Expert Opinion

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Treatment of onychomycosis with oral antifungal agents

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Onychomycosis is the most common nail disease and describes the invasion of the nail by fungi. Different clinical patterns of infection depend on the way and the extent by which fungi colonise the nail: distal subungual onychomycosis, proximal subungual onychomycosis, white superficial onychomycosis, endonyx onychomycosis and total dystropic onychomycosis. The type of nail invasion depends on both the fungus responsible and on host susceptibility. Treatment of onychomycosis depends on the clinical type of the onychomycosis, the number of affected nails and the severity of nail involvement. The goals for antifungal therapy are mycological cure and a normal looking nail. In this paper the treatment of onychomycosis with oral antifungal agents will be reviewed.

Keywords: nail, onychomycosis, oral antifungal, therapy

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1. Introduction

Onychomycosis is the most common nail disease and describes the invasion of the nail by fungi [1].

Although different molds and yeasts can be isolated from healthy and dystropic nails, the diagnosis of onychomycosis must follow strict clinical and mycological criteria, especially when dealing with non-dermatophytic molds (NDMs) [2]. NDMs account for 5 – 15% of all onychomycosis [2-5].

Onychomycosis affect toenails more frequently than fingernails, and this may be due to the growth rate which is three times slower for toenails than fingernails [4,6].

The progressive slowing of the nail growth rate observed with age may also explain why the prevalence of onychomycosis increases with age; the disease is uncommon in children.

Tinea pedis plantaris and interdigital tinea pedis often precede by years the onset of onychomycosis and are considered important factors for the development of the disease [7,8].

Different clinical patterns of infection depend on the way and the extent by which fungi colonise the nail [9]:

- distal subungual onychomycosis (DSO): when fungi reach the nail from the hyponychium and colonise the nail bed;
- proximal subungual onychomycosis (PSO): when fungi penetrate the nail via the proximal nail fold and localise under the proximal nail plate;
- white superficial onychomycosis (WSO): when fungi are localised on the nail plate surface;
- endonyx onychomycosis (EO): when the medial part of the nail plate is invaded with sparing of the nail bed;
- total dystropic onychomycosis (TDO): when the nail plate is diffusely invaded and friable.

The type of nail invasion depends on both the fungus responsible and on host susceptibility.

PSO is a typical example of how important the balance is between host susceptibility to onychomycosis and fungal pathogenicity for the development of the disease. For example, *Trichophyton rubrum* PSO only occurs in severely immunodepressed patients with a pre-existing tinea pedis by the same fungus, and it is considered to be a marker for HIV infection [10]. PSO due to NDMs (*Scopulariopsis brevicaulis*, *Fusarium* sp., *Aspergillus* sp.) is not a sign of immunodepression and occurs in healthy individuals [2].

Predisposing factors for onychomycosis include old age, diabetes, HIV infection, peripheral vascular impairment and peripheral neuropathies, podiatric abnormalities, sports activities and traumatic nail disorders [11].

The treatment of onychomycosis depends on the clinical type of the onychomycosis, the number of affected nails and the severity of nail involvement.

From a practical point of view, in patients with DSO we prescribe systemic treatment as first choice when more than three nails are affected and/or more than two-thirds of the nail.

WSO 'deep' are WSO that always require a systemic treatment [12,13]. PSO and EO can only be cured with systemic therapy.

The goals for antifungal therapy are mycological cure and a normal looking nail [14].

2. Onychomycosis due to dermatophytes

DSO is the most common type of onychomycosis due to dermatophytes, and is most frequently due to *T. rubrum* [8]. PSO caused by *T. rubrum* is rare and typical of HIV patients, where it is a marker of the disease [10]. The 'classical' form of WSO is usually caused by *Trichophyton mentagrophytes* var. interdigitale [12].

In HIV-infected patients and children, WSO is usually due to *T. rubrum* and is not only seen in the toenails but can also affect the fingernails. It may be difficult to discriminate between a WSO that has extended deeply and a PSO that has extended superficially.

EO is rare type of onychomycosis and is caused by *Trichophyton soudanense* and *Trichophyton violaceum* [8].

TDO may occur rarely as a primary condition and most commonly, in fact, represents the secondary evolution of untreated DSO, PSO, WSO and EO. Primary TDO is usually due to *Candida* and typically affects immunocompromised patients [8].

