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Review

# Global perspectives for the management of onychomycosis

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## Abstract

Onychomycosis is a fungal nail infection caused by dermatophytes, nondermatophyte molds, and yeasts. This difficult-to-treat chronic infection has a tendency to relapse despite treatment. This paper aims to offer a global perspective on onychomycosis management from expert physicians from around the world. Overall, the majority of experts surveyed used systemic, topical, and combination treatments approved in their countries and monitored patients based on the product insert or government recommendations. Although the basics of treating onychomycosis were similar between countries, slight differences in onychomycosis management between countries were found. These differences were mainly due to different approaches to adjunctive therapy, rating the severity of disease and use of prophylaxis treatment. A global perspective on the treatment of onychomycosis provides a framework of success for the committed clinician with appreciation of how onychomycosis is managed worldwide.

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## Introduction

Onychomycosis is a fungal infection of the nail caused by dermatophytes (e.g., *Trichophyton, Microsporum, and Epidermophyton*), nondermatophyte molds (e.g., *Scopulariopsis, Aspergillus, Fusarium*), yeasts (e.g., *Candida*), or a combination thereof.[1] This condition may present on both the toenails and fingernails, with toenails more commonly involved.[1] Clinical signs of this condition include nail discoloration, nail plate thickening, hyperkeratosis, and onycholysis.[2] Population-based studies have reported varied approximations of prevalence, ranging from <1% to 8% in Europe and the United States and <1% in central Africa.[3] In addition, the prevalence of culture-proven dermatophyte, yeast, and nondermatophyte mold (NDM) toenail onychomycosis in at-risk populations found pooled prevalence rates of 3.22%, 0.40%, and 0.37%, respectively.[4] There may be a genetic element in the susceptibility of an individual for fungal infections such as defects in the innate and adaptive immune system.[5] Genetics along with exposure to environmental risk factors can lead to chronic onychomycosis.[6] There are a myriad of procedures and protocols used to diagnose and treat onychomycosis worldwide. We sought to compare the use of laboratory techniques and treatments used globally through surveying experts across the following countries: Canada, the United States, Italy, the United Kingdom, Israel, India, and Brazil.

## Epidemiology

In Western countries, 80%–90% of onychomycosis cases are primarily caused by dermatophytes, with 5–17% due to yeasts and 2–3% due to NDMs. In southern European countries, dermatophytes are causative organisms in 40–68% of cases, with 21–55% of cases due to yeasts. In Asian and Middle Eastern countries, dermatophytes account for 40–48% of cases, 43–46% due to yeasts, and 8–11% due to NDM-related infections. Comparatively, in Africa, onychomycosis-related infections are predominantly caused by yeasts[7] (Fig. 1).

The high prevalence of fungal infections in North America is largely due to the immigration of dermatophytes from other areas of the world such as West Africa and Southeast Asia. The global prevalence of onychomycosis is estimated to be around 5.5%, attributing to 50.0% of all nail disease cases.[8–15] The risk of onychomycosis increases with age due to poor peripheral circulation, diabetes, repeated nail trauma, longer exposure to pathogenic fungi, suboptimal immune function, inactivity, and/or the inability to maintain good foot care.[4,15–17]

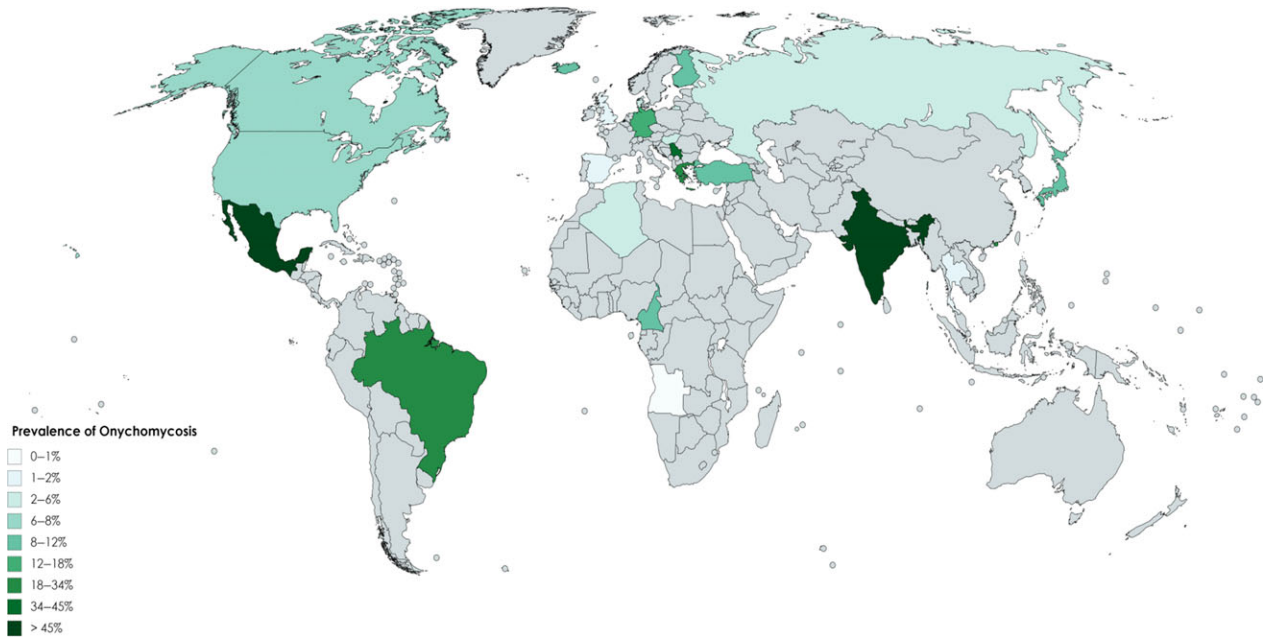


**Figure 1** Global prevalence of onychomycosis [3,100]

 

Toenail onychomycosis is more common in males[15,18,19] with *Candida* fingernail onychomycosis more common in women.[20,21] Onychomycosis is more likely to develop if there is a family history of onychomycosis (Table 1).[5,22]

## Diagnosis

The experts surveyed agree that correctly identifying the causal organisms is important to effectively treat onychomycosis. Collectively, experts recommend that clinicians look for thickened, discolored, dystrophic nails, multiple toenail involvement, and the presence of tinea pedis. However, diagnosing onychomycosis based on clinical features alone is not always precise, thus laboratory isolation of the fungus remains the diagnostic gold standard (e.g., light microscopic identification and culture).[23]

