

# Management of cutaneous fungal infections.

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## Introduction

The cutaneous mycoses are superficial fungal infections of the skin, hair or nails. Essentially no living tissue is invaded, however a variety of pathological changes occur in the host because of the presence of the infectious agent and/or its metabolic products. The principle aetiological agents are dermatophytic moulds belonging to the genera *Microsporum*, *Trichophyton* and *Epidermophyton* which cause ringworm or tinea of the scalp, glabrous skin and nails; *Malassezia furfur*, a lipophilic yeast responsible for pityriasis versicolor, follicular pityriasis, seborrhoeic dermatitis and dandruff; and *Candida albicans* and related species, causing candidiasis of skin, mucous membranes and nails. The usual approach to the management of cutaneous infections is to treat with topical agents if possible, but nail and hair infections, widespread dermatophytosis and chronic non-responsive yeast infections are best treated with oral antifungal agents. Topical agents include Nystatin; the Imidazoles such as Clotrimazole, Miconazole, Econazole, Ketoconazole and Bifonazole; Terbinafine and Tolnaftate. Oral agents include Griseofulvin, Ketoconazole, Fluconazole, Itraconazole, and Terbinafine.

## **Pityriasis (tinea) versicolor, follicular pityriasis, seborrhoeic dermatitis and dandruff.**

Pityriasis versicolor is a chronic, superficial fungal disease of the skin characterised by well-demarcated white, pink, fawn, or brownish lesions, often coalescing, and covered with thin furfuraceous scales. The colour varies according to the normal pigmentation of the patient, exposure of the area to sunlight, and the severity of the disease. Lesions occur on the trunk, shoulders and arms, rarely on the neck and face, and fluoresce a pale greenish colour under Wood's ultra-violet light. Young adults are affected most often, but the disease may occur in childhood and old age. The causative agent is *Malassezia furfur*, a lipophilic yeast living on the skin as part of the normal flora. The diagnosis may be confirmed in most cases by direct microscopic examination of skin scrapings mounted in 10% KOH with Parker ink to show the characteristic spherical yeast cells and short pseudohyphal elements typical of the fungus. Culture is unnecessary as direct microscopy is diagnostic.

The most appropriate antifungal treatment for pityriasis versicolor is to use a topical imidazole or terbinafine in a solution, gel or lathering preparation. Ketoconazole shampoo has proven to be very effective. Alternative treatments include zinc pyrithione shampoo or selenium sulfide lotion applied daily for 10-14 days or the use of propylene glycol 50% in water twice daily for 14 days. In severe cases with extensive lesions, or in cases with lesions resistant to topical treatment or in cases of frequent relapse oral therapy with either ketoconazole [400 mg single dose or 200 mg/day for 5-10 days] or itraconazole [200 mg/day for 5-7 days] is usually effective. Mycologically, yeast cells may still be seen in skin scrapings for up to 30 days following treatment, thus patients should be monitored on clinical grounds. Patients also need to be warned that it may take many months for their skin pigmentation to return to normal, even after the infection has been successfully treated. Relapse is a regular occurrence and prophylactic treatment with a topical agent once or twice a week is often necessary to avoid recurrence.

Pityriasis folliculitis is characterised by follicular papules and pustules localised to the back, chest and upper arms, sometimes the neck, and more seldom the face. These are itchy and often appear after sun exposure. Scrapings or biopsy specimens show numerous yeasts occluding the mouths of the infected follicles. Most cases respond well to topical imidazole treatment, however patients with extensive lesions often require oral treatment with ketoconazole or itraconazole. Once again, prophylactic treatment once or twice a week is mandatory to prevent relapse.

Current evidence suggests *M. furfur*, combined with multifactorial host factors is also the direct cause of seborrhoeic dermatitis, with dandruff being the mildest manifestation. Host factors include genetic predisposition, an emotional component (possible endocrine or neurologically mediated factors), changes in quantity and composition of sebum (increase in wax esters and a shift from triglycerides to shorter fatty acid chains), increase in alkalinity of skin (due to eccrine sweating) and external local factors such as occlusion. Patients with neurological diseases such as Parkinson's disease and those with AIDS are commonly affected. Clinical manifestations are characterised by erythema and scaling in areas with a rich supply of sebaceous glands ie the scalp, face, eyebrows, ears and upper trunk. Lesions are red and covered with greasy scales and itching is common in the scalp. The clinical features are typical and skin scrapings for a laboratory diagnosis are unnecessary. Once again, the use of a topical imidazole is recommended, especially ketoconazole which has proved to be the most effective agent. Relapse is common and retreatment when necessary is the simplest approach for long term management.

