suggested that *Malassezia* degradation products induce an inflammatory process in predisposed individuals (32, 34, 35).

The role of *Malassezia* spp. in the pathogenesis of infantile SD has been investigated less thoroughly. However, studies have demonstrated that *Malassezia* can be isolated in infants with infantile SD more frequently than in children with normal skin or other skin diseases (36, 37).

The prevalence of SD in immunocompetent adults is 1–3% (35). The prevalence is highest in puberty and early adulthood, followed by a second peak around the age of 50 years (35). Risk factors are immunosuppression, such as HIV infection (associated with a prevalence of SD of 34–83%), neurologic disorders such as Parkinson's disease (33, 38) as well as genetic disorders such as trisomy 21 (39). Infantile SD is seen in up to 70% of children within the first 3 months of life, but the lesions normally resolves spontaneously at the age of 8–12 months (40).

Clinical presentation

SD is characterised by poorly defined erythematous, flaking, and greasy-looking patches. Itching may occur. The scalp is almost invariably affected (41); other sites are the nasolabial folds, eyebrows, chest, genitals and intertriginous areas. The disease may become generalised in immunoincompetent individuals. Blepharoconjunctivitis may occur in isolation or it may be associated with skin lesions. SD frequently improves after sun exposure and gets worse in the winter period (33). However, flares have been reported after treatment with a combination of psoralen and UVA light (PUVA) (42). Infantile SD is characterised by cradle cap or napkin dermatitis. Cradle cap is often found together with flaking, greasy lesions affecting the eyebrows, intertriginous areas or nasolabial folds.

Diagnosis

The diagnosis is based on the clinical features. Microscopic examination of a specimen of a superficial skin scraping may demonstrate the *Malassezia* cells reproducing by unipolar budding. A positive microscopy supports the clinical diagnosis; however, a negative does not exclude it. Identification of *Malassezia* to the species level has no clinical implication or influence on the choice of treatment and is therefore, although interesting from an epidemiological perspective, not regarded necessary for routine purposes.

Treatment

In most cases, topical treatment will be sufficient (Table III). Systemic therapy may be indicated for widespread SD or lesions refractory to topical treatment.

Traditionally, treatment of SD has involved keratolytic agents or topical corticosteroids. Based on the presumed causative association between *Malassezia* and SD the current treatment is primarily based on topical antifungal agents alone or in combination with corticosteroids. Due to the relapsing nature of this disease among adults maintenance treatment will often be necessary.

Topical treatment. Shampoo with 2% ketoconazole has been shown to be more effective than the 1% formulation (Table III) (43). Topical ketoconazole, corticosteroid and calcineurin inhibitors were all found to be highly and apparently equally effective, and superior to zinc pyrithione (39, 43–52). In two different open trials of ketoconazole shampoo 2% twice weekly for 4 weeks clinical cure rates between 73% and 88% were found (43, 53). The recurrence rate after 6 months in one of these studies was reported to be 47%; a number that could be reduced to 31% and 19% by maintenance treatment with ketoconazole shampoo 2% weekly or every second week, respectively (53). A randomised trial compared hydrocortisone, miconazole and the combination of both in a 3 weeks study and found them equally effective, while maintenance treatment 2 times monthly favoured miconazole-containing preparations (54) (Table III). In the case of topical corticosteroids,

Table III. Dosage regimens of topical and oral treatment for seborrhoeic dermatitis

Products	Formulation (Treatment areas)	Instruction	Evidence level and strength of recommendation	References
<i>Topical treatments</i>				
<i>Antifungal agents</i>				
Ketoconazole	2% Shampoo (skin and scalp)	1–2 times weekly for 4 weeks. Maintenance therapy weekly or less frequent.	A I-ii	(39, 59, 52, 53, 59–60)
	2% cream (skin)	1–2 times daily for 4 weeks. Maintenance therapy weekly or less frequent.	A I-ii	
Ciclopirox olamine	1.5% shampoo (scalp)	2–3 times per week for 4 weeks. Maintenance therapy once a week.	B I-ii	(61, 62)
Miconazole	Cream (skin)	1–2 times daily	B I-ii	(54)
<i>Miscellaneous products</i>				
Selenium sulphide	2.5% shampoo (scalp)	Twice weekly for 2 weeks, followed by once weekly for 2 weeks. The treatment is repeated after 4–6 weeks.	B I-ii	(39, 63)
Zinc pyrithione	1% Shampoo (scalp)	2–3 times per week	B I-ii	(39, 43, 64, 65)
Propylene glycol	50% in water (skin)	Used at bedtime and washed out the next morning for 5 days.	B I-ii	
Tar containing products	Shampoo (scalp)	1–2 times per week	C IV	(33, 39)
<i>Adjuvant treatments</i>				
Low-potency corticosteroids	Cream, cutaneous solution (skin and scalp)	1–2 times daily.	A I-ii	(35, 41, 44, 68)
Pimecrolimus	1% cream (skin)	1–2 times daily.	A I-ii	(39, 48, 69)
Tacrolimus	0.1% ointment (skin)	1–2 times daily.	A I-ii	
<i>Systemic treatment</i>				
Itraconazole		200 mg per day for 7 days. Maintenance therapy with 200 mg per day for 2 days every month	A II-ii	(35, 57, 58, 70)

