REVIEW

Onychomycosis nailed

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Abstract

Fungal infection of the nail is a common condition that causes much concern because of its disfiguring appearance. Although specific treatment is available for this condition, treatment outcome is variable and persistent nail dystrophy post-treatment may cause distress to both the patient and the physician. This article describes the current available treatment options for onychomycosis, management approach and the expected treatment outcome to enhance primary care physicians' confidence in managing this condition. Oral antifungal agents such as terbinafine and itraconazole are good treatment options for onychomycosis. Combination therapy using oral antifungal agents with topical lacquer preparations may provide added benefits. Evaluation of patient's expectations, providing information on treatment outcome, clinical cure and recurrence rates are essential in the management of onychomycosis. This article is intended to guide primary care physicians to achieve realistic treatment goals and for a satisfactory experience in the overall management of this challenging condition.

Introduction

Onychomycosis or fungal infection of the nail is a common presentation in primary care, which is responsible for almost 50% of all nail diseases.[1] It may be caused by dermatophytes, non-dermatophyte moulds or candida species. Onychomycosis is commonly classified as distal lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO) and total dystrophy (TD) based on the pattern and the site of infection involving the nail complex.

It is estimated that about 32% of the elderly population are affected by onychomycosis and the prevalence increases with advancing age.[2] Toenails are more frequently affected compared to fingernails and almost 30% of this condition occurs concurrently with cutaneous fungal infection, especially tinea manum and tinea pedis. Risk factors for onychomycosis include diabetes, immunosuppression, advancing age, peripheral arterial disease, sports activities and pre-existing dysmorphic nails due to disease such as psoriasis or trauma.[3]

The first step in managing onychomycosis is to make an accurate diagnosis. This requires both clinical identification and laboratory confirmation using microscopy and culture.[4] Clinical features suggestive of onychomycosis, based on nail morphology, include thickened nail plate, discolouration, onycholysis and subungual hyperkeratosis. Laboratory identification of fungal element requires proper nail sampling technique with adequate amount of specimen to ensure a good culture yield.[5] Laboratory features include positive microscopic findings of septate hyphae and/or arthroconidia as well as a positive culture for dermatophytes (e.g. Trichophyton, Microsporum, Epidermophyton) or non-dermatophyte nail pathogens.[4] Although 30% to 50% of nail cultures yield false negative results, most guidelines recommend fungal culture to confirm diagnosis of onychomycosis prior to treatment initiation. This is because treatment duration is long and is associated with potential adverse drug reactions. It is also difficult to exclude treatment failure in the event of lack of response to therapy.

Treatment options and duration

The aim of treating onychomycosis is to achieve both clinical (clinically normal nails) and mycological cure (negative microscopy and culture). Although appropriate treatment may restore the clinical appearance of the nails, the rates are disappointingly low (35-50%),[6] which, coupled with high relapse rates (10-53%), are the biggest challenge in the management of onychomycosis. However, treatment is required to prevent complications such as cellulitis and gangrene, especially among high risk patients such as diabetics.[7,8] The choice of treatment depends on the causative organism, the type of onychomycosis (classification), the number and the severity of nails involved, whether the infection is confined to fingernails, toenails or involve both and previous treatment history pertaining to treatment failures.[9] Treatment options include systemic agent, topical nail lacquer, nail avulsion and combination of these modalities.

a) Systemic agents

Oral antifungal agents are the mainstay of therapy for onychomycosis and are considered as first line in most cases. Terbinafine and itraconazole are the two main systemic agents used and both have shown good results.

Terbinafine is currently the most effective oral antifungal agent for onychomycosis achieving mycological and clinical cure rates of 78% and 53%, respectively, at 1 year post-treatment using continuous dosing between 12 and 16 weeks.[10] Terbinafine can be used for dermatophytes, *Candida* species and non-dermatophyte moulds, especially *Aspergillus fumigatus* and *Scopulariopsis brevicaulis.*[11] The recommended dosage of terbinafine is 250 mg daily for 6 weeks for fingernail and 12 weeks for toenail onychomycosis. Pulse dosing of terbinafine may be considered as its pharmacological properties persist in the nail for several weeks after withholding treatment.[12,13] Side effects of terbinafine are minimal, mainly consisting of gastrointestinal symptoms. Abnormalities of the liver enzyme, drug-induced hepatitis and drug interactions are less frequent compared to itraconazole. Although all species of fungus respond well to terbinafine, non-dermatophyte moulds are less responsive and may require longer treatment duration.[14]