There are three conventional ways to diagnose onychomycosis: potassium hydroxide (KOH), culture, and periodic acid-Schiff (PAS). KOH is a direct technique involving degraded keratin and allows visual inspection of the fungal structures.[24] KOH is a sensitive diagnostic test, whereas culture is more specific (Table 2).[25] Culture allows for the isolation of the causal agent, species differentiation, and evidence of viability.[24] PAS is a good alternative to use instead of culture; in some cases, it has been known to be the more sensitive method of diagnosis (Table 2).[26]

For best patient care decisions, it is important to perform mycological testing in all cases of suspected onychomycosis, and certainly prior to prescribing oral therapy.[27] Unfortunately, most North American physicians, especially general practitioners (GPs) and podiatrists, do not perform mycology for diagnosis prior to initiating treatment. Comparatively, dermatologists generally perform mycology, wait for diagnosis confirmation before starting oral therapy, and do not always use confirmatory testing prior to prescribing topical treatment. Additionally, some GPs and podiatrists perform mycology in the event of a poor or suboptimal response to reconfirm diagnosis; however, in a clinical setting it is uncommon to perform mycology at the end of therapy. In a clinical trial setting, this mycological evaluation at the end of treatment is a common practice. Molecular diagnosis can assist in the diagnosis of mixed infections or NDMs.[28] Mixed onychomycosis infections may be more prevalent than previously described, with reported prevalence rates of 41% in onychomycosis patients.[29] Understanding the identity of the causative organisms (dermatophytes vs. yeast vs. NDM) before initiating antifungal therapy can aid in the selection of appropriate treatment.

**Table 1** Risk factors for infection or recurrence of onychomycosis

| Risk factors |
|---|
| >50% nail affected |
| Abnormal nail morphology |
| Age >60 years |
| Asymmetric gait nail unit syndrome |
| Concomitant disease |
| Diabetes |
| Genetic susceptibility |
| Immunodeficiency |
| Immunosuppression |
| Incorrect dosage/treatment time too short |
| Lateral nail disease |
| Matrix involvement: total dystrophic onychomycosis |
| Mixed infection |
| Obesity |
| Peripheral vascular disease |
| Poor patient compliance/hygiene/choice of footwear |
| Psoriasis |
| Repeated exposure to moisture without drying in-between |
| Resistant organisms |
| Smoking |
| Thickness in nail plate |
| Tinea pedis |
| Trauma, faulty biomechanics |
| Yellow spike (distal-proximal) and dermatophytoma |

## Oral Therapy

### Treatment recommendations

If there is greater than 50% nail plate involvement, more than three nails involved, or presence of dermatophytoma, then systemic therapy should be considered. The experts surveyed identified oral terbinafine (continuous or pulse) as their first choice of therapy. In toenail dermatophyte onychomycosis studies, pulse terbinafine treatment has shown similar efficacy rates as continuous dosing.[30] These experts also identified itraconazole and fluconazole (used off-label in North America) as second line treatments. Fluconazole is advantageous as it has a long half-life requiring only one dose per week.[31] Despite fluconazole's advantages, its minimal inhibitory concentration (MIC) for dermatophytes is higher than those associated with itraconazole and terbinafine and is not as efficacious against dermatophytes. Itraconazole also has some drawbacks such as clinical drug interactions, negative inotropic effect, and related Black Box warnings (Table 3).[32] Recommended dosing regimens of the three treatments is as follows: terbinafine (250 mg) or itraconazole (200 mg) daily for 6 and 12 weeks for fingernail and toenail onychomycosis,[6] respectively. Pulse terbinafine is recommended at 250 mg/day for 4 weeks on, 4 weeks off, and then 4 weeks on.[30] Two pulses of itraconazole is recommended for fingernails and three pulses for toenails, where one pulse consists of 200 mg itraconazole twice daily for 1 week, followed by 3 weeks off.[6] Fluconazole 150 mg weekly for more than 24 weeks is recommended for both fingernails and toenails until the diseased nail plate has grown out.[6] It should be noted that the recommendations provided by our experts are somewhat different from those previously published in the British Association of Dermatologist (BAD) guidelines.[33] The BAD guidelines state that terbinafine and itraconazole are both first-line treatments for dermatophyte onychomycosis and fluconazole that should be considered a useful

**Table 2** : Characteristics of diagnostic methods used to confirm onychomycosis

| Method | Fungal viability | Species identification | Relative sensitivity | Relative specificity | PPV | NPV | Test length |
|---|---|---|---|---|---|---|---|
| Culture | Yes | Yes | ++ | ++++++ | ++++ | +++ | 3 weeks |
| KOH | No | No | ++++ | +++++ | +++++ | +++ | Rapid |
| PAS | No | No | +++++ | +++++ | ++++ | ++++++ | 24 h |
| PCR | No | Yes | +++++ | ++++ | ++++++ | + | 24 h |

KOH, potassium hydroxide preparation; PAS, periodic acid–Schiff stain; PCR, polymerase chain reaction; PPV, positive predictive values; NPV, negative predictive values.
+ 40–50%, ++: 50–60%, +++: 60–70%, ++++: 70–80%, +++++: 80–90%, ++++++: 90–100%.

alternative in patients unable to tolerate terbinafine or itraconazole.

### Patient monitoring

Prior to initiating systemic therapy, the experts surveyed usually monitor with liver function tests (LFTs) and some also do a complete blood count (CBC) prior to terbinafine and itraconazole treatment. When using itraconazole, clinicians should consider electrocardiography (ECG), especially in elderly patients and those with preexisting cardiac dysfunction. It is also important to monitor when clinically indicated by history and examination. Some of the experts monitored with LFTs during therapy and at the end of therapy. The authors recommend monitoring LFTs at baseline and, when indicated, CBC for terbinafine, discontinuing treatment when LFTs are two to three times the upper limit of normal or if clinical symptoms or examination indicate stoppage.[34]

Additional monitoring is also advised in specific patient populations. Studies have found that terbinafine and itraconazole elimination are significantly prolonged in subjects with liver cirrhosis compared to healthy subjects.[32,35] Terbinafine elimination is also significantly decreased in subjects with renal impairment,[32,35] whereas itraconazole's pharmacokinetics are variable between renal impairment subjects, resulting in no significant differences compared to normal subjects.[32,34] Fluconazole is mainly excreted unchanged in urine thus renal impairment patients administered with fluconazole should also be monitored.[35] As the aforementioned drugs have been associated with hepatotoxicity,[35,36] these oral agents are not recommended for use in patients with chronic or active hepatic disease.[34,37,38] The authors suggest that patients with hepatic dysfunction who are treated with oral therapy should be monitored carefully with specialist internal medicine/hepatologist supervision.

