Invited Article

Malassezia (Pityrosporum) Infections of the Skin

Jan Faergemann

Department of Dermatology Sahlgrenska University Hospital

=Abstract=

The lipophilic yeast *Pityrosporum ovale* (*Malassezia* sp.) is a member of the normal human cutaneous flora in adults but also associated with several skin diseases.

Treatment of *P. ovale* related diseases include topical and systemic antifungal therapy. In pityriasis versicolor, under the influence of predisposing factors, *P. ovale* changes from the round blastospore form to the mycelial form. Pityriasis versicolor may be treated with topical treatment. However, with more extensive lesions, in patients with recurrence of the disease or patients not responding to topical therapy short term treatment with oral antifungal drugs is very effective. Recurrence is a great problem in pityriasis versicolor with a recurrence rate of 60% within 1 year. To avoid this oral ketoconazole 400 mg once monthly or 200 mg on 3 consecutive days every months have a documented effect. *Pityrosporum* folliculitis is a chronic disease characterized by pruritic follicular papules and pustules located primarily on the upper trunk, neck and upper arms. In direct microscopy clusters of round budding yeast cells are found. The same treatments used for pityriasis versicolor are effective in the treatment of *Pityrosporum* folliculitis. However, the treatment period has to be prolonged. With topical therapy 3 to 4 weeks of daily treatment and then prophylactic therapy once or twice weekly is often necessary to first clear the disease and then to avoid recurrence. However, due to the presence of *P. ovale* deep down in the follicle several patients will not be completely cleared with topical therapy and systemic therapy may be necessary. There are now many studies indicating that *P. ovale* plays an important role in seborrheic dermatitis. Many of these are treatment studies showing a good effect of antimycotics parallelled by a reduction in number of organisms. Severe seborrheic dermatitis often difficult to treat is associated with AIDS. In peripheral blood from a high number of patients with seborrheic dermatitis we found an increase in number of natural killer T-cells and decreased PHA and Con-A stimulation. Secondary we found low serum IgG antibody titres in patients compared to controls. Other studies have found a reduced lymphocyte stimulation reaction when lymphocytes from patients with seborrheic dermatitis were stimulated with a *P. ovale* extract. Additionally, IL-2 and IFNγ pruduction by lymphocytes from patients was markedly depressed and IL-10 sythesis were increased after stimulation with *P. ovale* extract. Several studies have clearly documented that antifungal therapy is very effective in the treatment of seborrheic dermatitis. **[Kor J Med Mycol 3(1): 7-14]**

Key Words: *Malassezia* infection, *Pityrosporum* folliculitis, Pityriasis versicolor, Seborrheic dermatitis

Corresponding author: Jan Faergerman, M.D., Ph.D. Department of Dermatology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden

INTRODUCTION

Pityrosporum or *Malassezia* can now be divided into 7 different species, 6 are lipophilic and 1 is non-lipophilic. However, if this has any practical clinical relevance is still too early to say. The lipophilic *Pityrosporum (Malassezia)* yeasts requires the addition of lipids to the culture medium for optimal growth[1,2]. They are members of the normal human cutaneous flora and can be cultured from almost all body areas[3~6]. However, under the influence of predisposing factors they become pathogenic and they are associated with several diseases such as pityriasis versicolor, *Pityrosporum* folliculitis, seborrheic dermatitis, some forms of atopic dermatitis, some forms of confluent and reticulate papillomatosis and systemic infections. For practial reasons the word *P. ovale* will be used for the lipophilic *Pityrosporum* or *Malassezia* yeasts in the rest of this section.

PITYRIAISIS VERSICOLOR

Pityriasis versicolor is a chronic superficial fungal disease usually located on the upper trunk, neck or upper arms. Lesions are slightly scaling and papular or nummular. They may coalese to involve greater parts of the body and may vary in color from red to brown to white. The spores and short hyphae of *P. ovale* can be detected by microscopy. Under the influence of predisposing factors *P. ovale* changes in pityriasis versicolor from the round blastospore form to the mycelial form. The most important exogenous factors are high temperatures and a high relative humidity which probably explain why pityriasis versicolor is more common in the tropics. The most important endogenous factors are greasy skin, hyperhidrosis, hereditary factors, corticosteroid treatment and immunodeficiency.