### **Dermatophytosis (tinea or ringworm) of the scalp, skin and nails.**

Dermatophytosis of the scalp, glabrous skin, and nails is caused by a closely related group of fungi known as dermatophytes which have the ability to utilise keratin as a nutrient source, i.e. they have a unique enzymatic capacity [keratinase]. The disease process in dermatophytosis is unique for two reasons: Firstly, no living tissue is invaded the keratinised stratum corneum is simply colonised. However, the presence of the fungus and its metabolic products usually induces an allergic and inflammatory eczematous response in the host. The type and severity of the host response is often related to the species and strain of dermatophyte causing the infection. Secondly, the dermatophytes are the only fungi that have evolved a dependency on human or animal infection for the survival and dissemination of their species. In fact, the common anthropophilic species seen in Australia (Table 1), are primarily parasitic on man. They are unable to colonise other animals and they have no other environmental sources. On the other hand, geophilic species normally inhabit the soil where they are believed to decompose keratinaceous debris. Some species may cause infections in animals and man following contact with soil. Zoophilic species are primarily parasitic on animals and infections may be transmitted to humans following contact with the animal host (Table 1). Zoophilic infections usually elicit a strong host response and on the skin where contact with the infective animal has occurred ie arms, legs, body or face.

**Table 1. Ecology of Common Human Dermatophyte Species in Australia**

<b>Species</b>	<b>Natural Habitat</b>	<b>Incidence</b>
<i>Epidermophyton floccosum</i>	Humans	Common
<i>Trichophyton rubrum</i>	Humans	Very Common
<i>T. mentagrophytes</i> var. <i>interdigitale</i>	Humans	Common
<i>Trichophyton tonsurans</i>	Humans	Common
<i>Trichophyton violaceum</i>	Humans	Less Common
<i>T. mentagrophytes</i> var. <i>mentagrophytes</i>	Mice, rodents	Common
<i>Trichophyton equinum</i>	Horses	Rare
<i>Trichophyton verrucosum</i>	Cattle	Rare
<i>T. mentagrophytes</i> var. <i>quinckeanum</i>	Mice	Rare*
<i>Microsporum canis</i>	Cats	Common
<i>Microsporum gypseum</i>	Soil	Common
<i>Microsporum nanum</i>	Soil/Pigs	Rare
<i>Microsporum cookei</i>	Soil	Rare

Infections by anthropophilic dermatophytes are usually caused by the shedding of skin scales containing viable infectious hyphal elements [arthroconidia] of the fungus. Desquamated skin scales may remain infectious in the environment for months or years. Therefore transmission may take place by indirect contact long after the infective debris has been shed. Substrates like carpet and matting that hold skin scales make excellent vectors. Thus, transmission of dermatophytes like *Trichophyton rubrum*, *T. mentagrophytes* var. *interdigitale* and *Epidermophyton floccosum* is usually via the feet. In this site infections are often chronic and may remain subclinical for many years only to become apparent when spread to another site, usually the groin or skin. It is important to recognise that the toe web spaces are the major reservoir on the human body for these fungi and therefore it is not practical to treat infections at other sites without concomitant treatment of the toe web spaces. This is essential if a "cure" is to be achieved. It should also be recognised that individuals with chronic or subclinical toe web infections are carriers and represent a public health risk to the general population, in that they are constantly shedding infectious skin scales.

For a laboratory diagnosis, clinicians should be aware of the need to generate an adequate amount of suitable clinical material. Unfortunately many specimens submitted are either of an inadequate amount or are not appropriate to make a definitive diagnosis. The laboratory needs enough specimen to perform both microscopy and culture. Routine turn around times for direct microscopy should be less than 24 hours, however culture may take several weeks (Table 2). In patients with suspected dermatophytosis of skin [tinea or ringworm] any ointments or other local applications present should first be removed with an alcowipe. Using a blunt scalpel, tweezers, or a bone curette, firmly scrape the lesion, particularly at the advancing border. In cases of vesicular tinea pedis, the tops of any fresh vesicles should be removed as the fungus is often plentiful in the roof of the vesicle. In patients with suspected dermatophytosis of nails [onychomycosis] the nail should be pared and scraped using a blunt scalpel until the crumbling white degenerating portion is reached. Any white keratin debris beneath the free edge of the nail should also be collected. Skin and nail specimens may be scraped directly onto special black cards which make it easier to see how much material has been collected and provide ideal conditions for transportation to the laboratory.

It must be stressed that up to 30% of suspicious material collected from nail specimens may be negative by either direct microscopy or culture. A positive microscopy result showing fungal hyphae and/or arthroconidia is generally sufficient for the diagnosis of dermatophytosis, but gives no indication as to the species of fungus involved. Culture is often more reliable and permits the species of fungus involved to be accurately identified. Repeat collections should always be considered in cases of suspected dermatophytosis with negative laboratory reports.