## Topical Therapy

In most countries, if there is less than 50% involvement of diseased nail plate and less than three nails involved, topical therapy is an appropriate consideration. Topical treatment should also be used for treatment of white superficial onychomycosis. All experts reported using topical antifungals for tinea pedis whilst treating onychomycosis with topical treatment or laser therapy. Several of the surveyed experts prefer to prescribe topical treatments, such as efinaconazole 10%, ciclopirox 8% (once a day), amorolfine 5% (once a week), or tavaborole 5%, in children, diabetic individuals, and mixed infections.[39] The authors also suggest that patients with hepatic dysfunction may benefit from topical treatment. When appropriate, topical treatments can be paired with other therapies, such as oral antifungals or devices, to potentially increase cure rates.

## Physical Modalities

Lasers are an emerging device-based therapy for onychomycosis management. Photothermal reactions are among the proposed mechanism of action for lasers. Lasers can elicit a fungicidal effect by photothermally heating the fungal mycelium through selective photothermolysis.[40,41] Targeting fungal chromophores (e.g., chitin, xanthomegnin, and melanin) is an additional method that can be used by lasers to elicit fungicidal effects.[42] As of January 2012, the US Food and Drug Administration (FDA) has approved four laser systems for the "temporary increase of clear nail in onychomycosis".[43] Published studies have provided evidence that lasers may improve the aesthetic appearance of onychomycotic nails on a temporary basis; however, reported clinical cure rates (100% clear nail) are estimated to be 13%.[44] Current research suggests that lasers do not provide efficacy rates for medical endpoints that equate to or exceed those found with oral and topical treatments.

Another emerging therapy for onychomycosis management is photodynamic therapy (PDT). PDT is a noninvasive therapy that utilizes light to activate a photosensitizing agent that can be applied topically or systemically. Reactive oxygen species are generated that initiate the destruction of cells by necrosis or apoptosis. Photosensitizers then absorb energy from ultraviolet or visible light, transferring it to adjacent molecules. Fungi are able to absorb photosensitizers so PDT can be an alternative way of treating onychomycosis. A few clinical trials have been published on PDT,[45–51] demonstrating that PDT is effective and well tolerated. PDT appears to be a promising alternative to conventional antifungal therapy.

 

**Table 3** Monitoring guidelines

| Drug | Warnings and Precautions | | Boxed warning | Contraindicated drugs | Contraindications |
|---|---|---|---|---|---|
| Fluconazole[35] | *Liver* | -Caution with administration to patients with liver dysfunction.<br>-Discontinue treatment if clinical signs and symptoms of liver disease develop.<br>-If abnormal liver function tests develop, monitor treatment for development of more severe hepatic injury. | n/a | Cisapride, Astemizole, Erythromycin, Pimozide, Quinidine, Terfenadine (with fluconazole 400 mg or higher). | -Hypersensitivity to fluconazole or its excipients.<br>-Caution if hypersensitivity to other azoles.<br>-There may be risk if patient is pregnant or becoming pregnant while taking fluconazole. |
| | *Allergy* | -Anaphylaxis has been reported. | | | |
| | *Skin* | -Skin conditions may develop; patients with fungal infections should be monitored. | | | |
| Griseofulvin[107] | *Liver* | -Caution with administration to patients with liver dysfunction.<br>-Discontinue treatment if clinical signs and symptoms of liver disease develop.<br>-If abnormal liver function tests develop, monitor treatment for development of more severe hepatic injury. | n/a | n/a | -Should not be prescribed to pregnant patients.<br>-Hypersensitivity to griseofulvin or its excipients.<br>-Contraindicated in patients with porphyria or hepatocellular failure. |
| | *Skin* | -Severe skin reactions and erythema may develop.<br>-The possibility of cross sensitivity with penicillin exists<br>-Lupus erythematosus, lupus-like syndromes or exacerbation of existing lupus erythematosus have been reported.<br>-Patients should be warned to avoid exposure to intense or prolonged natural or artificial sunlight. | | | |
| Itraconazole[36] | *Liver* | -Rare cases of hepatotoxicity. If clinical signs and symptoms of liver disease develop, discontinue use and perform liver testing.<br>-Continued use discouraged unless serious or life-threatening condition where benefit exceeds risk. | Not to be administered in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. | Methadone, Disopyramide, Dofetilide, Dronedarone, Quinidine, ergot alkaloids, Irinotecan, Lurasidone, oral midazolam, Pimozide, Triazolam, Felodipine, Nisoldipine, Ranolazine, Eplerenone, Cisapride, Lovastatin, Simvastatin, Colchicine (in subjects with renal or hepatic impairment). | -Hypersensitivity to itraconazole and caution if hypersensitivity to other azoles.<br>-Should not be administered if patient is pregnant or contemplating pregnancy. |
| | *Heart* | -Cardiac dysrhythmia has occurred with drugs; thus, cisapride, quinidine, pimozide, and methadone are contraindicated.<br>-Review the risks and benefits when patients have risk factors for CHF.<br>-Calcium channel blocker coadministration should proceed with caution (felodipine and nisoldipine contraindicated). | | | |

## Concomitant Medication

Antifungal therapies can affect the pharmacokinetics or pharmacodynamics of concomitant medications. These effects can vary from reduced efficacy to increased toxicity. Monitoring dosing regimens can help in mitigating this. Plasma concentrations of topical antifungals are generally very low so these types of drug interactions are a concern only for the use of systemic antifungals.

## Global approvals

With a few exceptions, oral treatments, such as terbinafine, itraconazole, griseofulvin, ketoconazole, and fluconazole, are

**Table 3 Continued**

| Drug | Warnings and Precautions | | Boxed warning | Contraindicated drugs | Contraindications |
|---|---|---|---|---|---|
| Ketoconazole[108] | *Liver* | -Caution with administration to patients with liver dysfunction.<br>-Discontinue treatment if clinical signs and symptoms of liver disease develop.<br>-If abnormal liver function tests develop, monitor treatment for development of more severe hepatic injury. | Serious cases, incl. fatal or ones requiring liver transplant, have occurred w/oral use, even in pts w/o hepatic dz risk factors; inform pts of risk and monitor closely. | Dofetilide, Quinidine, Pimozide, Cisapride, Methadone, Disopyramide, Dronedarone, or Ranolazine due to QT prolongation risk; Ketoconazole may incr. drug levels and prolong QT interval, resulting in life-threatening ventricular dysrhythmias such as torsades de pointes. | -Contraindicated in patients with acute or chronic liver disease.<br>-Contraindicated in patients who have shown hypersensitivity to the drug. |
| | *Allergy* | -Anaphylaxis has been reported. | | | |
| Terbinafine[34] | *Liver* | -Liver failure has occurred.<br>-Pretreatment serum transaminases should be obtained and treatment discontinued if liver injury develops. | n/a | n/a | -Individuals with a history of allergic reaction to oral terbinafine due to risk of anaphylaxis. |
| | *Allergy* | -Taste and smell disturbances are possible.<br>-Discontinue use if this occurs. | | | |
| | *Blood* | -Severe neutropenia has occurred.<br>-If neutrophil count is ≤1,000 cell/ml, discontinue use. | | | |
| | *Other* | -Depressive symptoms have been reported.<br>-Discontinue if signs or symptoms of drug reaction occur—Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, bullous dermatitis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. | | | |