Pityriasis versicolor has a worldwide distribution. In tropical areas it has been reported in 30 to 40% of the population. The incidence is much lower in temperate climates (1 to 4%). Pityriasis versicolor is generally a disease of postpubertal and mature ages when the sebaceous glands are most active and is generally seen in otherwise healthy people. It is found on skin where sebaceous glands are present, and it is most often localized to the sebaceous areas of the trunk, often occluded by clothing. However, in the tropics it is more often localised to the face. Lesions are slightly scaling, papular, nummular or confluent and vary from red to brown to white. Without treatment pityriasis versicolor is a chronic disease and after treatment recurrence is an outstanding problem, reaching 60% one year after treatment and 80% after 2 years.

The diagnosis is primarily based on the typical clinical picture in combination with bright yellow fluorescence under Wood's light examination and direct microscopy. Direct microscopy is of major importance. Potassium hydroxide (20%) wet smears can be used, but the tape method is very easy. Thin layers of stratum corneum containing the fungus can be obtained by stripping with tape. The section of the tape containing the fungi can be stained with methylene blue (1%, 1 minute). The round budding cells and hyphae ("spaghetti and meatballs") can easily be identified.

There are numerous ways of treating pityriasis versicolor topically, with many different formulation alternatives[7~17]. The patients should treat the whole trunk, neck, arms and legs down to the knees even when small areas are involved. A cheap, effective and cosmetically elegant treatment is to use propylene glycol 50% in water[7]. This is applied twice daily for 2 weeks with excellent results and with very little risk of skin irritation. Another treatment is to use ketoconazole as a cream[14] or more recently even in a foam solution[17]. Topical application of bifonazole[13], clotrimazole[8], econazole[10], or miconazole[9] once or twice daily for 2 weeks, is also effective. Another effe-

ctive treatment is zinc pyrithione shampoo[33]. It is applied on affected areas after showering, allowed to remain for approximately five minutes, and then rinsed off. This procedure should be repeated every evening for two weeks. Selenium sulphide is also effective[12], but the patient sometimes complains about the offensive odor and stinging sensation on the skin after application.

Ciclopiroxolamine 0.1% solution (Hoechst, Germany) applied once daily for 4 weeks were effective in 86% of 90 treated patients at a follow up visit 4 weeks after the last day of treatment[16]. Terbinafine, a new orally and topically active allylamine antifungal derivative is orally active primarily against dermatophytes. Topically it has been effective in the treatment of pityriasis versicolor in a 1% cream formulation aplied once daily for 4 weeks[15]. In a single blind comparative study against bifonazole 1% cream 100% were cleared in the terbinafine group after 4 weeks[15].

Systemic therapy is primarily indicated for extensive lesions, for lesions resistant to topical treatment, and for frequent relapse. However, with short term treatment the risk of side effects with systemic therapy may be minimized and oral antifungals may therefore be used even for other indications (Table 1). Ketoconazole is an effective oral drug, with a broad antmycotic spectrum[18]. Overall, results have shown cure rates of 92% with a mean treatment period of four weeks[18~21]. However, with longer treatment periods the risk for serious liver reactions, seen with oral ketoconazole, will increase[18]. Hay et al have treated patients successfully with 200 mg tablets once daily for 5 days[20]. Rausch and Jacobs have shown that even one single dose of 400 mg may be effective[21]. The risk of side effects is minimized with short-term treatment.

Itraconazole, a triazole derivative developed by Janssen, Belgium, has been shown to be effective orally in several well conducted, controlled trials[22~23]. An effective treatment schedule is 200 mg daily for five to seven days[22]. The risk for serious side effects ecpecially liver toxicity is much lower for itraconazole than for ketoconazole.

Fluconazole, a triazole derivative developed by Pfizer, Central Research, England has also been used in the treatment of pityriasis versicolor in a single dose of 400 mg[24].

