Onychomycosis

Evaluation, Treatment Options, Managing Recurrence, and Patient Outcomes

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KEYWORDS

• Onychomycosis • Efinaconazole • Tavaborole • Laser • Toenail
• Trichophyton rubrum • Mycosis • Tinea pedis

KEY POINTS

- Onychomycosis is a common disease that requires effective management to prevent progression to a severe and debilitating condition.
- Confirming the diagnosis of onychomycosis is paramount especially before starting a systemic medication.
- Onychomycosis can be managed with either topical or systemic agents, and new topical agents afford better options to tailor appropriate therapy for our patients.
- Combination therapy (topical and systemic) may be an important consideration in more difficult to treat patients. Prophylaxis with topical agents may help prevent disease recurrence.
- Treatment of coexisting tinea pedis is critical and a number of strategies may be used to minimize the long-term consequences of the disease.

INTRODUCTION

Onychomycosis is a common superficial fungal infection of the nails leading to discoloration, nail plate thickening, and onycholysis. Mycotic nail disease is the most common nail pathology worldwide, reaching all cultures and ethnicities. Onychomycosis is increasing, accounting for up to 90% of toenail and at least 50% of fingernail infections.[1] The most common etiology in the United States is owing to dermatophytes, typically *Trichophyton rubrum* and *Trichophyton mentagrophytes*.[2] In Europe, *T rubrum* is the chief agent followed by *T mentagrophytes* and *T interdigitale*.[3,4] Nondermatophyte molds and yeasts also play a role with varying frequency.

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Because the initial diagnosis is predicated on the nail's appearance, the diagnostic gold standard is direct microscopy (potassium hydroxide [KOH]) and fungal culture. However, visual nail plate changes are used to classify onychomycosis,[5] including distal subungual (also known as distal lateral subungual onychomycosis [DLSO], the most common form), proximal subungual, superficial white, and total dystrophic.[6]

Onychomycosis occurs in 10% of the general population, 20% of individuals 60 years and older, and 50% of individuals over 70 years.[6] Peripheral vascular disease, immunologic disorders, and diabetes mellitus correlate with the increased prevalence in older adults. The risk of onychomycosis is 1.9 to 2.8 times greater in persons with diabetes mellitus, and in patients with HIV infection prevalence rates range from 15% to 40%.[6] Other predisposing factors include older age, sex (male > female), genetic predisposition, tinea pedis (interdigital or moccasin types), peripheral arterial disease, smoking, nail trauma, inappropriate nail hygiene, and family background of onychomycosis and hyperhidrosis.[6]

Adult patients constitute the bulk of those seeking treatment, but there are increasing numbers of pediatric cases, possibly owing to increasing childhood obesity and pediatric diabetes. With prevalence ranging from 0% to 2.6% worldwide, pediatric onychomycosis is relatively rare compared with adults, but still one of the most common nail disorders in children.[7] DLSO is the most common type seen in children, followed by proximal subungual and white superficial. The most common pathogen is *T rubrum*.

In the last several years, novel treatments and considerations regarding the diagnosis and management of onychomycosis have arisen. This review discussed emerging conservative and surgical methods to treat the disease.

PATIENT EVALUATION

To evaluate a patient presenting with nail dystrophy, the practitioner should begin by completing a thorough history and physical evaluation. With treatment options ranging from systemic to surgical, knowledge of medical history, current medications, and family history will aid in the differential diagnosis and formulating the treatment plan. Key questions include: how long have you had the nail changes, is it painful, has it affected your quality of life? Daily shoe gear choices, work and athletic activities, and the home and work environments will all assist treatment plan selection. Level of immunosuppression, vascular status, and the ability to take oral or apply topical medication should be taken into account. Discussion and examination of any other skin rashes or conditions should be completed, because psoriasis and eczema can mimic mycotic nails.

Visual assessment is imperative. Since the Zaias classification was proposed in 1972, modifications have been proposed and published to reflect the wide array of dermatophytes, nondermatophyte molds, and yeasts as well as the complications of various patterns occurring in the same nail or other inflammatory diseases copresenting with mycosis.[8] Nail plate changes include DLSO where the invasion begins at the hyponychium and disturbs the distal nail bed; proximal subungual, where invasion begins proximally; superficial white, where the upper surface of the nail plate is first attacked[8]; total dystrophic, which describes total nail plate involvement and surrounding periungual tissue; and endoynx, which describes distal nail plate attack resulting in a deeper penetration of hyphae.

In addition, the physician should determine how many toenails are involved on 1 or both feet, percent involvement of the nail, any biomechanically aggravating factors that could contribute to nail dystrophy (adductovarus fifth digit, hammertoe, or hallux abductovarus), and the presence of tinea pedis interdigitally or plantarly.