These are guidelines only (2018) based on the authors' experience; please review the most up-to-date package inserts in your country and national guidelines/expert's opinions before prescribing.

consistently used worldwide (Table 4). In North America (USA and Canada), the European Union as well as India, oral ketoconazole should no longer be used as first-line therapy for the treatment of onychomycosis given the relatively high rate of hepatotoxicity it produces compared to other available oral agents.[52] In South America, the use of ketoconazole has been restricted to tinea capitis. In addition to ketoconazole, Canada does not use griseofulvin as a treatment for onychomycosis (Table 4).

There are significant differences in the use of topical treatments in North America as compared to the rest of the world. Efinaconazole is only approved in Canada, the United States, and Japan with tavaborole only approved in the USA.[53,54] Comparatively, amorolfine is used in all countries other than North America, and ciclopirox is available worldwide. South America uses topical ciclopirox or amorolfine alone in the instance of mild disease (Fig. 2). Nail debridement is not a common practice in North America. When used, podiatrists generally prefer mechanical versus chemical debridement. This is in contrast to the European Union that prefers the use of chemical debridement and in South America where a combination of mechanical and chemical debridement is favored.

The majority of clinical trials published on devices originate from South American (e.g., Brazil) and East Asian countries (e.g., Japan, Korea, China).[45,47,49–51,55–58] Device-based treatments in combination with other therapies may help improve the penetration of antifungal drugs and treatment efficacy.[58–60] For instance, mycological and clinical cure rates after 24 weeks of treatment were significantly higher when topical terbinafine treatment was combined with laser therapy as compared to terbinafine or laser therapy alone ($P < 0.05$).[61] Further randomized controlled trials should be conducted to verify the efficacy of devices in treating onychomycosis.

 

## Special Populations

### Children

The prevalence of childhood onychomycosis ranges worldwide from 0.35% to 5.5%, causing 15.5% of all child nail dystrophies.[14,62,63] Recent studies have suggested that the occurrence of onychomycosis in children has increased.[62,64–67] Onychomycosis is less common in children as compared to adults (0.14% and 3.2%, respectively)[4] potentially due to reduced micro- and macro-trauma at the hyponychium, junction between the nail plate, and nail bed.[67] As compared to adults, children are less likely to frequent high-risk areas such as gymnasium floors, locker rooms in sport facilities, and surfaces adjacent to swimming pools.[6] Children also have a smaller area of nail bed and nail plate available for attack by fungal organisms with a faster nail plate growth rate.[68]

Very few clinical trials have been published on the efficacy and safety of onychomycosis treatments in children with preliminary evidence suggesting currently available onychomycosis treatments are effective and appear safe to use in children.[69] Dosing regimens must be readjusted according to the child's weight.[67,70] As the pharmacokinetics of antifungals are generally different in children versus adults, understanding the adverse effects associated with antifungal medications is an important factor in appropriately managing fungal infections.[71,72]

**Table 4** International treatment approvals.

| System | International approvals for onychomycosis |
|---|---|
| Oral | |
| Fluconazole | South Africa, Brazil, Canada, Italy, India, USA |
| Griseofulvin | Brazil, Italy, India, USA |
| Itraconazole | South Africa, Brazil, Canada, Italy, India, USA |
| Terbinafine | South Africa, Brazil, Canada, Italy, India, USA |
| Topical | |
| Efinaconazole (Jublia) | USA, Canada |
| Ciclopirox | USA, Canada |
| Tavaborole (Kerydin) | USA |

USA, United States of America.

| Method | Drug | Canada | | | USA | | | European Union | | | South America | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | Mild | Moderate | Severe | Mild | Moderate | Severe | Mild | Moderate | Severe |
| Oral | Fluconazole | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| | Griseofulvin | | | | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| | Itraconazole | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| | Terbinafine | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| Topical | Amorolfine | | | | | | | ✓ | ✓ | | ✓ | | |
| | Ciclopirox | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | ✓ | | |
| | Efinaconazole | ✓ | ✓ | | ✓ | ✓ | | | | | | | |
| | Tavaborole | | | | ✓ | ✓ | | | | | | | |
| Devices | Lasers | | | | | | | | | | ✓ | ✓ | |

**Figure 2** Global severity for treatments of onychomycosis

### Elderly

Onychomycosis is found more frequently in the elderly.[15,73] Age-related nail changes can affect the success of antifungal treatment.[74,75] Impaired peripheral circulation and variations in nail thickness can limit the access of antifungal treatment to the site of infection. If the nail growth rate decreases, a longer period of treatment is necessary to achieve cure. The elderly may also be more susceptible to eukaryotic pathogens as their immune competence may be compromised.[76,77]

### Diabetics

Complications associated with diabetes can influence the safety and efficacy of antifungal therapy. Diabetes is associated with vascular impairment, which can be a precursor to neuropathy and retinopathy.[78] Damage to important vascular organs and the kidneys can change the pharmacokinetics of antifungal drugs. In this population, it is important to keep a higher index of suspicion for nondermatophyte molds and *Candida* species compared to younger immunocompetent patients.[79]

As treatment response of a well-controlled diabetic patient may be comparable to that of a nondiabetic patient, no specific treatment recommendations may be necessary for this population. Terbinafine is the safest antifungal to use in diabetic patients.[80] Topical treatments may also be an option for diabetic patients as it encourages regular inspection of the foot, but it can be impractical in elderly or obese patients who may have difficultly applying the lacquer.[78] Due to the high risk of infection in diabetic patients, nail avulsion is discouraged.[81] Prophylaxis treatment is strongly recommended as a high recurrence rate is seen in diabetic patients.[82] The authors recommend efinaconazole 10% nail solution or tavaborole 5% solution twice weekly to prevent recurrence.