less potent formulations should be used and the duration should be limited in order to reduce cutaneous side effects. A main advantage of topical calcineurin inhibitors (tacrolimus and pimecrolimus) is that they, in contrast to corticosteroids, do not cause skin atrophy or telangiectasia. The most common adverse effect related to calcineurin inhibitors is a transient burning and tingling sensation at the application site. In 2005, the FDA raised concerns about the safety of topical calcineurin inhibitors, which resulted in a boxed warning and a medication guide about the possible cancer risk for these drugs¹. Although a direct causal link has not been established, rare reports of lymphoma and skin cancer have been reported in patients who had been receiving topical calcineurin inhibitors (45, 55).

In infants with cradle cap, treatment with oil or other moisturisers, followed by mechanical removal with a fine-tooth comb is effective. Ketoconazole 2% cream is also shown to be an effective choice with a clinical cure rate of 79% (56). Topical corticosteroids are generally effective, but should be used with caution in infants. Very mild corticosteroids are to be preferred.

Systemic treatment. Systemic treatment with itraconazole should be reserved for widespread SD and cases refractory to topical treatment (33, 34). The clinical response rates were 83% in 2 different studies after treatment with 200 mg itraconazole for 7 days (57, 58). Systemic treatment with ketoconazole should be avoided due to the risk of adverse effect in terms of liver toxicity (Table III).

MALASSEZIA FOLLICULITIS

Definition

Malassezia (pityrosporum) folliculitis is an inflammatory condition caused by infection with *Malassezia* of the sebaceous glands.

Background and epidemiology

The condition is caused by a *Malassezia* that triggers an inflammatory reaction with lymphocytes, histiocyte and neutrophils along with a focal rupture of the follicular epithelium. The ability of *Malassezia* lipases to hydrolyse triglycerides into free fatty acid may be an important factor, though the exact mechanism is still unknown (71) *Malassezia* can be detected in the sebaceous glands histologically or by direct microscopy (13). Oily skin or occlusion of the skin and hair follicles

with skin care products or cosmetics can predispose to *Malassezia* folliculitis. A warm sweaty skin is also a risk factor (72) and deterioration after sun exposure is often observed (73).

The typical patient is a young woman (12, 72), and the disease is more frequent in tropical parts of the world, most likely due to the combination of a humid and warm climate. It is common among immunosuppressed patients, diabetics, as well as in patients in broad-spectrum antibiotic treatment (13).

Clinical presentation

On the back, chest, upper arms, neck and rarely the face (12, 13) a rash of uniform, 2–3 mm large erythematous papules or pustules is seen (72). The condition may be confused with acne but comedones are absent and itching is common. In immunosuppressed patients the itchiness may, however, be less pronounced (5).

Diagnosis

The diagnosis is made on the basis of clinical findings, which should be supplemented with a specimen for fungal microscopy. A pustule is punctured with a needle and the content is applied on a microscope slide for direct microscopic examination. The fungus can also be obtained by tape stripping after the follicle top has been removed. The tape is then placed on a microscope slide where the typical microscopic finding is multiple conidia with unipolar budding and occasionally also hyphae (72). A histological examination can be performed to distinguish fungal folliculitis from other follicular diseases by fungal staining of serial sections through a hair follicle. A biopsy, microscopy or microbiological culture will distinguish *Malassezia* folliculitis from bacterial folliculitis.

