SKIN

CLINICAL MANAGEMENT RECOMMENDATIONS

How to Manage Onychomycosis

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The role of oral antifungal medications in treating onychomycosis continues to be revisited as new topical antifungal medications are developed. Efinaconazole and tavaborole, for example, are generally safe and may be preferred by patients. However, oral antifungals may be required for some patients to be adequately treated.

The purpose of this article is to provide a quick reference for the clinical management of onychomycosis with maximum efficacy and minimal side effects in mind. We will address the following questions: 1) How do you diagnose onychomycosis? 2) What is the role of oral antifungals? 3) What is the role of topical antifungals? 4) When are oral medications *really* necessary? 5) What are dermatophytomas and how should they be treated?

We conclude that terbinafine is the current gold standard for treating tinea unguium, particularly when patients suffer from comorbidities such as diabetes, immunosuppression, or psoriasis. Topical antifungals may stand alone or act as adjunct therapy to improve efficacy and maintain response, though ease of application for patients and cost are important considerations. Further, efinaconazole solution applied to the subungual space has proven effective in cases of onychomycosis complicated by a dermatophytoma.

HOW DO YOU DIAGNOSE ONYCHOMYCOSIS?

Only 50% of nail dystrophies are caused by fungal pathogens, so confirmatory laboratory testing to establish the diagnosis of onychomycosis is important before treatment is initiated, and can be done by PAS or KOH (showing septate hyphae) and/or by fungal culture or PCR to identify the causative pathogen. While PAS stain is considered more sensitive than KOH preparation, it is significantly more expensive. Although both fungal culture and PCR identify the pathogen, it may take up to 6 weeks for a result. Alternatively, a recent paper suggested treatment with oral terbinafine after clinical confirmation alone without laboratory testing is cost-effective.[1]

WHAT IS THE ROLE OF ORAL ANTIFUNGALS?

Oral antifungals for onychomycosis include terbinafine, itraconazole, or fluconazole, and all of these are effective against dermatophyte fungi that most commonly cause onychomycosis. Of these, terbinafine has a low cost, superior efficacy, and lacks significant drug-drug interactions, so is usually considered first line treatment.[2-3] It is effective against dermatophytes, but not *Candida* or non-dermatophyte molds.

Terbinafine is dosed at 250 mg daily for 6 weeks in fingernails and for 12 weeks in toenail involvement, but a more prolonged course is often required in patients with extensive infection. The most common adverse event associated with terbinafine is gastrointestinal upset, but dysgeusia and cutaneous drug reactions ranging from a mild morbilliform eruption to toxic epidermal necrolysis have been reported which is why empiric treatment is not always without consequence.[4-5] Also, be on the alert for terbinafine resistance which has been recently reported.[6]

Itraconazole is more expensive than terbinafine but may be useful in cases of terbinafine intolerance or non-responsiveness and in non-dermatophyte infections. Its spectrum of activity includes dermatophytes, non-dermatophyte molds and yeasts including *Candida*. Itraconazole is dosed at 200 mg daily for three to four continuous months or alternatively (pulsed) 400 mg daily for one week per month for three to four months. Caution is needed in patients with congestive heart failure and patients who are taking statins due to the drug's potent inhibition of CYP3A4 leading to an increased risk of rhabdomyolysis.[7] There are other drug-drug interactions as well, so intermittent dosing may be preferred in patients on multiple medications.

Fluconazole is not FDA-approved for the treatment of onychomycosis but is approved for this indication in many other countries and, like itraconazole, has a broad spectrum of activity. A pivotal study compared once weekly dosing of 150, 300, or 450 mg fluconazole and showed excellent results (Table 1).[8] However, one or two 200 mg tablets taken together once weekly is a practical option that can be continued until the nail is clear. This drug is generally well tolerated and is even approved in children for different indications. Complete and mycologic cure rates from phase III clinical studies are in Table 1.

Table 1. Complete and mycologic cure rates for commonly used oral and topical antifungals.

