



# Fighting fungal nail infections

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## Key points

- Other conditions can mimic onychomycosis clinically; 50% of apparent fungal nail infection has another cause.
- Proper testing for fungal nail infection is essential.
- New oral treatments for fungal nail infection are very effective compared with previous treatments.
- Treatment needs to be long term; therefore, costs and risks need to be considered and discussed with patients.
- Toenails may have residual traumatic dystrophy after treatment.

Fungal nail infection is an important health problem, especially in older people as it can limit patients' mobility and affect self-esteem. Correct diagnosis is vital as many conditions mimic its appearance. New oral treatments offer good cure rates for these patients.

**F**ungal infection of the nails (onychomycosis) is an important public health problem because of its high prevalence, especially in older people, and its associated morbidity. Apart from cosmetic effects, there can be pain, difficulty walking or performing certain tasks and effects on self-esteem.

Making the correct diagnosis is vital as there are many nail conditions that closely resemble fungal infection, such as psoriasis and traumatic dystrophy. Nail biopsy as well as scrapings and clippings for microscopy and culture can help.

Current oral treatments for fungal nail

infections can lead to cures with minimal adverse effects. Adding topical or surgical treatment to oral therapy can lead to a higher cure rate.

## EPIDEMIOLOGY AND SOCIAL EFFECTS

Fungal infection of the nails is an increasingly common problem within an ageing population. It affects 3 to 5% of the population as a whole, and about 20% of the population over the age of 60 years, men more than women.<sup>1</sup> A study in nursing home patients in Queensland found 22.5% had onychomycosis.<sup>2</sup>

Reasons for an age-related increase in onychomycosis include poor circulation,

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Figure 1. Total dystrophic onychomycosis.



Figure 2. Distal subungual onychomycosis.

diabetes, inability to attend to foot care and an increase in trauma because of changes in shape of the feet and nails due to ageing and arthritis. Tinea pedis is a well-recognised precursor to cellulitis of the leg.

Onychomycosis affects toenails more commonly than fingernails. Occlusive footwear aids fungal growth and sporting venues such as swimming pool and gym showers harbour organisms.

Fungal-infected nails become thickened, discoloured and distorted. This can cause pain, discomfort in wearing shoes, and lead to physical and occupational limitations.

Many people with onychomycosis of the toenails have difficulties with work-related activities that require them to be on their feet for a long time. In the case of fingernails, the ability to pick up fine objects can be impaired. Nails can be very difficult to trim. Research has shown that onychomycosis can adversely affect patients' quality of life, in terms of self-esteem and social interaction.<sup>1</sup>

In immunocompromised patients, such as those with AIDS, fungal infections are more common, harder to eradicate and more infectious due to a larger number of fungal pathogens that are present in these patients.

## CLINICAL FEATURES

### History

Onychomycosis is usually asymptomatic; therefore, patients often first present for cosmetic reasons without any physical complaints. As the disease progresses, onychomycosis may

interfere with standing, walking and exercising. Patients may report paraesthesia, pain, discomfort and loss of dexterity. They may also report loss of self-esteem and lack of social interaction.

### Physical

Repeated nail trauma due to unsuitable footwear and changes in the anatomy of the foot with ageing and arthritis frequently lead to nail changes in the toenails. Nails distorted by repeated microtrauma are more likely to become secondarily infected by tinea, or look as though they are infected even when they are not. It can also lead to confusion at the end of antifungal treatment when patients expect perfect toenails but are left with thickened or distorted nails.

Onychomycosis can be classified into subtypes, which may be distinguished by their usual presenting clinical features. The main subtypes are:

- distal lateral subungual onychomycosis
- white superficial onychomycosis
- proximal subungual onychomycosis
- candidal onychomycosis.

Patients may have a combination of these subtypes. Total dystrophic onychomycosis refers to the most advanced form of any subtype (Figure 1).

### Pathophysiology

The types of onychomycosis described below are most commonly caused by dermatophytes: fungi that are able to live on keratinised tissue.



Figure 3. Onychomycosis due to *Candida*.



Figure 4. Onychomycosis due to *Candida* after treatment with ketoconazole.



Figure 5. Onychomycosis caused by *Scopulariopsis*.



Figure 6. Psoriasis mimicking onychomycosis.