Treatment

In general, the documentation for the treatment of *Malassezia* folliculitis is sparse and most published studies include only few patients. Systemic antifungal treatment is probably more effective than topical treatment, since it eliminates *Malassezia* located deeply within the hair follicles (Table IV, evidence level II-ii) (13, 74, 75). Combined systemic and topical treatment may be favourable. Maintenance treatment will often be necessary in order to avoid relapses. It may be beneficial to combine topical antifungals with a topically applied acne preparation, which has a keratolytic effect on the occluded sebaceous glands (evidence level II-ii) (76).

Topical treatment. Selenium disulphide and propylene glycol are products, which have keratolytic and antifungal activity. The clinical response rates are in a small study reported to be 88% and 100%, respectively (72). Monotherapy with miconazole or ketoconazole

¹A concern was the risk of lymphoma based on information from animal studies. Another concern was an increased risk of skin cancer, a warning which was based on the known risk of photo carcinogenicity amongst post-transplant patients, as many of them are treated with systemic calcineurin inhibitors.

Table IV. Dosage regimens of topical and oral treatment for *Malassezia folliculitis*

Product	Formulation	Instruction	Evidence level and strength of recommendation	Reference
<i>Topical treatments</i>				
<i>Antifungal agents</i>				
Ketoconazole in combination with topical acne treatment	2% shampoo	Applied on affected skin twice weekly for 2–4 weeks	A IV	(12, 80)
Ketoconazole	2% shampoo	Applied on affected skin twice weekly for 2–4 weeks	B IV	
Miconazole	Cream	Twice daily for 4 weeks	C II-ii	(75)
<i>Miscellaneous products</i>				
Selenium sulphide	2.5% shampoo	Applied on affected skin once daily for 3 days. Maintenance therapy once a week	B II-ii	(72)
Propylene glycol	50% in water	Twice daily for 3 weeks. Maintenance therapy twice weekly	B II-ii	(72)
<i>Systemic treatment</i>				
Itraconazole		200 mg daily up to 3 weeks	A I-ii	(77, 78)
Fluconazole		100–200 mg daily for 1–4 weeks	B III	(79, 80)
Fluconazole		300 mg once weekly for 1–2 months	B IV	(82)
Isotretinoin		Dosed as in the treatment of acne	C III	(81)

have response rates of 10–12% (74, 75). Econazole as monotherapy has a response rate of 10–80% (Table IV) (72, 75).

Systemic treatment. Treatment with itraconazole 200 mg daily for 3 weeks resulted in clinical improvement in 93% (77), whereas 84% responded to treatment with itraconazole 200 mg daily for one week (78). Treatment with fluconazole has also been reported to be effective (79, 80). Systemic treatment with isotretinoin, which is sebo-suppressive, may be used in severe cases. The evidence is, however, limited to a single case report (81) (Table IV).

CONCLUSION

PV, SD and *Malassezia folliculitis* are frequent skin diseases. The clinical diagnosis of PV or *Malassezia folliculitis* can be confirmed by a microscopic examination of the yeasts and this is recommended prior to systemic antifungal treatment. A positive microscopy supports the clinical diagnosis of SD but a negative does not exclude it. A fungal culture of *Malassezia* has no clinical relevance. Most patients with SD or PV will be sufficiently treated with topical agents but maintenance therapy is often necessary to prevent relapses. Topical antifungal azoles are the most extensively studied and are recommended as first line treatment. A short course of topical corticosteroid or topical calcineurin inhibitors has an anti-inflammatory effect and may be beneficial in the treatment of SD. For widespread lesions of PV and in cases refractory to topical treatment systemic therapy with fluconazole or itraconazole may be used. The effect of these 2 agents seems to be equivalent. However, due to the variable bioavailability of itraconazole and greater potential for drug interactions and side effects fluconazole should be the preferred agent when systemic treatment is required. Furthermore, itraconazole has a broader antifungal spectrum compared to fluconazole

which may contribute to the selection of azole resistant species. Owing to the lack of scientific evidence of the effect of fluconazole, itraconazole should be first choice if systemic agents are needed in the treatment of SD. Still, more studies are needed in order to clarify the optimal dose and duration of systemic treatment. In the treatment of *Malassezia folliculitis* systemic antifungal treatment is probably more effective than topical treatment but a combination of the two may be favourable. Maintenance treatment is often necessary. Scientific evidence for the treatment of *Malassezia folliculitis* is sparse and calls for well conducted clinical trials.

These expert recommendations by the Danish Society of Dermatology and approved by the Danish Society for Clinical Microbiology constitute the first detailed, evidence-based clinical guidelines for the management of *Malassezia* related skin disease.

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