**Table 2. Routine Laboratory Turn Around Times.**

Organism	Direct Micro	Culture	Identification	Total
<i>C. albicans</i>	24 hrs	48 hrs	3 hrs	2-3 days
Other yeasts	24 hrs	48 hrs	72-96 hrs	5-8 days
Dermatophytes	24 hrs	14-28 days	1-28 days	14-42 days
Other Moulds	24 hrs	5-28 days	1-28 days	5-42 days

Treatment of dermatophytosis is often dependant on the clinical setting. For instance uncomplicated single cutaneous lesions can be adequately treated with a topical antifungal agent, however topical treatment of scalp and nail infections is often ineffective and systemic therapy is usually needed to cure these conditions. Chronic or widespread dermatophyte infections, acute inflammatory tinea and “Moccasin” or dry type *T. rubrum* infection involving the sole and dorsum of the foot usually also require systemic therapy. Ideally, mycological confirmation of the clinical diagnosis should be gained before systemic antifungal treatment is commenced. Oral treatment options for dermatophytosis are listed in Table 4.

### **Candidiasis of skin, mucous membranes and nails.**

Candidiasis is a primary or secondary mycotic infection caused by members of the genus *Candida*. The clinical manifestations may be acute, subacute or chronic to episodic. Involvement may be localised to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs, or the gastrointestinal tract, or become systemic as in septicemia, endocarditis and meningitis. In healthy individuals, *Candida* infections are usually due to impaired epithelial barrier functions and occur in all age groups, but are most common in the newborn and the elderly. They usually remain superficial and respond readily to treatment. Systemic candidiasis is usually seen in patients with cell-mediated immune deficiency, and those receiving aggressive cancer treatment, immunosuppression, or transplantation therapy.

Several species of *Candida* may be aetiological agents, most commonly, *Candida albicans* and rarely *C. tropicalis*, *C. krusei*, *C. parapsilosis*, *C. guilliermondii*, *C. kefyr* (*C. pseudotropicalis*) and *C. (Torulopsis) glabrata*. All are ubiquitous and occur naturally on humans, especially *C. albicans* which is recognised as a commensal of the gastrointestinal tract.

Acute oral candidiasis is rarely seen in healthy adults but may occur in up to 5% of newborn infants and 10% of the elderly. However, it is often associated with severe immunological impairment due to diabetes mellitus, leukemia, lymphoma, malignancy, neutropenia and HIV infection where it presents as a predictor of clinical progression to AIDS. The use of broad-spectrum antibiotics, corticosteroids, cytotoxic drugs, and radiation therapy are also predisposing factors. Clinically, white plaques that resemble milk curd form on the buccal mucosa and less commonly on the tongue, gums, the palate or the pharynx. Symptoms may be absent or include burning or dryness of the mouth, loss of taste, and pain on swallowing.

Intertriginous candidiasis is most commonly seen in the axillae, groin, inter- and sub-mammary folds, intergluteal folds, interdigital spaces, and umbilicus. Moisture, heat, friction and maceration of the skin are the principle predisposing factors in the normal patient, however obesity, diabetes mellitus, warm water immersion or occlusion of the skin and the use of broad-spectrum antibiotics are additional factors. Lesions consist of a moist, macular erythematous rash with typical satellite lesions present on the surrounding healthy skin.

Diaper candidiasis is common in infants under unhygienic conditions of chronic moisture and local skin maceration associated with ammonitic irritation due to irregularly changed unclean diapers. Once again characteristic erythematous lesions with erosions and satellite pustules are produced, with prominent involvement of the skin folds and creases.

Paronychia of the finger nails may develop in persons whose hands are subject to continuous wetting, especially with sugar solutions or contact with flour, that macerates the nail folds and cuticle. Lesions are characterised by the development of a painful, erythematous swelling about the affected nails. In chronic cases the infection may progress to cause onychomycosis with total detachment of the cuticle from the nail plate.

Chronic *Candida* onychomycosis often causes complete destruction of nail tissue and is seen in patients with chronic mucocutaneous candidiasis or other underlying factors that affect either the hormonal or immunologic status of the host. These include diabetes mellitus, hypoparathyroidism, Addison's disease, dysfunction of the thyroid, malnutrition, malabsorption and various malignancies. The use of steroids, antibiotics and antimitotics may also be contributing factors.

Vulvovaginal candidiasis is a common condition in women, often associated with the use of broad-spectrum antibiotics, the third trimester of pregnancy, low vaginal pH and diabetes mellitus. Sexual activity and oral contraception may also be contributing factors and infections may extend to include the perineum, the vulva and the entire inguinal area. Chronic refractory vaginal candidiasis, associated with oral candidiasis, may also be a presentation of HIV infection or AIDS. Symptoms include intense vulval pruritus, burning, erythema and dyspareunia associated with a creamy white, curd-like discharge.