2.1 Systemic treatment

2.1.1 Terbinafine

Terbinafine is an allylamine derivative that inhibits the biosynthesis of the principal sterol in fungi, ergosterol, at the level of squalene epoxidase. Squalene epoxidase inhibition results in ergosterol-depleted fungal cell membranes (fungistatic effect) and the toxic accumulation of intracellular squalene (fungicidal effect) [15].

Following oral administration, terbinafine is rapidly absorbed and widely distributed to body tissues including the nail matrix. Nail terbinafine concentrations are detected within 1 week of starting therapy and persist for ≥ 30 weeks after the completion of treatment. It is usually administered at a dose of 250 mg/day or as pulse therapy at a dose of 500 mg/day for 1 week a month every month [16,17]. Treatment duration is 6 weeks for fingernails and 12 weeks for toenails.

Recently it has been used to treat great toenail DSO due to *T. rubrum* at the pulsed dosage of 250 mg/day for 1 week a month every 2 – 3 months [18].

Dosages in children are: < 20 kg: 62.5 mg/day; 20 – 40 kg: 125 mg/day; > 40 kg: 250 mg/day [19].

Interactions with other drugs are extremely rare, even if terbinafine is a competitive inhibitor of the cytochrome P450-linked enzyme 2D6 (CYP 2D6) [20] (**Table 1**). Adverse effects may involve the gastrointestinal function and the skin. Patients with known lupus erythematosus or photosensitivity are predisposed to drug-induced or drug-exacerbated disease. Taste alterations (metallic taste) typically occur 5 – 8 weeks after starting treatment. It is not recommended in patients with liver disorders, and serum transaminase tests are mandatory before starting treatment. Pancytopenia may also occur.

2.1.2 Itraconazole

Itraconazole is a synthetic triazole with a fungistatic activity and a broad spectrum of action. It can be detected in nails 1 (fingernails) – 2 weeks (toenails) after the start of therapy and it is still detectable in nails 27 weeks after stopping administration [21]. It is administered as pulse therapy at a dose of 400 mg/day for 1 week a month [22]. Treatment duration is 6 weeks for fingernails and 12 weeks for toenails. Dosages in children are 5 mg/kg/day as pulse treatment (1 week a month). Duration is two pulses for fingernails and three pulses for toenails [19].

This drug should be administered with a high-fat meal and/or acidic beverage to improve its absorption. Agents that increase gastric alkalinity (histamine H_2 blockers, antacids, proton pump inhibitors) reduce itraconazole absorption. If there are no therapeutic alternatives, itraconazole should be administered 2 h before one of these agents.

With itraconazole the basis of some drug interactions is the inhibition/induction of the CYP P450-linked enzyme 3A4 (CYP 3A4). This enzyme is the most common isoform found in the liver and is responsible for drug metabolism [20] (**Table 1**).

Drug interactions are considered to be clinically significant if the therapeutic effectiveness of one of the drugs is decreased or if an adverse event manifests itself.

Adverse effects are rare and may involve gastrointestinal symptoms and skin alterations. Data from the US FDA's Adverse Event Reporting System suggest that the use of itraconazole is associated with congestive heart failure. Labelling of itraconazole has been changed to alert physicians to this new finding.

Table 1. Drug interactions with oral antifungals.

Oral antifungals	Drug interactions
Terbinafine	Dosage adjustment requested: tricyclic antidepressants; cimetidine; cyclosporin; rifampin; theophyilline; warfarin
Itraconazole	Contraindicated: alprazolam; astemizole; cisapride; HMG-Co reductase inhibitors; midazolam; terfenadine; triazolam; vincristine Itraconazole efficacy reduced: carbamazepine; isoniazid; phenytoin; phenobarbital; rifampin; rifabutin Dosage adjustment requested: buspirone; busulfan; cyclosporin; digoxin; dihydropiridines; HIV protease inhibitors; hypoglicemic agents; metylprednisolone; quinidine; sidenafil citrate; tacrolimus; warfarin
Fluconazole	Controindicated: astemizole; terfenadine Dosage adjustment requested: tricyclic antidepressants; cisapride; cyclosporin; hydrochlorothiazide; phenytoin; rifampicin; oral contraceptives; sulfonylurea; theophylline; tolbutamide; warfarin; zidovudine

HMG-Co: 3-Hydroxy-3-methylglutaril coenzyme.

