

Management of fungal nail infections

Key Reviewer: Dr Amanda Oakley, Specialist Dermatologist and Clinical Associate Professor, Tristram Clinic, Hamilton

Key concepts

- Laboratory diagnosis of onychomycosis is recommended before starting oral or topical treatment
- Onychomycosis is diagnosed with microscopy and culture of nail clippings
- Treatment may not be necessary for everybody and may be inappropriate for elderly people
- Oral terbinafine is first line treatment for dermatophyte infection of nails
- Itraconazole is the treatment of choice for onychomycosis due to candida infection
- Topical amorolfine or ciclopirox may be suitable for superficial or minor infection and for those unable to take oral antifungal therapy
- Treatment failure or relapse will require mycological confirmation and possibly alternative treatment

Fungal infection accounts for approximately half of all nail disease

Fungal infection of the nails or onychomycosis accounts for about 50% of all nail disease. It becomes more common with increasing age and mostly affects toenails (80% of cases). Other risk factors for onychomycosis include: nail trauma, frequent immersion in water, occlusive footwear, athlete's foot, diabetes mellitus, immunosuppression and smoking^{1, 2, 3}

Dermatophytes are the most common cause of fungal nail infection

In 90% of cases onychomycosis is caused by a dermatophyte, mostly *Trichophyton rubrum*. Other causes of infection include yeasts; mainly *Candida* infection of the fingernails, which is often accompanied by paronychia (inflammation of the proximal nail fold).¹ Non-dermatophyte moulds (*Fusarium*, *Scopulariopsis* and *Scytalidium*) account for about 2–3% of fungal nail infections.^{2, 4}

Distal and lateral subungual onychomycosis is the most common morphology of fungal nail infection

Most cases of onychomycosis are characterised by thickening of the nail, discolouration (ranging from white to black) and onycholysis (separation of the nail from the nail bed).^{1, 5}

There are different morphological types of onychomycosis, the most common being distal and lateral subungual onychomycosis (Figure 1), usually caused by dermatophyte infection.^{1, 5} This begins in the distal or lateral part of the nail plate and spreads proximally under the nail.

Superficial white onychomycosis (Figure 2) is also mostly caused by dermatophyte infection (usually *Trichophyton interdigitale*) and accounts for about 10% of onychomycosis. It presents as small, white, powdery patches on the surface of the nail.^{2, 6}

Proximal onychomycosis (Figure 3) is the least common type of onychomycosis and usually presents in patients who are immunosuppressed (e.g. HIV), have diabetes, or



Figure 1: Typical lateral onychomycosis (*T. rubrum*)



Figure 2: Extensive superficial white onychomycosis (*T. interdigitale*)



Figure 3: Proximal onychomycosis (*T. interdigitale*)



Figure 4: Typical onychomycosis and paronychia due to *C. albicans*

Differential diagnoses^{1,2}

Psoriasis affecting the nail – pitting, onycholysis, discolouration, thickening and irregular ridging. Look for psoriatic plaques on typical sites (scalp, ears, elbows, knees and flexures).

Onychogryphosis – thickening and distortion of the nails, most often the big toe. This is more common in elderly people.

Other differential diagnoses include – lichen planus, nail trauma, squamous cell carcinoma and malignant melanoma and nail dystrophy caused by systemic disease.

in those with peripheral vascular disease.^{1,2} This begins as discolouration of the proximal end of the nail.

Candidal onychomycosis (Figure 4) is often associated with paronychia and most often occurs in the fingernails of people who frequently immerse their hands in water.^{1,2}

Laboratory diagnosis is recommended before any treatment is started

Laboratory diagnosis is recommended before starting treatment because other conditions (see differential diagnoses over page) can present similarly to onychomycosis, particularly psoriasis. Also, treatment of onychomycosis is lengthy, may have adverse effects and can be expensive.^{1,2,3}

Diagnose onychomycosis with microscopy and culture of nail clippings⁷

Microscopy of a sample of affected nail plate can identify fungal elements and culture determines the causative organism.⁸

In most cases patients will be sent to the laboratory for collection of samples, however in some cases (e.g. rural practice) the doctor may collect the sample. Nail clippings (chiropraxy clippers may be the best tool to use) from the diseased part of the nail and curettings of subungual debris should be taken. If superficial white onychomycosis is suspected, a scalpel can be used to scrape the surface of the nail to obtain a sample.^{1,2}

It is best to provide the laboratory with a generous amount as there are usually few fungi in a typical specimen. If necessary, delay the investigation to allow the nail to grow longer.^{2,8}

Problems with laboratory tests – false negatives and delayed results

Accurate microscopy of specimens depends on the skill of the laboratory personnel. The false negative rate can be 30–40%.⁵ Mycological culture increases the sensitivity but results may take several weeks because dermatophytes are slow growing. A culture plate is incubated for four weeks before it is declared negative.⁹

Treatment options

Treatment may not be necessary for everybody and may be inappropriate for elderly people

For patients who do not have troublesome symptoms, the decision to treat can be based on the patient's choice, after they have been informed of risks and benefits of treatment.