Another effective oral agent is itraconazole. Itraconazole is effective against dermatophytes, yeasts and non-dermatophyte moulds.[15] Itraconazole, either continuous (200 mg daily for 3 months) or in pulses, has similar mycological cure rates of 66% and 69%, respectively, at 12 months.[16] Pulse regime is administered using 200 mg twice daily dosing for 1 week, followed by 3 weeks of drug-free period. Fingernail onychomycosis requires two, whereas toenails require three such pulses. Although itraconazole is an effective agent for onychomycosis, it has lower long-term mycological and clinical cure rates for onychomycosis compared to terbinafine.[10] Drug-induced hepatitis secondary to itraconazole is a rare side effect, accounting for less than 2% of cases and commonly presents as liver enzyme abnormalities or cholestasis. This adverse effect is more common with continuous therapy of itraconazole beyond 1 month, whereas pulse therapy appears to be safer. It is recommended that liver enzymes are evaluated at baseline and monitored during continuous therapy.[17] The benefits of itraconazole should be weighed against the risks in patients with pre-treatment liver enzyme abnormality or disease.

Fluconazole may be used but it requires longer treatment duration compared to itraconazole and provides only moderate success. Oral ketoconazole should not be used as a first-line therapy for onychomycosis or any other fungal infection because of the risk of severe liver injury and adverse drug interactions.[18] Griseofulvin should be avoided because of its low cure rates. Newer antifungal agents such as ravuconazole and posaconazole are currently being studied and may be available in the near future.[14]

b) Topical agents

Topical antifungal cream used for cutaneous fungal infections is generally ineffective for the treatment of onychomycosis because it has poor nail plate penetrating ability. It may be beneficial in treating concurrent nail fold disease such as paronychia or tinea pedis secondary to candida.[19]

New topical agents in lacquer preparations that are applied as nail polish to the affected nails are currently available. These agents have enhanced penetrating and fungicidal activity with minimal side effects. Lacquer preparations provide prolonged drug contact time on the nail and enhance antifungal concentration by evaporation.[14] Ciclopirox 8% and amorolfine 5% nail lacquers are the two most commonly used topical antifungal agents. Ciclopirox nail lacquer is applied daily to the nail for about 4 months or till clinical cure is achieved. Amorolfine nail lacquer is applied 1 to 2 times a week for 6 months up to 1 year and may produce higher cure rates compared to ciclopirox.[19] The use of nail lacquers as a post-treatment prophylactic agent to prevent recurrence and relapses may also be considered, as two studies have shown benefits, whereas one showed no association.[20-22]

Monotherapy using ciclopirox and amorolfine lacquers yields lower mycological and clinical cure rates (47-67% and 38-54%, respectively) compared to a combination of systemic and topical therapies (72.3-93.9%).[14] However, monotherapy may be considered in superficial white onychomycosis (SWO), distal nail disease involving less than 50% of the nail, in the absence of dermatophytoma (longitudinal yellow

bands or spikes) and as a long-term prophylactic agent. Topical monotherapy should be avoided if the onychomycosis affects more than 50% of the nail, in proximal subungual onychomycosis (PSO), multiple nail involvement or when lunula of the nail is involved. Systemic agents should be considered if there is no response to topical monotherapy after six months of treatment.[15] Topical ciclopirox is also effective against non-dermatophyte moulds such as *Scopulariopsis brevicaulis*, *Scytalidium dimidiatum*, *Aspergillus* and *Acremonium* species in addition to dermatophytes and yeast.[23]

c) Combination therapy

Combination therapy may produce better treatment outcomes possibly due to different mechanisms of action and drug synergy.[14] Studies have shown that the combination of oral antifungal agents and topical nail lacquer is more effective in the treatment of onychomycosis. Lecha et al. demonstrated excellent global response (mycological and clinical cure rate) of 94% using combination of 200 mg daily itraconazole (for 3 months) and weekly application of 5% amorolfine nail lacquer (for 6 months).[24] Another well-designed study also demonstrated higher global response rate of 72.3% using a combination of oral terbinafine 250 mg daily for 3 months and weekly 5% amarolfine nail lacquer for 15 months compared to terbinafine monotherapy for 3 months (37.5%).[25]