### HIV positive or organ transplant patients

Due to their weakened immune system, immunocompromised patients such as human immunodeficiency virus (HIV-1) positive and organ transplant patients are more susceptible to onychomycosis as they cannot fight infection as adequately as healthy individuals. Interestingly, there have been reported cases of HIV-positive patients cured for onychomycosis after their immune systems were restored by combined antiretroviral therapy or highly active antiretroviral therapy.[83,84] It should be noted that fungal infections can spread faster in immunocompromised patients, and clinical presentations that are generally more difficult to treat are more frequently encountered in this subpopulation.[84–95]

Due to the extensive nature of the fungal infection and high recurrence rate, it is recommended that systemic antifungals are used in HIV-1 positive patients.[37,94] Terbinafine is preferred over itraconazole as terbinafine has fewer drug interactions. When treating with fluconazole, higher doses and/or longer durations may be required.[96,97] The CD4 count and the antiretroviral therapy (ART) status of the patient may dictate the choice of antifungal agent. Those with a good CD4 count (>500) can be managed as a normal immunocompetent patient, while being cautious of drug interactions. Careful consideration of treatment should be taken in patients with falling CD4 counts. It may be prudent to rely more on topical treatment, debridement, and laser-based therapy in order to minimize potential drug interactions. The authors recommend the use of oral terbinafine or topical therapy and monitoring of organ transplant recipients.

### Hepatitis B and Hepatitis C

For patients who have hepatitis B or hepatitis C, prescription should occur only in consultation with their hepatologist and requires careful and regular monitoring of LFTs. Clinicians should ensure there are no other reasons for elevated LFTs such as use of alcohol or concomitant drugs. In these patients, effective topical therapy may be a consideration. Any coexisting tinea pedis must be treated appropriately.

## Management of Recurrence

If there is recurrence of infection, consideration should be given to the immune status of the patient and mycology should be repeated.[18] There may be anatomic abnormalities in the foot, nail plate, or nail bed that result in incomplete cure.[98] If the repeated mycology is positive, a longer duration of the selected antifungal agent may be needed.[99–101] Disinfection of shoes and socks should be attempted.[102] Lifestyle changes to prevent recurrence of onychomycosis should be instituted.

## Terminology

One of the main challenges in the onychomycosis literature is finding a consensus when defining cure rates. Large scale clinical trials that use the most rigorous efficacy criteria often report lower rates of response than seen in clinical practice or published studies due to the variances in the definitions of cure. Mycological cure should be defined as negative KOH and culture, clinical success as 80-100% improvement in the appearance of the nail and complete cure as negative KOH, negative culture, and 100% clear nail.

## Considerations for Healthcare Professionals

Research has previously been carried out examining the prevalence of asthma among podiatrists in the UK. Podiatrists were four times more likely to have asthma than the UK's national average, and a high prevalence of eye irritation and respiratory complaints has been reported in this occupational group.[103] Additionally, podiatrists have also been shown to have a higher prevalence of precipitating antibodies for *T. rubrum* compared to the general public.[104,105] A recent questionnaire found that 32% of respondents had a respiratory condition with asthma

 

being the most prevalent condition reported.[106] Only 15.8% of respondents used mechanical room ventilation, 47.5% used nail drills with local exhaust ventilation systems, and 11% used nail drills with water spray dust suppression.[106] Therefore, when performing mechanical debridement of fungal nails, a good ventilation system, an appropriate exhaust system, masks, and goggles are recommended.

## Conclusion

Although the prevalence of onychomycosis is widespread, physicians around the globe treat onychomycosis in a similar manner. Options for treating onychomycosis include, but are not limited to, terbinafine, itraconazole, fluconazole, ciclopirox 8% nail lacquer, amorolfine 5% nail lacquer, efinaconazole 10% nail solution, and tavaborole 5% nail solution. Nondermatophyte molds or mixed infection can be managed with terbinafine or itraconazole, with or without topical therapy. Itraconazole, fluconazole, and efinaconazole can be used for *Candida* infections. For dermatophyte infections, topical therapies should be considered for mild to moderate onychomycosis and oral monotherapy used for moderate to severe cases. If drug interactions are a possibility, the authors recommend consideration of terbinafine with proper monitoring with contraindications taken into consideration. Further research into the efficacy of device-based therapies is required before they can be widely recommended.

A global perspective on the treatment of onychomycosis provides a framework of success for the committed clinician. Researchers and decision-makers in public health and health planning have much to gain from this comprehensive perspective. Healthcare can be more effective if physicians learn from each other and global differences and similarities are considered for the treatment of onychomycosis.