	Complete Cure (%)*	*Mycologic Cure (%)*
Terbinafine[9]	38	70
Itraconazole[10]	14	54
Fluconazole[11]	37 – 48**	47 – 62**
Efinaconazole[12]	15.2 – 17.8	53.4 – 55.2
Tavaborole[13]	6.5 – 9.1	31.1 – 35.9
Ciclopirox[15]	5.5 – 8.5	29 – 36

*Complete cure is defined as normal nail plus mycologic cure.
**Per package label.

WHAT IS THE ROLE OF TOPICAL ANTIFUNGALS?

Topical antifungals may be used either alone or in combination with systemic agents and include efinaconazole 10% solution and tavaborole 5% solution. Both of these agents are effective in vitro against dermatophytes, non-dermatophyte molds, and yeasts but were studied exclusively in cases of nail dermatophytosis. Efinaconazole 10% was approved in 2014, and phase III studies showed a 53.4 - 55.2% mycologic cure rate and a 15.2-17.8% complete cure rate when applied daily for 48 weeks (Table 1).[12]

Tavaborole 5% is a novel boron-containing solution with a low molecular weight that easily penetrates the nail plate. Phase III trials showed a 31.1 – 35.9% mycologic cure rate and a 6.5-9.1% complete cure rate when

applied daily for 48 weeks (Table 1).[13] The superior efficacy of efinaconazole 10% is likely due to its low surface tension which allows for greater subungual distribution.[14] However, our experience is that these agents have better clinical efficacy than data suggest.

Other topical options include ciclopirox 8% or amorolfine 5% lacquer. Both medications are applied to the nail plate and contiguous skin for 48 weeks. Mycologic and complete cure rates for ciclopirox 8% lacquer are 29-36% and 5.5-8.5% respectively, and are similar to tavaborole.[15] Amorolfine is not available in the US. The limitation of ciclopirox and amorolfine is the lacquer vehicle that leaves behind a film on the nail plate surface which, after multiple applications, can compromise diffusion of the agent through the nail plate. Additionally, it is difficult to apply the lacquer in the subungual space where the dermatophyte resides.

Topical treatment also has a role in improving efficacy and maintaining response to systemic treatment. Topical treatment may also reduce the total amount of antifungal agent required. For example, the addition of daily ciclopirox 8% lacquer to intermittent oral terbinafine (250 mg daily for four weeks followed by a four-week drug holiday and an additional four weeks of terbinafine) has shown comparable efficacy to 12 weeks of continuous terbinafine.[16] Limiting exposure to oral agents over time may limit adverse effects.

Additional data has shown that 250 mg terbinafine for 12 weeks plus amorolfine 5% applied once every 2 weeks delayed recurrence of nail disease by 200 days.[17] While these data include the older topical antifungals, it is reasonable to assume that adjunct therapy with newer topical agents would show similar results. Although treatment with topical antifungals avoids systemic side effects, it is important to remember that topical therapies may not be feasible for patients whose movements are limited by severe arthritis or body habitus.

WHEN ARE ORAL MEDICATIONS *REALLY* NECESSARY?

Certain patients may require treatment with oral antifungals and are unlikely to respond to topical agents. These include patients with primary or secondary immunosuppression. Impaired cell-mediated immunity often manifests itself in changes in the nails, hair, and skin. A study by Chang *et al.* in non-dermatological patients reported that 70% of patients with mycotic leukonychia, a mixed form of white superficial onychomycosis (WSO) and proximal subungual onychomycosis (PSO), also suffered from immunosuppression.[18]

While primary immunodeficiency syndromes are rare, patients with HIV or patients on chronic immunosuppressive therapies are commonly encountered. Other comorbidities such as diabetes, peripheral vascular disease, and nail psoriasis result in relative immunodeficiency from compromised blood flow at the site of infection. For example, a multi-center study looked at psoriatic patients with toenail onychodystrophy and found that 27% of these patients had positive mycology (defined as either KOH positive or culture positive for a dermatophyte). [19] A later systematic review found a prevalence of 18% among psoriatic patients compared to 9.1% among the control group.[20]

Thus, these patients need agents that readily absorb through the nail plate and accumulate at high concentrations for adequate treatment of their infection. Terbinafine is the most economical and effective treatment for

dermatophytosis in these patients. Itraconazole is preferred when covering non-dermatophyte molds and yeasts.