Patients should be informed about treatment including:¹

- Nail may not look completely normal, even after treatment
- Treatment with oral antifungals is only successful in about 70-80% of cases (and clinical trials usually exclude people aged over 60 years) and can relapse.⁸ Topical treatment is less effective.¹⁰
- Length of treatments: three months for oral medication and up to two years for topical medication

- Potential adverse effects and interactions with oral treatment

Treatment with oral antifungals may not be appropriate for elderly people, or people taking multiple medicines, as there is an increased risk of adverse effects and interactions.²

Treatment should be considered for those at risk of complications

People with diabetes, peripheral vascular disease or connective tissue disorders are at higher risk of complications such as secondary bacterial infections (e.g. cellulitis). In these people treatment should be considered. However, treatment is less likely to be successful in these patients, who also have higher rates of drug-induced complications.^{1, 11}

Pharmacological treatments

Oral antifungals (terbinafine, itraconazole) and topical antifungals (ciclopirox, amorolfine) are available for the treatment of onychomycosis.

Oral treatment is more effective than topical therapy and is recommended for most people in whom treatment is appropriate

Oral antifungal treatment is more effective than topical treatment except for cases of superficial white onychomycosis or in a few cases of minor distal onychomycosis. Oral therapy is considered first line for most patients who opt for treatment.⁸

Terbinafine is first line for dermatophyte infection

Terbinafine and itraconazole are both effective for treating dermatophyte infection however terbinafine is more effective and is considered first line.^{2, 8, 11}

In adults, 250 mg terbinafine is given once daily for an initial course of six weeks for typical fingernail infection, or 12 weeks for toenail infection.

Gastrointestinal effects such as dyspepsia, nausea and diarrhoea, skin reactions (morbilliform rash, urticaria) and

taste disturbance are the most common adverse effects associated with terbinafine.^{1, 2}

Rarely, serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome and angioneurotic oedema) and haematological disorders have occurred with terbinafine therapy.² Psoriasis may be aggravated by terbinafine treatment.²

Oral terbinafine is not recommended for people with liver disease. Patients taking terbinafine should be advised to promptly report any symptoms that may suggest liver toxicity such as anorexia, nausea, vomiting or fatigue.¹² In elderly or unwell people, liver function and blood count should be monitored at baseline and then after four to six weeks of treatment.

Terbinafine interacts with a small number of drugs (Table 1).

Itraconazole is the treatment of choice for onychomycosis due to candida infection

Itraconazole is the most effective treatment for onychomycosis due to candida infection.^{8, 11} Terbinafine can be used but is less effective.¹

For the treatment of onychomycosis in adults, 200 mg itraconazole is taken twice daily for seven consecutive days of the month, for two months for fingernails and three months for toenails (although candidal onychomycosis is much less common in toenails).⁸ Alternatively, 200 mg itraconazole can be taken once daily for three months. There is no evidence that continuous or intermittent regimens produce significantly different cure rates or adverse events.¹³

Adverse effects associated with itraconazole also include gastrointestinal effects and skin reactions as well as reversible increases in hepatic enzymes. Uncommon adverse effects include hepatotoxicity, severe skin conditions, nervous system disorders (peripheral neuropathy, headache, dizziness) and congestive heart failure.²

Table 1: Interactions with antifungals^{2, 3, 14}

Drug or class	Terbinafine	Itraconazole
Benzodiazepines		Concurrent use of midazolam or triazolam is contraindicated, risk of excessive or prolonged sedation
Statins		Avoid concomitant use as rhabdomyolysis has been reported
Rifampicin	Decreased plasma levels of terbinafine possible	
Warfarin	Bleeding events reported rarely, however avoiding concurrent use is not necessary	Increased risk of bleeding, increased INR monitoring may be required
Calcium channel blockers		Increases the plasma level of felodipine which may increase its adverse effects, particularly ankle and leg oedema

N.B. This is not a comprehensive list of interactions

Itraconazole should not be used in patients with congestive heart failure or in those with liver disease or raised liver enzymes.

LFTs should be monitored at baseline and after four to six weeks of treatment for courses lasting more than one month.¹

Itraconazole is an inhibitor of CYP3A4 and has a number of significant drug interactions (Table 1).

Topical treatment may be suitable for superficial infection and for those unable to take oral antifungal therapy

Topical therapies are less effective than oral therapies but may be useful for superficial white onychomycosis or in early distal and lateral subungual onychomycosis.^{11, 15} Topical therapy can also be used where a patient is unable or unwilling to take oral antifungals.¹¹ Compliance with topical treatments can be an issue as they require application for extended periods, e.g. 6 to 12 months.