## References


1 Westerberg DP, Voyack MJ. Onychomycosis: current trends in diagnosis and treatment. *Am Fam Physician* 2013; **88**(11): 762–770.
2 Elewski BE, Rich P, Tosti A, *et al.* Onchomycosis: an overview. *J Drugs Dermatol* 2013; **12**(7): s96–s103.
3 Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. *J Eur Acad Dermatol Venereol* 2014; **28**(11): 1480–1491.
4 Gupta AK, Daigle D, Foley KA. The prevalence of culture-confirmed toenail onychomycosis in at-risk patient populations. *J Eur Acad Dermatol Venereol* 2015; **29**(6): 1039–1044.
5 Zaias N, Tosti A, Rebell G, *et al.* Autosomal dominant pattern of distal subungual onychomycosis caused by *Trichophyton rubrum*. *J Am Acad Dermatol* 1996; **34**(2 Pt 1): 302–304.
6 Gupta AK, Paquet M. Management of onychomycosis in Canada in 2014. *J Cutan Med Surg* 2015; **19**(3): 260–273.
7 Gupta AK, Daigle D. Potential role of tavaborole for the treatment of onychomycosis. *Future Microbiol* 2014; **9**(11): 1243–1250.
8 Dubljanin E, Džamić A, Vujčić I, *et al.* Epidemiology of onychomycosis in Serbia: a laboratory-based survey and risk factor identification. *Mycoses* 2017; **60**(1): 25–32.
9 Maraki S. Epidemiology of dermatophytoses in Crete, Greece between 2004 and 2010. *G Ital Dermatol Venereol* 2012; **147** (3): 315–319.
10 Silva-Rocha WP, de Azevedo MF, Chaves GM. Epidemiology and fungal species distribution of superficial mycoses in Northeast Brazil. *J Mycol Medicale* 2017; **27**(1): 57–64.
11 Gupta C, Jongman M, Das S, *et al.* Genotyping and *in vitro* antifungal susceptibility testing of fusarium isolates from onychomycosis in India. *Mycopathologia* 2016; **181**(7–8): 497–504.
12 Otašević S, Barac A, Pekmezovic M, *et al.* The prevalence of *Candida* onychomycosis in Southeastern Serbia from 2011 to 2015. *Mycoses* 2016; **59**(3): 167–172.
13 Wlodek C, Trickey A, de Berker D, *et al.* Trends in pediatric laboratory-diagnosed onychomycosis between 2006 and 2014 in the southwest of England. *Pediatr Dermatol* 2016; **33**(6): e358–e359.
14 Totri CR, Feldstein S, Admani S, *et al.* Epidemiologic analysis of onychomycosis in the San Diego pediatric population. *Pediatr Dermatol* 2017; **34**(1): 46–49.
15 Gupta AK, Gupta G, Jain HC, *et al.* The prevalence of unsuspected onychomycosis and its causative organisms in a multicentre Canadian sample of 30 000 patients visiting physicians' offices. *J Eur Acad Dermatol Venereol* 2016; **30**(9): 1567–1572.
16 Gupta AK, Humke S. The prevalence and management of onychomycosis in diabetic patients. *Eur J Dermatol* 2000; **10** (5): 379–384.
17 Martínez E, Ameen M, Tejada D, *et al.* Microsporum spp. onychomycosis: disease presentation, risk factors and treatment responses in an urban population. *Braz J Infect Dis Off Publ Braz Soc Infect Dis* 2014; **18**: 181–186.
18 Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. *Clin Microbiol Rev* 1998; **11**(3): 415–429.
19 Gupta AK, Lynde CW, Jain HC, *et al.* A higher prevalence of onychomycosis in psoriatics compared with non-psoriatics: a multicentre study. *Br J Dermatol* 1997; **136**(5): 786–789.
20 Mikaeili A, Karimi I. The incidence of onychomycosis infection among patients referred to hospitals in Kermanshah province, Western Iran. *Iran J Public Health* 2013; **42**(3): 320–325.
21 Gelotar P, Vachhani S, Patel B, *et al.* The prevalence of fungi in fingernail onychomycosis. *J Clin Diagn Res* 2013; **7**(2): 250–252.
22 Cooper DN, Krawczak M, Polychronakos C, *et al.* Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. *Hum Genet* 2013; **132**(10): 1077–1130.
23 Mahoney JM, Bennet J, Olsen B. The diagnosis of onychomycosis. *Dermatol Clin* 2003; **21**(3): 463–467.
24 Velasquez-Agudelo V, Cardona-Arias JA. Meta-analysis of the utility of culture, biopsy, and direct KOH examination for the diagnosis of onychomycosis. *BMC Infect Dis* 2017; **22**: 17.
25 Levitt JO, Levitt BH, Akhavan A, *et al.* The sensitivity and specificity of potassium hydroxide smear and fungal culture relative to clinical assessment in the evaluation of tinea pedis: a pooled analysis. *Dermatol Res Pract* 2010; 764843. http://dx.doi.org/10.1155/2010/764843


 