In cases of balanitis, diabetes mellitus should be excluded and the sexual partner should be investigated for vulvovaginitis. The symptoms include erythema, pruritus and vesiculopustules on the glan penis or prepuce. Infections are more commonly seen in uncircumcised men and poor hygiene may also be a contributing factor.

The first step in the management of candidiasis should be to correct the underlying conditions that allow *Candida* to colonise the skin or mucosa that is to restore the normal epithelial barrier function. For cutaneous candidiasis control of excessive moisture, heat and friction which cause local skin maceration and treatment with a topical imidazole compound is usually effective. Sometimes this is also given in combination with a topical steroid such as hydrocortisone. For oral candidiasis in infants, Nystatin suspension [100, 000 units/ml] dropped into the mouth at 4-6 hour intervals or after each feed is usually used. In older children and adults Amphotericin B lozengers miconazole oral gel [at 6 hour intervals] are recommended. Nystatin drops or lozengers may also be used, however they have a bitter taste and patient compliance is usually poor. For vaginal candidiasis, azole suppositories and creams are often used with good results, however many patients prefer to use a single dose treatment with fluconazole [150 mg] which has proven efficacious in up to 95% of cases. Women with recurrent vaginal candidiasis may also require intermittent prophylactic treatment to prevent symptomatic episodes.

When treating immunosuppressed patients it is often not possible to correct the underlying predisposing conditions that would prevent candidiasis and infections are usually more severe and generally do not respond well to topical imidazole treatment. Oral Fluconazole [100-400 mg/day for 1-2 weeks] is currently the drug of choice for controlling oropharyngeal candidiasis in AIDS patients. However, indefinite maintenance treatment with Fluconazole [150-300 mg/week] is required, and intermittent dosing depending on symptoms has now been advocated to prevent the emergence of Fluconazole resistant strains of *C. albicans*.

Basically, healthy individuals do not get candidiasis, therefore the key strategy in preventing a recurrence is to correct the underlying predisposing conditions that allow *Candida* to cause an infection, especially those affecting the immune system. Where this is not possible, ie in AIDS patients, then recurrence can only be prevented by prophylaxis.

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**Table 3. Oral treatment options for cutaneous fungal infections.**

<b>Infection</b>	<b>Recommended</b>	<b>Alternative</b>
Tinea unguium [Onychomycosis].	Terbinafine 250 mg/day 6 weeks for finger nails, 12 weeks for toe nails.	Itraconazole pulse doses 400 mg/day for one week per month; 2 pulses for fingernails; 3 pulses for toenails. Fluconazole 150-300 mg/week until cure [~ 30 weeks]. Griseofulvin 500-1000 mg/day until cure [~12-18 months].
Tinea capitis.	Griseofulvin 500 mg/day [not less than 10mg/kg/day] until cure [6-8 weeks].	Terbinafine 250 mg/day/4 weeks. Itraconazole 100 mg/day/4 weeks. Fluconazole 100 mg/day/4weeks.
Tinea corporis.	Griseofulvin 500 mg/day until cure [4-6 weeks], often combined with a topical imidazole agent.	Terbinafine 250 mg/day/2-4 weeks. Itraconazole 100 mg/day/15 days or 200 mg/day/1 week. Fluconazole 150-300 mg/week for 4wks.
Tinea cruris	Griseofulvin 500 mg/day until cure [4-6 weeks].	Terbinafine 250 mg/day/2-4 weeks. Itraconazole 100 mg/day/15 days or 200 mg/day/1 week. Fluconazole 150-300 mg/week for 4 wks.
Tinea pedis.	Griseofulvin 500 mg/day until cure [4-6 weeks].	Terbinafine 250 mg/day/2-6 weeks. Itraconazole 100 mg/day/4 weeks. Fluconazole 150-300mg/week for 4 weeks.
Chronic and/or widespread non responsive tinea.	Terbinafine 250 mg/day for 4-6 weeks.	Itraconazole 200 mg/day/4-6 weeks Griseofulvin 500-1000 mg/day until cure [3-6 months].
Chronic or severe non-responsive pityriasis versicolor or pityriasis capitis.	Ketoconazole 400 mg single dose or 200 mg/day for 5-10 days.	Itraconazole 200 mg/day/5-7 days. Fluconazole 400 mg single dose or 150 mg/week for 4 weeks.
Chronic/recurrent mucocutaneous candidiasis.	Fluconazole 150 mg/week for 4 weeks.	Itraconazole 200 mg/day/5-7 days. Ketoconazole 200 mg/day/5-10 days.
Vaginal candidiasis	Fluconazole 150 mg single dose.	Itraconazole 400 mg single dose [two 200 mg doses 8 hours apart].
Candidiasis of the nail.	Itraconazole 200 mg/day for 3-5 months or 400 mg/day for one week per month for 3-4 consecutive months.	Fluconazole 150-300 mg/week until cure [~6-12 months].
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