Box 1. Local and systemic reasons for treatment failure.

Local

- Lateral involvement
- Dermatophytoma
- Extensive onycholysis
- Massive hyperkeratosis
- Lunula involvement

Systemic

- Immunodepression
- Diabetes
- Impaired peripheral circulation
- Slow nail growth

2.1.3 *Fluconazole*

Fluconazole is a *bis*-triazole broad-spectrum fungistatic drug with high oral bioavailability.

Nail fluconazole concentrations are detected within 1 day of treatment and its uptake by the nail increases with the length of treatment. Its concentration falls slowly after the drug is stopped, and it is still detectable in nails 5 months after the end of treatment [21].

Fluconazole is administered at a dose of 50 mg/day or 300 mg/week [23,24]. Treatment should be prolonged for ≥ 6 months for fingernails and 12 months for toenails. Dosages in children are 3 – 6 mg/kg/week. Duration of treatment is 12 weeks for fingernails and 26 weeks for toenails [19].

It inhibits CYP P450-linked enzymes (CYP 3A4 and 2C9), thus intensifying the action of many other drugs [20] (**Table 1**). Adverse effects may involve gastrointestinal symptoms.

In conclusion, oral antifungals for children would ideally be available in liquid and/or tasteful formulations, but they are usually available as tablets that are difficult to swallow and cannot easily be divided into fractions to obtain the perfect pro-weight dosage. Although itraconazole is also available in an oral solution, this is not approved for onychomycosis and contains cyclodextrin that may cause diarrhoea in children. Like itraconazole, fluconazole exists in the form of oral suspension, which would be easily administered to children but again is not approved [25]. Strategies that can be utilised for administering systemic antifungals in children therefore include:

- chopping the terbinafine tablet into small pieces and putting them into the chocolate cream of a chocolate-filled biscuit
- opening the itraconazole capsule and mixing the content with fatty food such as peanut butter, jelly or bread.

Mycological cure of onychomycosis is obtained when both microscopic and cultural examination are negative. We usually control patients every 2 or 3 months and perform mycology.

Clinical cure may take several months to be achieved, due to the slow growth rate of toenails, thus rendering it necessary to continue to follow patients further after the discontinuation of treatment, both to assess mycology and to control gradual development of a healthy nail.

Clinical cure may be impossible to obtain when nails had previous non-mycotic onychodystrophies that persisted after the disappearance of the fungi. This can cause patient's dissatisfaction, especially if it is not explained clearly before starting treatment for onychomycosis.

Percentages of cure rates obtained in dermatophyte toenail DSO with the three different antifungals in various modalities of administration may vary [26,27], but in our experience, terbinafine and itraconazole are able to cure ~ 80% of toenail DSO.

Reasons for treatment failure, if we exclude poor patient compliance and impaired drug absorption, include local and systemic factors [11,28-30] (**Box 1**).

We always combine systemic treatment with mechanical or chemical avulsion of the affected nail plate in patients with DSO with the clinical features listed in **Box 1**.

In patients with systemic factors that contribute to possible treatment failure, the treatment options are:

- sequential therapy with itraconazole followed by terbinafine: the suggested regimen is two pulses of itraconazole

400 mg/day for 1 week a month followed by one or two pulses of terbinafine 500 mg/day for 1 week a month [31];
- supplemental therapy with terbinafine followed by itraconazole: the suggested regimen is terbinafine 250 mg/day for 3 months followed by itraconazole 400 mg/day for 1 week at month 6 if, after the 3 months of terbinafine treatment, culture is positive and/or onychomycosis has progressed proximally [32].

The authors approach, which includes all patients, is to prescribe 3 months of either terbinafine or itraconazole and perform a clinical and mycological evaluation after these 3 months. If mycology is positive or the fungus has progressed proximally 1 or 2 more months of the same antifungal is prescribed or the drug is changed.

3. Onychomycosis due to non-dermatophytic molds

Responsible agents for onychomycosis due to NDMs include *S. brevicaulis*, *Fusarium* sp., *Acremonium* sp., *Aspergillus* sp., *Scytalidium* sp. and *Onychocola canadiensis*.