26 Weinberg JM, Koestenblatt EK, Tutrone WD, *et al.* Comparison of diagnostic methods in the evaluation of onychomycosis. *J Am Acad Dermatol* 2003; **49**(2): 193–197.
27 Gupta AK, Versteeg SG, Shear NH. Confirmatory testing prior to initiating onychomycosis therapy is cost-effective. *J Cutan Med Surg* 2017; **1**: 1203475417733461.
28 Watanabe S, Ishida K. Molecular diagnostic techniques for onychomycosis: validity and potential application. *Am J Clin Dermatol* 2017; **18**(2): 281–286.
29 Gupta AK, Nakrieko K-A. Molecular determination of mixed infections of dermatophytes and nondermatophyte molds in individuals with onychomycosis. *J Am Podiatr Med Assoc* 2014; **104**(4): 330–336.
30 Yadav P, Singal A, Pandhi D, *et al.* Comparative efficacy of continuous and pulse dose terbinafine regimes in toenail dermatophytosis: a randomized double-blind trial. *Indian J Dermatol Venereol Leprol* 2015; **81**(4): 363–369.
31 Gupta AK, Drummond-Main C, Paquet M. Evidence-based optimal fluconazole dosing regimen for onychomycosis treatment. *J Dermatol Treat* 2013; **24**: 75–80.
32 Sporanox. Package insert: SPORANOX! (itraconazole) Capsules. Drugs@FDA: FDA approved drug products [Internet]. 2012. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2012/020083s048s049s050lbl.pdf
33 Ameen M, Lear JT, Madan V, *et al.* British Association of Dermatologists' guidelines for the management of onychomycosis 2014. *Br J Dermatol* 2014; **171**(5): 937–958.
34 Lamisil. Package Insert: LAMISIL (terbinafine hydrochloride) Tablets, 250 mg Drugs@FDA: FDA Approved Drug Products 2012 [Internet]. 2012. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2012/020539s021lbl.pdf
35 Diflucan. Package Insert (Fluconazole) Tablets, 50, 100, 150, or 200 mg [Internet]. 2011. Drugs@FDA: FDA Approved Drug Products. 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019949s051lbl.pdf
36 Sporanox. Package Insert (Itraconazole) Capsules, 100 mg [Internet]. Drugs@FDA: FDA Approved Drug Products. 2009. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020083s040s041s044lbl.pdf
37 Elewski B, Tavakkol A. Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease: a proven reality. *Ther Clin Risk Manag* 2005; **1**(4): 299–306.
38 Paredes AH, Lewis JH. Terbinafine-induced acute autoimmune hepatitis in the setting of hepatitis B virus infection. *Ann Pharmacother* 2007; **41**(5): 880–884.
39 Elewski BE, Rich P, Pollak R, *et al.* Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol* 2013; **68**(4): 600–608.
40 Altshuler GB, Anderson RR, Manstein D, *et al.* Extended theory of selective photothermolysis. *Lasers Surg Med* 2001; **29**(5): 416–432.
41 Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. *Science* 1983; **220**(4596): 524–527.
42 Vural E, Winfield HL, Shingleton AW, *et al.* The effects of laser irradiation on *Trichophyton rubrum* growth. *Lasers Med Sci* 2008; **23**(4): 349–353.
43 FDA U.S. Food and Drug Administration. Medical devices and clinical trial design for the treatment or improvement in the appearance of fungally-infected nails [Internet]. 2016. Available from: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM431312.pdf
44 Gupta AK, Versteeg SG. A critical review of improvement rates for laser therapy used to treat toenail onychomycosis. *J Eur Acad Dermatol Venereol* 2017; **31**(7): 1111–1118.
45 Morgado LF, Trávolo ARF, Muehlmann LA, *et al.* Photodynamic therapy treatment of onychomycosis with aluminium-phthalocyanine chloride nanoemulsions: a proof of concept clinical trial. *J Photochem Photobiol, B* 2017; **173**: 266–270.
46 Gilaberte Y, Robres M, Frias MP, *et al.* Methyl aminolevulinate photodynamic therapy for onychomycosis: a multicentre, randomized, controlled clinical trial. *J Eur Acad Dermatol Venereol* 2017; **31**: 347–354.
47 Figueiredo Souza LW, Souza SVT, Botelho ACC. Randomized controlled trial comparing photodynamic therapy based on methylene blue dye and fluconazole for toenail onychomycosis. *Dermatol Ther* 2014; **27**(1): 43–47.
48 Sotiriou E, Koussidou-Eremonti T, Chaidemenos G, *et al.* Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by *Trichophyton rubrum*: preliminary results of a single-centre open trial. *Acta Derm Venereol* 2010; **90**(2): 216–217.
49 Tardivo JP, Del Giglio A, de Oliveira CS, *et al.* Methylene blue in photodynamic therapy: from basic mechanisms to clinical applications. *Photodiagnosis Photodyn Ther* 2005; **2**(3): 175–191.
50 Souza LW, Souza SV, Botelho AC. Endonyx toenail onychomycosis caused by *Trichophyton rubrum*: treatment with photodynamic therapy based on methylene blue dye. *An Bras Dermatol* 2013; **88**: 1019–1021.
51 Souza LWF, Souza SVT, Botelho AC. Distal and lateral toenail onychomycosis caused by *Trichophyton rubrum*: treatment with photodynamic therapy based on methylene blue dye. *An Bras Dermatol* 2014; **89**: 184–186.
52 Yan JY, Nie XL, Tao QM, *et al.* Ketoconazole associated hepatotoxicity: a systematic review and meta- analysis. *Biomed Environ Sci BES* 2013; **26**(7): 605–610.
53 LLC VPNA. Jublia (Efinaconazole) Package Insert [Internet]. Bridgewater, NJ, USA; 2014. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203567s000lbl.pdf
54 Anacor Pharmaceuticals Inc. FDA approves Anacor Pharmaceuticals' KERYDIN™ (tavaborole) topical solution, 5% for the treatment of onychomycosis of the toenails [Internet]. 2014 [cited 2014 Nov 24]. Available from: http://investor.anacor.com/releasedetail.cfm?ReleaseID=858211
55 Li Y, Yu S, Xu J, *et al.* Comparison of the efficacy of long-pulsed Nd:YAG laser intervention for treatment of onychomycosis of toenails or fingernails. *J Drugs Dermatol* 2014; **13**(10): 1258–1263.
56 Noguchi H, Miyata K, Sugita T, *et al.* Treatment of onychomycosis using a 1064 nm Nd:YAG laser. *Med Mycol J* 2013; **54**(4): 333–339.
57 Moon SH, Hur H, Oh YJ, *et al.* Treatment of onychomycosis with a 1,064-nm long-pulsed Nd:YAG laser. *J Cosmet Laser Ther Off Publ Eur Soc Laser Dermatol* 2014; **16**: 165–170.
58 Lim E-H, Kim H, Park Y-O, *et al.* Toenail onychomycosis treated with a fractional carbon-dioxide laser and topical antifungal cream. *J Am Acad Dermatol* 2014; **70**(5): 918–923.
59 Shemer A, Gupta A, Amichai B, *et al.* An open comparative study of nail drilling as adjunctive treatment for toenail onychomycosis. *J Dermatoligical Treat* 2016; **27**: 480–483.


 