Surgical or chemical nail avulsion (using 40% urea) in combination with oral antifungal is another option. This option is suitable for thick painful nails. However, the procedure itself may cause pain and disfigurement of the nail. The overall clinical results using this mode of therapy may not be satisfactory.[14]

Newer treatment modalities such as laser, light therapy, ultrasound-mediated delivery of drug system, boosted antifungal therapy all currently under study and may be available in the near future.[14] The current treatment options for onychomycosis are summarised in Table 1.

Table 1. Treatment options for onychomycosis[12-14]

Drug	Dose	Duration	Contraindication/ Adverse effects
ORAL **Terbinafine**	**Continous dosing** 250 mg daily **OR** **Pulse dosing** 500 mg daily for 1 week followed by 3-weeks drug-free period (1 pulse)	6 weeks for fingernails 12 weeks for toenails 2 pulses for fingernails 4 pulses for toenails	Contraindicated in pregnancy Gastro-intestinal disturbances
Itraconazole	***Continuous dosing** 200 mg daily **OR** **Pulse dosing** 200 mg twice daily for 1 week followed by 3 weeks of the drug-free period (1 pulse)	3 months 2 pulses for fingernails 3 pulses for toenails	Contraindicated in pregnancy Used with caution in congestive cardiac failure Drug-induced hepatitis and gastro-intestinal disturbances Drug interaction with statins, benzodiazepines and anticoagulants
TOPICAL **Ciclopirox 8%** **Amorolfine 5%**	Applied daily on nail Applied 1 to 2 times a week on nail	For 4 months For 6 months to 1 year	Minimal local irritation Minimal local irritation

Drug	Dose	Duration	Contraindication/ Adverse effects
COMBINATION TREATMENT	**Combination 1** Itraconazole 200 mg daily **PLUS** Weekly application of amorolfine 5% nail lacquer **OR** **Combination 2** Terbinafine 250 mg daily **PLUS** Weekly amorolfine 5% nail lacquer	3 months 6 months 3 months 15 months	Similar to side effects of the individual drugs Similar to side effects of the individual drugs

*Drug-induced hepatitis is more common with continuous therapy of itraconazole when used for more than 1 month.

Prognosis

The morphology of the nail, causative pathogen, host and environment factors influence the treatment outcome of onychomycosis. The superficial white onychomycosis (SWO) type has the best treatment outcome compared to the other types of onychomycosis. Larger area of nail involvement such as total dystrophic type and involvement of the lateral edge of the nail predicts poorer prognosis.

The presence of sub-ungual hyperkeratosis also predicts poor treatment outcome as these contain air pockets, which facilitate the survival of dormant fungal spores. These spores form dermatophytoma, which is refractive to antifungal treatment. Dermatophytoma is clinically identified as longitudinal yellow bands also known as spikes seen in the nail plate.[26] Other factors such as older age, immunosuppression, poor peripheral circulation and infection with non-dermatophyte moulds also predict less favourable treatment outcome.[4,14]

Treatment end point

Treatment success is difficult to measure as the definition of cure for onychomycosis is variable. Mycological cure generally refers to the absence of fungi post-treatment, detected on microscopy using potassium hydroxide or by culture. Clinical cure measures the percentage of nail free from clinical signs of fungal infection based on nail morphology such as thickened nail plate, discolouration, onycholysis and subungual hyperkeratosis measured post-treatment. Complete cure or global response refers to the combination of clinical and mycological end points. Variable study designs and inconsistent definitions of cure stated in the literature results in a wide range of documented treatment responses in various trials. This makes the evaluation and comparison of cure for onychomycosis difficult.[4]