*Trichophyton rubrum* is the most common dermatophyte causing infection, followed by *Trichophyton mentagrophytes*. Dermatophytes produce a keratinolytic protease allowing nail invasion, giving rise to the commonly seen yellow streaks.

#### Distal lateral subungual onychomycosis

The most common form of onychomycosis is distal lateral subungual onychomycosis, in which the fungus spreads from plantar skin and invades the nail bed via the hyponychium (Figure 2). Inflammation occurring in these areas of the nail apparatus causes the typical physical signs of onycholysis (separation of the nail from the nail bed) and subungual

hyperkeratosis. Toenail invasion is 20 times more common than fingernail invasion because tinea of the feet is much more common than tinea of the hands.

#### White superficial onychomycosis

White superficial onychomycosis is a rare presentation caused by direct invasion of the surface of the nail plate.

#### Proximal subungual onychomycosis

In proximal subungual onychomycosis, the least common subtype, fungi penetrate the nail matrix via the proximal nail fold and colonise the deep portion of the proximal nail plate. This is common in patients with AIDS and is considered an early clinical sign of HIV infection.

#### Total dystrophic onychomycosis

Total dystrophic onychomycosis involves the entire nail unit, and can be the end stage of any of these other patterns of fungal infection (Figure 1).

#### Candidal infection

Candidal nail infection is not very common as *Candida* does not readily invade the nail unless there is an impaired immune response. *Candida* is frequently isolated from the proximal nail fold in chronic paronychia, and from the subungual space in onycholysis, but it is usually a secondary coloniser.

In long-standing onycholysis, *Candida* may be grown from nail clippings, and sometimes treatment with oral anticandidal agents may help the nail to reattach (Figures 3 and 4). In chronic mucocutaneous candidiasis the yeast infects the nail plate and eventually the proximal and lateral nail folds.

#### Moulds

Moulds can cause infection of the nails, although sometimes there is an underlying dermatophyte infection too. *Scytalidium* and *Scopulariopsis* (Figure 5) are two moulds that may digest keratin and therefore could be causative agents. *Alternaria*, *Aspergillus* and *Fusarium* probably can also. Other agents are likely to be contaminants.

#### DIAGNOSIS

About 50% of thickened, discoloured toenails are caused by fungal infection of the nail bed, matrix or nail plate. Many other conditions can mimic fungal infection; therefore, a proper diagnosis is essential before starting treatment.

A negative mycological result does not rule out onychomycosis because negative results may occur in direct microscopy in up to 10% of cases and in cultured specimens in up to 30% of cases. Taking an insufficient specimen may be one cause, an issue that is addressed below.

## Differential diagnoses

### *Psoriasis*

Psoriasis of the nails is one of the most common differential diagnoses, as it can present with onycholysis and subungual hyperkeratosis as seen in onychomycosis. Psoriasis often affects fingernails, which is less common in onychomycosis. GPs should search for other skin signs of psoriasis (and indeed other signs of fungal infection of the skin), including pitting of the nail and the oil spot sign (Figure 6).

### *Lichen planus*

Lichen planus can cause severe nail changes (Figure 7). Although lichen planus is a less common disease, nail involvement occurs in approximately 10% of cases. Trachyonychia (rough nails), thinning of the nail plate and subungual hyperkeratosis can occur. Rarely, a severe form of lichen planus causes total destruction of the nail and scarring.

## Taking the nail specimen

A negative culture when there is fungal infection present is reasonably common and may be due to an inadequate specimen. If the nail is onycholytic this can be cut back and material scraped from the underneath of the nail as well as from the nail bed.

Patients should not use topical antifungal preparations for several days before specimen collection.

### *Distal lateral subungual onychomycosis*

With distal lateral subungual onychomycosis, the specimen should consist of as many nail clippings as possible, as well as scrapings under the nail of nail bed and subungual debris. Dermatophyte onychomycosis is primarily a disease of the nail bed rather than the nail plate, so the subungual debris from the most proximal part of the infection will yield the best results.



Figure 7. Lichen planus of the fingernails.

### *White superficial onychomycosis*

With white superficial onychomycosis, the surface of the nail should be scraped with a number 15 scalpel blade.