The high rate of recurrence, reaching 60% in one year and 80% after two years, is an outstanding problem in pityriasis versicolor. Recurrence is due to the presence of predisposing factors, which may be difficult to eradicate. A permanent cure is therefore difficult to achieve, which explains the chronicity. Consequently, a prophylactic treatment regimen is necessary to avoid recurrence (Table 2). An effective prophylactic treatment is 200 mg ketoconazole on three consecutive days every month[19]. Rausch and Jacobs have used a single dose of 400 mg ketoconazole every month as an effective prophylaxis in pityriasis versicolor[21]. Topically prophylactic treatment shedules may also be used but the patient compliance is much lower.

Table 1. Systemic treatment for pityriasis versicolor

Ketoconazole: 400 mg single dose. More effective is 200 mg once daily for 7 days.
Itraconazole: 200 mg once daily for 7 days.
Fluconazole: 300 mg once weekly 2 or 3 times.

PITYROSPORUM FOLLICULTIS

Pityrosporum folliculitis is characterized by follicular papules and pustules localized to the

Table 2. Prophylactic treatment of pityriasis versicolor

The recurrence rate is 60 % after one year.
Ketoconazole 400 mg once monthly.
Ketoconazole 200 mg on 3 consecutive days every month.
Topical treatment?

Table 3. Treatment of *Pityrosporum* folliculitis

Topical treatment for 3 to 4 weeks.
Ketoconazle 200 mg for 4 weeks.
Itraconazole 200 mg daily for 1 week/month twice.
Fluconazole 300 mg once weekly 4 to 6 times.
Prophylactic topical treatment once or twice every week.

back, chest, upper arm, sometimes the neck, and more seldom the face. It is often associated with a troublesome itching. The first well-documented study of *Pityrosporum* folliculitis was reported by Potter and co-workers in 1973[25]. This was later questioned, but today several studies indicate that *P. ovale* is the etiologic agent of *Pityrosporum* folliculitis[25~28].

Under the influence of predisposing factors, *Pityrosporum* folliculitis may be explained by an extensive growth following dominance of *P. ovale* in the hair follicle. Local occlusion may play an important role. The inflammation may be due both to products produced by the yeast and to free fatty acids produced as a result of the lipase activity of the fungus. The diagnosis is based on a typical clinical picture with itching papules and pustules as the dominating symptoms, direct microscopy in combination with histopathology and the effect of antimycotic treatment. The distribution of lesions, the itching and the lack of comedones differentiate the condition from acne. Other important differential diagnoses are other forms of folliculitis, systemic and cutaneous candidiasis, neurotic excoriations, chronic urticaria and other pruritic conditions.

The effect of antimycotic treatment is often dramatic[26~28] (Table 3). Many different treatments and treatment schedules have been used [26~28]. I prefer propylene glycol, 50% in water is an effective treatment. It is applied twice daily with a gauze pad for 3 weeks and, after that, twice weekly as maintenance therapy[26]. Other documented effective topical treatments include the imidazoles and selenium sulfide[26,28].

Not all cases respond well to topical treatment. In patients with extensive lesions or in those who do not respond to topical treatment, oral ketoconazole may be an effective alternative[28]. Itraconazole and fluconazle are also effective (Table 3). Lesions and itching will recur in most patients if treatment is not maintained intermittently. Therefore, a prophylactic treatment schedule, such as treatment once or twice a week, is mandatory.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is characterized by inflammation and desquamation in areas with a rich supply of sebaceous glands, namely the scalp, face and upper trunk. Dandruff id the mildest manifestation of the disease. Seborrheic dermatitis is a common disease, and the prevalence ranges from 2 to 5% in different studies[29~31]. It is more common in males than in females[31]. The disease usually starts during puberty and is more common around 40 years of age[31].

There are many studies indicating that *P. ovale* plays an important role in seborrheic dermatitis[32~36]. Many of these are treatment studies which describe effectiveness of antimycotics, paralleled by a reduction in number of *P. ovale*, and recolonization leading to a recurrence of seborrheic dermatitis[33~35].