60 Bhatta AK, Keyal U, Huang X, *et al.* Fractional carbon-dioxide (CO2) laser-assisted topical therapy for the treatment of onychomycosis. *J Am Acad Dermatol* 2016; **74**(5): 916–923.
61 Xu Y, Miao X, Zhou B, *et al.* Combined oral terbinafine and long-pulsed 1,064-nm Nd: YAG laser treatment is more effective for onychomycosis than either treatment alone. *Dermatol Surg* 2014; **40**(11): 1201–1207.
62 Rodriguez-Pazos L, Pereiro-Ferreiros M, Pereiro M, *et al.* Onychomycosis observed in children over a 20-year period. *Mycoses* 2011; **54**(5): 450–453.
63 Solís-Arias MP, García-Romero MT. Onychomycosis in children. A review. *Int J Dermatol* 2017; **56**(2): 123–130.
64 Sigurgeirsson B, Kristinsson K, Jonasson P. Onychomycosis in Icelandic children. *J Eur Acad Dermatol Venereol* 2006; **20**(7): 796–799.
65 Lange M, Roszkiewicz J, Szczerkowska-Dobosz A, *et al.* Onychomycosis is no longer a rare finding in children. *Mycoses* 2006; **49**(1): 55–59.
66 Young LS, Arbuckle HA, Morelli JG. Onychomycosis in the Denver pediatrics population, a retrospective study. *Pediatr Dermatol* 2014; **31**(1): 106–108.
67 Gupta AK, Skinner AR. Onychomycosis in children: a brief overview with treatment strategies. *Pediatr Dermatol* 2004; **21** (1): 74–79.
68 Gupta AK. Onychomycosis in the elderly. *Drugs Aging* 2000; **16**(6): 397–407.
69 Gupta AK, Mays RR, Versteeg SG, *et al.* Onychomycosis in children: safety and efficacy of antifungal agents. *Pediatr Dermatol* 2018; **35**: 552–559.
70 Patel D, Castelo-Soccio LA, Rubin AI, *et al.* Laboratory monitoring during systemic terbinafine therapy for pediatric onychomycosis. *JAMA Dermatol* 2017; **153**(12): 1326–1327.
71 Chiou CC, Walsh TJ, Groll AH. Clinical pharmacology of antifungal agents in pediatric patients. *Expert Opin Pharmacother* 2007; **8**(15): 2465–2489.
72 Endo JO, Wong JW, Norman RA, *et al.* Geriatric dermatology: Part I. Geriatric pharmacology for the dermatologist. *J Am Acad Dermatol* 2013; **68**: 521.e1-10; quiz 531–532.
73 Onychomycosis Zaias N. *Dermatol Clin* 1985; **3**(3): 445–460.
74 Singh G, Haneef NS, Uday A. Nail changes and disorders among the elderly. *Indian J Dermatol Venereol Leprol* 2005; **71** (6): 386–392.
75 Baran R. The nail in the elderly. *Clin Dermatol* 2011; **29**(1): 54–60.
76 Levy LA. Epidemiology of onychomycosis in special-risk populations. *J Am Podiatr Med Assoc* 1997; **87**(12): 546–550.
77 Albright JW, Albright JF. Ageing alters the competence of the immune system to control parasitic infection. *Immunol Lett* 1994; **40**(3): 279–285.
78 Mayser P, Freund V, Budihardja D. Toenail onychomycosis in diabetic patients: issues and management. *Am J Clin Dermatol* 2009; **10**(4): 211–220.
79 Gruseck E, Abeck D, Ring J. Relapsing severe *Trichophyton rubrum* infections in an immunocompromised host: evidence of onychomycosis as a source of reinfection based on lectin typing. *Mycoses* 1993; **36**(7–8): 275–278.
80 Matricciani L, Talbot K, Jones S. Safety and efficacy of tinea pedis and onychomycosis treatment in people with diabetes: a systematic review. *J Foot Ankle Res* 2011; **4**(4): 26.
81 Barber K, Claveau J, Thomas R. Review of treatment for onychomycosis: consideration for special populations. *J Cutan Med Surg* 2006; **10**(Suppl 2): S48–S53.
82 Rich P. Special patient populations: onychomycosis in the diabetic patient. *J Am Acad Dermatol* 1996; **35**(3 Pt 2): S10–S12.
83 Tachikawa N, Yasuoka A, Oka S. Improvement of onychomycosis without antifungal therapy after initiation of highly active anti-retroviral therapy (HAART) in an HIV-infected patient. *Jpn J Infect Dis* 1999; **52**(6): 245–246.
84 Moreno-Coutiño G, Arenas R, Reyes-Terán G. Improvement in onychomycosis after initiation of combined antiretroviral therapy. *Int J Dermatol* 2013; **52**(3): 311–313.
85 Dompmartin D, Dompmartin A, Deluol AM, *et al.* Onychomycosis and AIDS. Clinical and laboratory findings in 62 patients. *Int J Dermatol* 1990; **29**: 337–339.
86 Moreno-Coutiño G, Arenas R, Reyes-Terán G. Clinical presentation of onychomycosis in HIV/AIDS: a review of 280 Mexican cases. *Indian J Dermatol* 2011; **56**(1): 120–121.
87 Surjushe A, Kamath R, Oberai C, *et al.* A clinical and mycological study of onychomycosis in HIV infection. *Indian J Dermatol Venereol Leprol* 2007; **73**(6): 397–401.
88 Kaviarasan PK, Jaisankar TJ, Thappa DM, *et al.* Clinical variations in dermatophytosis in HIV infected patients. *Indian J Dermatol Venereol Leprol* 2002; **68**(4): 213–216.
89 Sentamil Selvi G, Kamalam A, Ajithados K, *et al.* Clinical and mycological features of dermatophytosis in renal transplant recipients. *Mycoses* 1999; **42**(1–2): 75–78.
90 Ravnborg L, Baastrup N, Svejgaard E. Onychomycosis in HIV-infected patients. *Acta Derm Venereol* 1998; **78**(2): 151–152.
91 Herranz P, García J, De Lucas R, *et al.* Toenail onychomycosis in patients with acquired immune deficiency syndrome: treatment with terbinafine. *Br J Dermatol* 1997; **137** (4): 577–580.
92 Daniel CR, Norton LA, Scher RK. The spectrum of nail disease in patients with human immunodeficiency virus infection. *J Am Acad Dermatol* 1992; **27**(1): 93–97.
93 Milillo L, Lo Muzio L, Carlino P, *et al.* Candida-related denture stomatitis: a pilot study of the efficacy of an amorolfine antifungal varnish. *Int J Prosthodont* 2005; **18**(1): 55–59.
94 Millikan LE. Role of oral antifungal agents for the treatment of superficial fungal infections in immunocompromised patients. *Cutis* 2001; **68**(1 Suppl): 6–14.
95 Gupta AK, Taborda P, Taborda V, *et al.* Epidemiology and prevalence of onychomycosis in HIV-positive individuals. *Int J Dermatol* 2000; **39**(10): 746–753.
96 van't Wout JW. Fluconazole treatment of candidal infections caused by non-albicans *Candida* species. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 1996; **15**: 238–242.
97 Arévalo MP, Arias A, Andreu A, *et al.* Fluconazole, itraconazole and ketoconazole *in vitro* activity against *Candida* spp. *J Chemother Florence Italy* 1994; **6**(4): 226–229.
98 Oppel T, Korting H. Onychodystrophy and its management. *Ger Med Sci* 2003; **1**: 1–7.
99 Scher RK, Breneman D, Rich P, *et al.* Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38**(6 Pt 2): S77–S86.
100 Ling MR, Swinyer LJ, Jarratt MT, *et al.* Once-weekly fluconazole (450 mg) for 4, 6, or 9 months of treatment for distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38**(6 Pt 2): S95–S102.
101 Drake L, Babel D, Stewart DM, *et al.* Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the fingernail. *J Am Acad Dermatol* 1998; **38** (6 Pt 2): S87–S94.


 

102 Gupta AK, Elewski BE, Rosen T, *et al.* Onychomycosis: strategies to minimize recurrence. *J Drugs Dermatol* 2016; **15** (3): 279–282.
103 McLarnon N. The ocular risks of human nail dust in podiatry. *Glasg Caled Univ* 2000. Available from: https://www.researchgate.net/publication/34503834_The_ocular_risks_of_human_nail_dust_in_podiatry
104 Abramson C, Wilton J. Inhalation of nail dust from onychomycotic toenails. Part II: clinical and serological aspects. *J Am Podiatr Med Assoc* 1985; **75**: 111–115.
105 Davies RR. Human nail dust in chiropdial practice: irritant, allergen, and source of antibodies to *Trichophyton rubrum*. *J R Soc Health* 1984; **104**: 2–5.
106 Coggins MA, Hogan VJ, Kelly M, *et al.* Workplace exposure to bioaerosols in podiatry clinics. *Ann Occup Hyg* 2012; **56**(6): 746–753.
107 Gris-Peg. Package Insert (Griseofulvin Ultramicrosized) Tablets, 125 mg; 250 mg [Internet]. Drugs@FDA: FDA Approved Drug Products. 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050475s057lbl.pdf
108 Nizoral. Package Insert (Ketoconazole) Tablets, 200 mg [Internet]. Drugs@FDA: FDA Approved Drug Products. 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018533s040lbl.pdf

 