### *Proximal subungual onychomycosis*

With proximal subungual onychomycosis, a number 15 blade and curette may be needed to get appropriate material.

## Analysis of the specimen

Direct microscopy and culture on appropriate media should be carried out. Microscopy can sometimes be carried out by the clinician if she/he has appropriate specialist training, but culture should be carried out in a laboratory experienced in handling mycology specimens. Most laboratories in the country should be able to send specimens to central laboratories if they cannot do cultures on the spot. In some situations, histopathology of the nail plate can increase the positive yield, although there is extra expense for the patient.

False negatives on microscopy occur in 5 to 15% of cases, whereas negative cultures occur in up to half of onychomycotic nails. Treatment can be started on the basis of positive microscopy, but care should be taken especially in the case of 'fungal' infection of fingernails, where the organism may be candida. If there is any doubt, it is reasonable to refer the patient to a dermatologist.

## TREATMENT

Both topical and oral agents are available for treatment of fungal nail infection. The primary aim of treatment is to eradicate

the organism as demonstrated by microscopy and culture. It should be recognised that successful eradication of the fungus does not always lead to 'normal' looking nails as they may have been dystrophic prior to infection.

Treatment of onychomycosis depends on:

- the clinical type of onychomycosis
- the number of affected nails
- the severity of nail involvement.

A systemic treatment is always required in proximal subungual onychomycosis and in distal lateral subungual onychomycosis involving the lunular region. White superficial onychomycosis and distal lateral subungual onychomycosis limited to the distal nail can be treated with a topical agent. A combination of systemic and topical treatment increases the cure rate.

Because the rate of recurrence remains high, even with new agents, the decision to treat should be made with a clear understanding of the cost and risks involved, as well as the risk of recurrence. Treatment needs to be administered long term and enough time must elapse for the nail to grow out completely before the treatment can be said to be successful. Toenails take around 12 months to grow out and fingernails take six months. Photodynamic therapy and lasers may represent future treatment options.

Generally, moulds respond poorly to oral treatment. Patients with moulds can sometimes respond to itraconazole and fluconazole, but not to terbinafine. Removal of the nail can help.

True candidal nail infection due to chronic mucocutaneous candidiasis is extremely rare and usually these patients are treated by immunologists or infectious disease experts. Oral agents such as ketoconazole, itraconazole and fluconazole may be used. Terbinafine and griseofulvin are of no use in these patients.

### Topical agents

Topical treatments for onychomycosis include imidazoles (e.g. miconazole, econazole), allylamines (e.g. terbinafine) and amorolfine lacquer. Generally, they are ineffective alone, except for treatment of very limited distal subungual disease or white superficial onychomycosis. However, it may be helpful to add them to oral treatment regimens.

### Oral agents

#### *Griseofulvin*

Griseofulvin is a fungistatic agent effective only within the nail matrix. It does not persist in the nail plate; therefore, it needs to be taken until the new nail completely regrows, which can take about a year. Poor compliance is common, and cure rates of 3 to 30% are quoted.<sup>1</sup> The recommended dosage is 500 to 1000 mg/day.

Griseofulvin is usually well tolerated, although abdominal discomfort, nausea and headaches are the most common adverse effects. Hypersensitivity reactions such as urticaria may occur and photosensitivity can be an annoyance. Serious adverse effects include hepatotoxicity and bone marrow suppression. There are many drug interactions. In adults, it is contraindicated in pregnancy and men are cautioned against fathering a child for six months after therapy.

#### *Ketoconazole*

Ketoconazole is an azole agent active against dermatophytes and yeasts as well as some moulds. The recommended dosage is 200 mg/day.

Ketoconazole has significant adverse

effects and drug interactions that limit its long-term use in patients with nail infections. Abnormal liver function tests occur in about 15% of patients, and severe hepatitis occurs in one in 10,000 patients taking this drug. A full blood examination and liver function tests should therefore be undertaken after a few weeks.

#### *Terbinafine*

Terbinafine is an allylamine derivative that inhibits squalene epoxidase, leading to decreased ergosterol synthesis, causing fungal cell death. Taken orally, it is absorbed well, and concentrates in nails and skin. Terbinafine persists in nails for a couple of months after ceasing intake.