The increased incidence of seborrheic dermatitis in patients with immunosuppressive disorders suggests that the relationship between *P. ovale* and the immune system is of importance[37~38]. In one study we found that several patients with seborrheic dermatitis had an impaired immune response with increased frequencies of natural killer cells and subnormal mitogen stimulation responses[39]. Other studies have found a reduced lymphocyte stimulation reaction when lymphocytes from patients with seborrheic dermatitis were stimulated with a *P. ovale* extract[40]. Additionally, IL-2 and IFNγ pruduction by lymphocytes from patients was markedly depressed and IL-10 synthesis was

Table 4. Treatment of seborrheic dermatitis

Scalp: Antifungal shampoo e.g. ketoconazle shampoo twice weekly for 4 weeks and then once weekly as prophylaxis.
Skin: Antimycotic cream e.g ketoconazole twice daily for 3 to 4 weeks and then prophylactically once or twice weekly.

increased after stimulation with *P. ovale* extract. The lipid amount on the skin in patients with seborrheic dermatitis was significantly higher than in controls. In conclusion impaired cell mediated immunity may facilitate fungal survival in the skin and also contribute to a low T-cell dependent antibody response. The inflammatory response to *P. ovale* products would not be downregulated, and therefore an increased inflammatory response would occur and the dermatitis triggered.

Mild corticosteroid solutions, creams or ointments are effective in the treatment of seborrheic dermatitis due to a nonspecific antiinflammatory activity. However, they apparently have no effect on *P. ovale* because seborrheic dermatitis recurs quickly when corticosteroids are used, often within a few days after treatment has ended.

Antifungal therapy for *P. ovale* is effective in treating most cases of seborrheic dermatitis and prophylactic treatment with antifungal drugs reduces the recurrence rate much more than corticosteroids[32~35,41~46] (Table 4). Ketoconazole is very effective *in vitro* against *P. ovale* with mimimum inhibitory concentrations (MICs) in the range of 0.02 to 0.5 μg/ml. Oral ketoconazole has been effective in a double-blind placebo-controlled trial in patients with seborrheic dermatitis of the scalp and other areas[41]. However orally ketoconazole should be reserved for patients not responding to topical therapy. In another double-blind, placebo-controlled study ketoconazole 2% cream has been effective in the treatment of seborrheic dermatitis of the scalp and face[34], and in a comparative study between ketoconazole and hydrocortisone cream no difference was seen in effectiveness[42].

Ketoconazole shampoo used twice weekly is very effective in treating seborrheic dermatitis of the scalp[35,46]. In a double-blind placebo-controlled study of ketoconazole shampoo used twice weekly for 4 weeks, 89% of the ketoconazole group was cured, compared with only 14% in the placebo group[35]. Ketoconazole used once weekly has also been effective in preventing recurrence of dandruff in previously treated patients[46].

Other topical antimycotics are effective in the treatment of seborrheic dertmatitis[33,43~45]. Shampoos containing zinc pyrithione[43] or selenium sulfide[32] are effective and widely used. Propylene glycol solutions has also been used successfully[44].

In patients not responding to topical anfungal drugs itraconazole may be effective.

ATOPIC DERMATITIS

There are now several studies indicating that *P. ovale* may be an important allergen in some patients with atopic dermatitis, expecially in adult patients with atopic dermatitis localized to the scalp, face and neck[47]. We have found that 78% of patients with this distribution of atopic dermatitis were prick-test positive to a protein *P. ovale* extract[47]. In a double-blind study many of these patients were cured with oral ketoconazole[48]. Recently, in a study by Kroger and co-workers it has been shown that *P. ovale* extracts increased IL-4, IL-10 and IgE synthesis in patients with atopic dermatitis[49].

CONCLUSION

Our knowledge about pathogenesis and treatment of pityriasis versicolor, *Pityrosporum* folliculitis and seborrheic dermatitis has increased

tremendously during the last 10 years. Today we have more effective treatments for the more severe forms of these diseases. However, due to the presence of various predisposing factors recurrence is a major problem in all 3 diseases and to avoid this a prophylactic treatment schedule is mandatory.