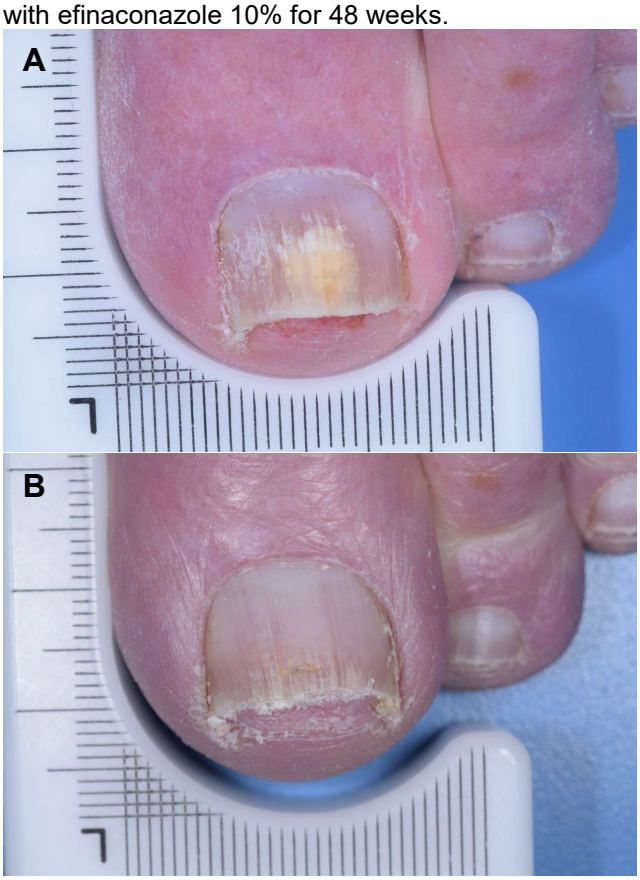
WHAT ARE DERMATOPHYTOMAS AND HOW SHOULD THEY BE TREATED?

Dermatophytomas are orange or yellow longitudinal streaks or patches in the nail bed composed of compacted dermatophyte hyphae and surrounded by a biofilm (Figure 1A). Dermatophytomas do not respond well to oral antifungal agents likely because the biofilm blocks penetration of the drug. Though patients with dermatophytomas were excluded from phase III efinaconazole trials, a recent case study indicated that topical efinaconazole 10% is effective as the sole treatment for a dermatophytoma.[21] An additional phase IV trial showed complete resolution of all 20 dermatophytomas that were treated with efinaconazole 10% for 48 weeks (Figure 1A and 1B).[22]

HOW SHOULD PHYSICIANS DISCUSS ONYCHOMYCOSIS WITH PATIENTS?

- Patients with onychomycosis desire to be treated, often because of embarrassment and disfigurement associated with their disease. Nails also provide a function that if lost can make simple tasks such as scratching or buttoning a shirt challenging.
- Oral antifungals used in onychomycosis have been available for about 25 years, and they are generally both effective and safe. Terbinafine is the current gold standard.
- Topical agents are also effective and may be used as adjunct treatment to systemic medications or as monotherapy. They are more expensive than the oral medications but offer an excellent safety profile and are generally preferred by patients. The newer solutions offer more flexibility in delivery and can be applied in the subungual space.

Figure 1: A) Left great toe with onychomycosis and a dermatophytoma present prior to treatment with efinaconazole 10%. B) Left great toe after treatment with efinaconazole 10% for 48 weeks.



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