Terbinafine is available in Australia and listed on the PBS for proven fungal infection of the nails, which can be demonstrated by microscopy and/or culture. If the culture is negative but the microscopy positive, and it is toenail disease, it is reasonable to try terbinafine.

The recommended dosage is 250 mg/day for a duration of six weeks for treatment of fungal fingernails and three months for toenails. More studies are needed to establish the efficacy of pulse regimens and the optimal duration of treatment.

Terbinafine is relatively safe. Minor side effects such as nausea, headaches, urticaria and taste disturbance occur occasionally.

Severe adverse effects include liver disease (less than 0.01%), neutropenia (less than 0.01%), allergic skin reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis.

A full blood examination and liver function tests should be undertaken after a few weeks. Drug interactions are not significant.

#### *Itraconazole*

Itraconazole is an azole medicine with fungistatic activity. It slows fungal cell

growth by inhibiting cytochrome P450-dependent synthesis of ergosterol, a vital component of fungal cell membranes. It has a broad spectrum of activity against dermatophytes, yeasts and some moulds. It is not listed on the PBS for treating nail infections.

Itraconazole is more easily absorbed with fatty food and persists in skin and nail for about four weeks after ceasing intake. Pulse dosing of 400 mg/day for seven days a week every four weeks is recommended, with a duration of two months for treatment of fungal fingernails and three months for toenails.

Itraconazole is relatively safe. Minor adverse effects include nausea, headache and urticaria. Serious adverse effects include abnormal liver function tests, adrenal suppression, gynaecomastia, and congestive cardiac failure.

There are many drug interactions that need to be checked when starting a patient on this medication. Drugs that interact with itraconazole include warfarin, digoxin, cisapride, lipid-lowering agents and calcium channel blockers.

**Fluconazole**

Fluconazole is an azole medication with fungistatic activity. It selectively inhibits fungal cytochrome P450 sterol C-14 alpha-demethylation, which prevents conversion of lanosterol to ergosterol, thereby disrupting cellular membranes. It does not seem to persist as long in the nails as terbinafine or itraconazole so treatment should continue until the infection resolves.

There are studies showing its effectiveness in nail infections at doses of 150 or 300 mg/week.<sup>1</sup> Long courses of treatment are needed, for example, nine to 12 months for toenails; therefore, cost may be a drawback.

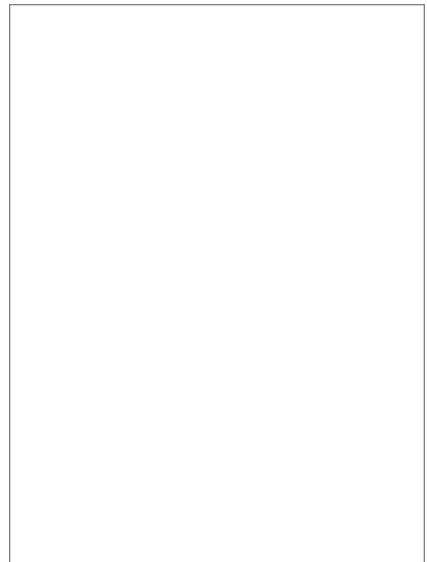
Adverse effects of this medication are minimal, especially with the weekly dose. Nausea, headaches and abnormal liver function tests are described, but monitoring is not usually needed.

**Additional treatment (surgery)**

Partial or total removal of diseased nails may be helpful, especially if only one or two toenails are involved.<sup>1</sup>

**Relapse after treatment**

A study has followed 36 patients with onychomycosis who were treated and



cured mycologically with either terbinafine or itraconazole for three years after treatment. The results showed that 22% of patients had some relapse and these numbers were equal in the terbinafine and itraconazole group.<sup>3</sup> The rate of relapse was 8% at 12 months, rising to 22% by three years. All cases were due to *Trichophyton rubrum*.

**CONCLUSION**

Dermatophyte infection causes 50% of dystrophic nail disease. Diagnosis using microscopy and culture should be attempted before treatment. Fingernail infection without toenail involvement may be due to yeast, for example, *Candida*.

Topical treatment is inferior to systemic treatment in all but a few cases of limited distal disease and white superficial onychomycosis. New oral treatments can give very good results for treatment of

onychomycosis, with cures in 70 to 80% of patients. MT

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**FURTHER READING**

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