REFERENCES

1. Porro MN, Passi S, Caprill F, et al. Growth requirements and lipid metabolism of *Pityrosporum orbiculare*. J Invest Dermatol 1976; 66: 178-182
2. Wilde PF, Stewart PS. A study of the fatty acid metabolism of the yeast *Pityrosporum ovale*. Biochem J 1968; 108: 225-231
3. Gordon MA. The lipophilic microflora of the skin. Mycologia 1951; 43: 524-534
4. Roberts SOB. *Pityrosporum orbiculare*: Incidence and distribution on clinical normal skin. Br J Dermatol 1969; 81: 264-269
5. Faergemann J, Aly R, Maibach HI. Quantitative variations in distribution of *Pityrosporum orbiculare* on clinically normal skin. Acta Derm Venereol (Stockh) 1983; 63: 346-348
6. Faergemann J, Fredriksson T. Age incidence of *Pityrosporum orbiculare* on human skin. Acta Derm Venereol (Stockh) 1980; 60: 531-533
7. Faergemann J, Fredriksson T. Propylene glycol in the treatment of tinea versicolor. Acta Derm Venereol (Stockh) 1989; 60: 92-93
8. Fredriksson T. Topical treatment with BAY b 5097, a new broad spectrum antimycotic agent. Br J Dermatol 1972; 86: 628-630
9. Svejgaard E. Double-blind trial of miconazole in dermatomycosis. Acta Derm Venereol (Stockh) 1973; 53: 497-499
10. Swartz KJ, Moch TH, Kenzelmann M. Poloklinische Prüfung von Econazole bei 594 Fallen von Hautmykosen. Dtsch Med Wchr 1975; 100: 1497-1500
11. Faergemann J, Fredriksson T. An open trial of the effect of a zinc pyrithione shampoo in tinea versicolor. Cutis 1980; 25: 667-669
12. Albright SD, Hitch JM. Rabbit treatment of tinea versicolor with selenium sulphide. Arch Dermatol 1966; 93: 460-461
13. Hernandez-Perez E. A comparison between one and two week's treatment with bifonazole in pityriasis versicolor. J Am Acad Dermatol 1986; 14: 561-564
14. Savin RC, Horwitz SN. Double-blind comparison of 2% ketoconazole cream and placebo in the treatment of tinea versicolor. J Am Acad Dermatol 1986; 15: 500-503
15. Aste N, Pau M, Pinna AL, Colombo MD, Biggio P. Clinical efficacy and tolerability of terbinafine in patients with pityriasis versicolor. Mycoses 1991; 34: 353-357
16. Corte M, Jung K, Linker U, et al. Topical application of a 0.1% ciclopiroxolamine solution for the treatment of pityriasis versicolor. Mycoses 1989; 32: 200-203
17. Rekacewicz I, Guillaume JC, Benkhraba F, et al. A double-blind placebo-controlled study of a 2 percent foaming lotion of ketoconazole in a single application in the treatment of pityriasis versicolor. Ann Dermatol Venereol 1990; 117: 709-711
18. Jones HE. Ketoconazole today. A review of clinical experience. ADIS Press, Manchester, England, 1987
19. Faergemann J, Djärv L. Tinea versicolor: Treatment and prophylaxis with ketoconazole. Cutis 1982; 30: 542-545
20. Hay RJ, Midgley G. Short course ketoconazole therapy in pityriasis versicolor. Clin Exp Dermatol 1984; 9: 571-573
21. Rausch LJ, Jacobs PH. Tinea versicolor: Treatment and prophylaxis with monthly administration of ketoconazole. Cutis 1964; 34: 470-471
22. Delescluse J. Itraconazole in tinea versicolor. A review. J Am Acad Dermatol 1990; 23: 551-554
23. Faergemann J. Treatment of pityriasis versicolor with itraconazole. A double-blind placebo-controlled study. Mykoses 1988; 31: 377-379
24. Faergemann J. Treatment of pityriasis versicolor with a single dose of fluconazole. Acta Derm Venereol (Stockh) 1992; 72: 74-75
25. Potter BS, Burgoon CF, Johnson WC. *Pityro-*