After treatment initiation, clinically normal nail plate can be seen growing at the proximal end of the nail. The duration for the entire nail to grow and appear normal may take anytime between 6 months for the fingernails and up to a year or more for toenails. This is the average nail plate growth turnover rate, which is the time taken to replace the damaged nail. Ageing, consumption of chemotherapeutic drugs such as methotrexate or azathioprine and pre-existing nail diseases such as yellow nail syndrome, lichen planus and onychomycosis itself can slow down the linear growth of nails and hence delay the much anticipated treatment response.[27]

Recurrence, relapse, prophylaxis and prevention

Recurrence of onychomycosis after treatment is quite common occurring in about 10% to 53% of cases.[10] Recurrence could be either due to relapse, which is due to inadequate or inappropriate treatment or re-infection, which is a new infection after completing treatment. Recurrence of onychomycosis secondary to non-dermatophyte moulds is common because of the lack of definitive treatment for these fungi.[3] A meta-analysis of five trials found that relapses are more common after treatment with itraconazole compared to terbinafine.[28] Pulse itraconazole therapy showed a relapse rate of 22%, whereas continuous treatment with terbinafine showed a relapse rate of 9%. In cases of relapse, a second treatment with the same dose of terbinafine conferred high mycological and

clinical cure rates (92% and 76%, respectively) at 18 months.[10] Drug resistance to antifungal agents may cause concern, as some studies have demonstrated this possibility.[29,30]

Prevention of onychomycosis includes adequate treatment of any concurrent tinea, screening and treating family members for co-existing tinea.[3] Recurrences can be prevented by improving feet hygiene, that is, keeping it dry, trimming nails short, using regular topical antifungals and avoid walking barefoot.[20] Post-treatment prophylaxis with topical lacquer amorolfine may also be considered.[10]

Non-dermatophyte moulds

A special mention of non-dermatophyte mould (NDM) is warranted as it is a common pathogen isolated in cases of onychomycosis in tropical climates.[31,32] The presence of NDM by culture poses a diagnostic dilemma as these pathogens are sometimes considered as contaminants. Hence, isolation of NDMs such as *Aspergillus* or *Fusarium* may require repeat cultures. In the presence of sequential cultures yielding similar pathogens, heavy growth colonies and a positive direct microscopy, a clinical correlation is required to determine its significance.[33] Six major criteria are generally used for the identification of NDMs. These are microscopic identification of the NDM using potassium hydroxide (KOH) preparation, isolation by culture, repeat isolation by culture, inoculum counting, failure to isolate a dermatophyte in culture and histology.[23] Gupta et al. have recommended using three out of these six criteria for a definitive diagnosis of non-dermatophyte mould, two of which should include positive microscopy and culture.[23] Hence, in primary care practice, identification of NDM by microscopy in the office as well as sequential positive fungal culture of the same pathogen can be used to diagnose NDM as the causative agent for onychomycosis.

Currently, there is yet a single effective treatment agent against these pathogens. Recent literature suggests that terbinafine and itraconazole are efficacious agents for NDMs, especially *Scopulariopsis brevicaulis* and *Aspergillus* species. Topical ciclopirox may be beneficial against *Scopulariopsis brevicaulis*. A combination of different modalities of treatment such as systemic, topical and nail avulsion may also be considered.[23]

Conclusion

Medical management of onychomycosis is challenging and often frustrating due to the unpredictable treatment outcome. At times, low rates of clinical cure and high rates of recurrences may be experienced. An accurate diagnosis of onychomycosis that fulfils both the clinical and laboratory criteria is mandatory before initiating treatment in view of long treatment duration and the potential side effects of the antifungal agents. While current evidence supports the use of terbinafine or itraconazole as effective therapies, the combination of oral antifungal and topical nail lacquer may prove to be more effective. The isolation of NDMs from nail culture may predict a less favourable treatment outcome as the current available treatment options are less effective against these pathogens. Management of onychomycosis should include the assessment of patient's expectations prior to starting treatment and explanation that treatment may not restore the normal appearance of the nail. Patients should also be informed of the lag time before treatment results can be appreciated and the risk of having recurrences. Knowledge of the currently available treatment options, awareness of patients' expectations and understanding the possible treatment outcomes will help physicians achieve realistic treatment goals. With all these issues addressed, the management of onychomycosis may prove to be a more rewarding experience for both patients and physicians.

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