DSO due to *Acremonium* sp. usually affects toenails and presents as one or few longitudinal white streaks. *Aspergillus* sp., *Fusarium* sp. and *S. brevicaulis* may produce DSO that usually involves 1 toenail with severe nail invasion associated with periungual inflammation.

In DSO due to *Scytalidium* sp., periungual tissues and nail plate show a black pigmentation.

PSO due to *Aspergillus* sp., *Fusarium* sp. and *S. brevicaulis* is typically associated with marked painful inflammation of the periungual tissues, and this is the typical clinical manifestation of onychomycosis due to these molds.

WSO are generally due to *Fusarium* sp., *Aspergillus* sp. and *Acremonium* sp. Clinically, they may show a diffuse involvement of the nail, both in its width and depth. This is especially seen in WSO due to *Fusarium* sp. and *Aspergillus* sp. As seen in the other types of onychomycosis due to NDMs periungual inflammation may be associated but usually without pus discharge.

3.1 Systemic treatment

DSO and PSO due to *Aspergillus* sp. can be treated with systemic terbinafine 250 mg/day for 2 – 3 months or itraconazole 400 mg/day for 1 week a month for 2 – 3 months [33].

Pulse terbinafine (500 mg/day for 1 week a month for 3 months) is also effective in *Aspergillus* sp. onychomycosis [34].

DSO and PSO due to *Acremonium* sp., *S. brevicaulis*, *Fusarium* sp., *O. canadensis* and *Scytalidium* sp. are very difficult to cure. The combination of topical antifungals in nail lacquer and/or periodic removal of the affected nail, with systemic treatment increases the percentage of cure. However, about a quarter of patients remain mycologically positive even after prolonged topical treatment.

4. Onychomycosis due to *Candida*

Primary nail plate invasion by *Candida* is rare in the absence of immunosuppression, and it is typically observed in chronic mucocutaneous canidiasis (CMCC) in HIV-positive patients and in patients with iatrogenic immunosuppression.

In CMCC, onychomycosis is associated with inflammation of the proximal nail fold, the nail matrix, nail bed and the hyponichium. In HIV-positive and in immunosuppressed patients clinical presentation is milder, with only one or few fingernails affected.

Candida albicans has been frequently isolated from the subungual area of onycholytic nails and from the proximal nail fold in chronic paronychia. In both these conditions, *Candida* colonisation is a secondary phenomenon because the antimycotics do not cure the nail abnormalities [35].

The improvement of chronic paronychia that can be observed after systemic antifungals is possibly due to the treatment-induced disappearance of *Candida* antigens that may, in some patients, induce an hypersensitivity reaction [36].

4.1 Systemic treatment

Treatment of *Candida* onychomycosis is complicated by the fact that underlying immunodeficiency causes repetitive relapses of the nail infection.

Itraconazole and fluconazole are equally effective in treating *Candida* onychomycosis [33].

Itraconazole can be utilised both as continuous treatment at a dose of 200 mg/day or as pulse therapy at a dose of 400 mg/day for 1 week a month.

Fluconazole can be utilised at a dose of 50 mg/day or as pulse therapy at a dose of 300 mg/week.

5. Conclusion

Because differential diagnosis of onychomycosis includes a large number of different diseases, treatment should only be started when the diagnosis is confirmed by a positive microscopy and/or culture.

Systemic treatment with terbinafine and itraconazole, for the 'standard' period of 3 months, produces mycological cure in > 90% of fingernail infections and in ~ 80% of toenail infections with an acceptable adverse-effect profile [37].

Partial nail avulsion and concomitant treatment with a topical antifungal agent increases the percentage of cure. Prolonging systemic treatment with the same or another antifungal until cure is obtained may be necessary.

6. Expert opinion

Onychomycosis of the toenails is more difficult to cure and recurs more frequently than onychomycosis of the fingernails. Relapses are not uncommon (≤ 25% of cured patients), and the patient should be evaluated periodically until clinical cure [28,38].

A positive mycology may indicate poor patient compliance, poor drug availability and, more rarely, fungal insensitivity to antifungals. A careful evaluation of any patient is necessary to decide whether to go on with the same treatment or to change antifungal.

When onychomycosis is cured, it is advisable to continue application of a topical antifungal in nail lacquer on the previously affected nails and a topical antifungal in cream or solution on soles and toe webs to reduce the chance of recurrences [39].

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