sporum folliculitis. Arch Dermatol 1973; 107: 388-391

26. Bäck O, Faergemann J, Hörnqvist R. *Pityrosporum* folliculitis: A common disease of the young and middle-aged. J Am Acad Dermatol 1985; 12: 56-61
27. Faergemann J, Johansson S, Bäck O. An Immunologic and cultural study of *Pityrosporum* folliculitis. J Am Acad Dermatol 1986; 14: 429-433
28. Ford GP, Ive FS, Midgley G. *Pityrosporum* folliculitis and ketoconazole. Br J Dermatol 1982; 107: 691-695
29. Johnson M-L T, Roberts J. Prevalence of dermatological diseases among persons 1 to 74 years of age. Publication no. (PHS). Washington DC, US Department of Health and Human Services. 1977; 79-1660
30. Garcie RL. Skin disorders in airforce recruits. J Ass Mil Dermatol 1976; 2: 61
31. Ratzer M. The incidence of skin diseases in the west of Scotland. Br J Dermatol 1969; 81: 456-461
32. Shuster S. The aetiology of dandruff and the mode of action of therapeutic agents. Br J Dermatol 1984; 111: 235-242
33. Faergemann J. Seborrheic dermatitis and *Pityrosporum orbiculare*: Treatment of seborrheic dermatitis of the scalp with miconazole-hydrocortisone (Daktacort), miconazole and hydrocortisone. Br J Dermatol 1986; 114: 695-700
34. Skinner RB, Noah PW, Taylor RM, et al. Double-blind treatment of seborrheic dermatitis with 2% ketoconazole cream. J Am Acad Dermatol 1985; 12: 852-857
35. Faergemann J. Treatment of seborrheic dermatitis of the scalp with ketoconazole shampoo. Acta Dermato-Venereol (Stockh) 1990; 70: 171-172
36. Bergbrant I-M. Seborrheic dermatitis and *Pityrosporum ovale*: Cultural, Immunological and Clinical Studies. Acta Derm Venereol (Stock) 1991, Suppl 167
37. Berger RS, Stoner MF, Hobbs ER, et al. Cutaneous manifestation of early human immunodeficiency virus exposure. J Am Acad Dermatol 1988; 19: 298-303
38. Mathes BM, Douglass MC. Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. J Am Acad Dermatol 1985; 13: 947-951
39. Bergbrant I-M, Johansson S, Robbins D, et al. An immunological study in patients with seborrheic dermatitis. Clin Exp Dermatol 1991; 16: 331-338
40. Neuber K, Kröger S, Gruseck E, Abeck D, Ring J. Effects of *Pityrosporum ovale* on proliferation, immunoglobulin (IgA, G, M) synthesis and cytokine (IL-2, IL-10, IFNγ) production of peripheral blood mononuclear cells from patients with seborrheic dermatitis. Arch Dermatol Res 1996; 288: 532-536
41. Ford GP, Farr PM, Ive FA, et al. The response of seborrheic dermatitis to ketoconazole. Br J Dermatol 1984; 111: 603-607
42. Stratigos ID, Katamboas A, Antoniu CH, et al. Ketoconazole 2% cream versus 1% hydrocortisone cream in the treatment of seborrheic dermatitis: A double-blind comparative study. J Am Acad Dermatol 1988; 19: 850-853
43. Marks R, Pears AD, Walker AP. The effects of a shampoo containing zinc pyrithione on the control of dandruff. Br J Dermatol 1985; 112: 415-422
44. Faergemann J. Propylene glycol in the treatment of seborrheic dermatitis of the scalp: A double-blind study. Cutis 1988; 42: 69-71
45. Faergemann J. Treatment of seborrheic dermatitis with bifonazole. Mycoses 1989; 32: 309-311
46. Brown M, Evans TW, Pounirt, et al. The role of ketoconazole 2% shampoo in the treatment and prophylactic management of dandruff. J Dermatol Treat 1990; 1: 177-179
47. Kieffer M, Bergbrant I-M, Faergemann J, et al. Immune reactions to *Pityrosporum ovale* in adult patients with atopic and seborrheic dermatitis. J Am Acad Dermatol 1990; 22: 739-742
48. Hjorth N, Clemensen OH. Treatment of Dermatitis of the head and neck with ketoconazole in patients with type I hypersensitivity for *Pityrosporum orbiculare*. Semin Dermatol 1983;

2: 26-29

49. Kroger S, Neuber K, Gruseck E, Ring J, Abeck D. *Pityrosporum ovale* extracts increase interleukin-4, interleukin-10, and IgE synthesis in patients with atopic eczema. Acta Derm Venereol (Stockh) 1995; 75: 357-360