Amorolfine and ciclopirox nail lacquers are available topical antifungals

Amorolfine 5% (Loceryl) and ciclopirox 8% (Batrafen) are two topical antifungals available in New Zealand. While

there is limited evidence that ciclopirox modestly improves symptoms of onychomycosis compared with placebo, there is a lack of evidence examining effectiveness of amorolfine.^{16, 17}

Amorolfine is applied to the affected nail twice weekly until infection is resolved, usually six months for fingernails and 9 to 12 months or longer, for toenails. The nail needs to be filed, cleansed and de-greased before application.^{1, 18} A transient burning sensation may occur after application of nail lacquer.¹

Ciclopirox is applied to the affected nails every second day for the first month, then application is reduced to twice weekly for the following month, and then reduced to once weekly for up to six months or longer. The nail lacquer should be removed with nail vanish once weekly and the nail filed.¹⁸ Irritation and pruritus may occur after application.

Both products are available over-the-counter as pharmacist-only-medicines or on prescription. There are part charges for both and these products may be too expensive for some patients.

Measure treatment response as nail grows

To determine if treatment is effective, photograph the nail, or make a groove with a nail file at the proximal end of the infected area. The infection should not progress proximal to this groove if treatment is effective. The groove may need to be redefined over time because it can take 12 months or longer for a big toenail to grow out.²

All people, whether they are being treated with medicines or not, should be provided with lifestyle advice

Foot care advice is integral to the treatment of onychomycosis and may lessen the discomfort of the infected nail(s).^{2, 3, 15}

Advise patients to:^{2, 3, 15}

- Keep feet cool and dry by wearing cotton socks and breathable footwear

- Trim nails and file down hypertrophic nails
- Avoid high heels and narrow toed shoes to prevent nail trauma
- Recognise and treat athlete's foot if present
- Wear footwear in communal showers

Treatment failure or relapse

If initial treatment fails or infection recurs, the first step is to confirm mycology.³ Earlier positive culture may have been secondary infection of nail dystrophy due to another cause. In addition, check adherence and if treatment is required, an alternative drug, a combination of oral and topical treatment or nail avulsion may be considered. However, there is little evidence that nail avulsion increases cure rates.^{2, 11}

Images contributed by NZ DermNet, the website of the New Zealand Dermatological Society.

References

1. Clinical Knowledge Summaries. Fungal and candidal nail infections. Available from <http://cks.library.nhs.uk/impetigo> (Accessed January 2009).
2. How should fungal nail be treated? *Drug Ther Bull* 2008; 46(1): 3-8.
3. Rogers P, Bassler M. Treating onychomycosis. *Am Fam Physician* 2001; 63(4): 663-72.
4. Lang S. Guide to pathogens and antibiotic treatment. *Diagnostic Medlab* 2004. Available from <http://www.dml.co.nz/> (Accessed January 2009).
5. Olde Hartman TC, van Rijswijk E. Fungal nail infection. *BMJ* 2008; 337:295.
6. Fungal nail infections. *DermNet NZ* 2008. Available from www.dermnet.org.nz (Accessed January 2009).
7. The Royal College of Pathologists of Australasia Manual 2004. Available from <http://www.rcpamanual.edu.au/> (Accessed January 2009).
8. Roberts DT, Taylor WD, Boyle J. Guidelines for treatment of onychomycosis. *Br J Dermatol* 2003; 148: 402-10.
9. Waikato Hospital. Available from http://www.waikatodhb.govt.nz/laboratory/tests/microbiology_tests/mycology_skin_scrapings.htm
10. Hainer BL. Dermatophyte Infections. *Am Fam Physician* 2003; 67(1):101-8.
11. National Prescribing Service. Onychomycosis (nail infections) – who needs treatment? *NPS News* 2008; 61.
12. Medsafe. Terbinafine: serious hepatic and haematological reactions. *Prescriber Update* 2006; 27(2):18-20.
13. Crawford F, Young P, Godfrey C, et al. Oral treatments for toenail onychomycosis. *Arch Dermatol* 2002; 138:811-6.
14. Baxter K (ed). *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press. <http://www.medicinescomplete.com> (Accessed January 2009).
15. Finch JJ, Warshaw EM. Toenail onychomycosis: current and future treatment options. *Dermatol Ther* 2007; 20:31-46.
16. Hunt D. Fungal toenail infections. *BMJ Clin Evid* 2008; 12:1715.
17. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev* 2007; 3: CD001434.
18. MIMS New Ethicals Issue 10. Jan-Jun 2009. *CMPMedica*.