Approximately 50% of nail disease is caused by onychomycosis[9]; the remainder conditions that mimic onychomycosis, having similar signs and symptoms, include psoriasis, lichen planus, reactive arthritis, allergic/irritant contact dermatitis, and eczema. Other differential diagnoses include alopecia, nail changes secondary to biomechanical issues, melanoma (and other skin cancers), traumatic onycholysis, 20-nail dystrophy, and pachyonychia.[10–12]

Because not all presenting nail disease is mycotic, it is important to confirm with laboratory diagnosis if the treatment plan includes oral antifungal therapy, if there is concomitant skin disease difficult to distinguish in the nails, and if the patient has been on antifungal therapy previously and disease has recurred. Laboratory diagnostic methods include direct microscopy (KOH test), nail plate biopsy for periodic acid Schiff stain, and fungal culture. Generally, KOH and fungal culture are done together; KOH shows the presence of hyphae, and culture the species present. Unfortunately, fungal cultivation is a slow process ($\leq$4 weeks) and may generate false-negative results in 40% of the cases that are microscopically positive.[13] As an alternative periodic acid Schiff stain involves sending nail plate (commonly referred to as, but not a true, biopsy) for staining to determine presence of dermatophytes. Periodic acid Schiff staining provides quicker results and is more sensitive, whereas culture is more specific (regarding species).[14–16]

Standard mycological tests, KOH, and fungal culture may yield false-negative or false-positive results, and require time to verify the pathogens.[17] Accurate diagnoses are often delayed owing to lack of both specific and rapid methods of pathogen identification. When the mycological analyses are negative and the clinical picture is highly suggestive of onychomycosis, polymerase chain reaction (PCR) testing may be an option.[18] Antifungal drug efficacy and dosages may differ for different causative pathogens, and it has been hypothesized that mixed and nondermatophyte onychomycosis may be cause for high rate of treatment failures.[19] A rapidly sensitive method for detection and identification will better guide an appropriate treatment strategy. PCR detects a specific DNA sequence; moreover, fungi species-specific PCR diagnostic methods are available,[20,21] deepening our understanding and treatment of onychomycosis.[22] Because DNA is extremely resistant and can persist even in the absence of viable hyphae, DNA amplification techniques such as PCR may represent a useful addition to standard procedure.[23] Time will tell how truly beneficial PCR will be both in the physician office and in clinical trials.

PHARMACOLOGIC TREATMENT OPTIONS: FOCUS ON TOPICAL THERAPY

Onychomycosis can be managed with topical or systemic agents. The current standard of care is an oral antifungal agent (either terbinafine or itraconazole) because they are more effective than topical agents, owing to issues of penetrance into the nail apparatus with topical agents. Drug interactions and the risk of hepatic injury may limit their desirability, especially in the elderly where the disease is most prevalent.

Guidelines suggest monotherapy with topical antifungals is limited to:

- Superficial white, except in transverse or striate infections,
- DLSO, except in the presence of longitudinal streaks, when less than 80% of the nail plate is affected with lack of involvement of the lunula, or
- When systemic antifungals are contraindicated.[24]

Developing effective topical treatments for onychomycosis has been complicated by low permeation rates through the nail plate to the site of infection.[25–28] The nail

may be more permeable to agents formulated in an aqueous vehicle.[29] Unlike ciclopirox and amorolfine nail lacquers, new topical agents, efinaconazole and tavaborole, are now available as solutions.

Studied in separate trials with similar, but not identical inclusion criteria, reported complete cure rates of tavaborole were 6.5% to 9.1%.[30] Efinaconazole results were 15.2% to 17.8%.[31] Mycologic cure rates were 53.4% to 55.2% for efinaconazole, whereas the mycologic cure for tavaborole was 31.1% to 35.9% (**Table 1**). Although much emphasis has been placed on the need for active ingredient to pass through the nail plate, recent data suggest that efinaconazole may reach the infection site after transungual and subungual application[32,33]; subungual delivery data with tavaborole is pending.

Lacquer-based topical therapies are applied primarily to the exterior nail plate, with the drug reaching the infection site mostly through nail permeation.[34–36] Efinaconazole is applied to the clean, dry nail plate surface, lateral and proximal nail folds, hyponychium, and undersurface of the nail plate.[37] Application to the hyponychium and ventral aspect of the nail plate may be important in patients wishing to continue to use nail polish.[32] Although nail polish does not seem to influence efinaconazole penetration into the nail, it can become tacky with repeated application.[38] Up to 4 layers of nail polish does not seem to inhibit penetration of tavaborole either.[39] In neither case has the impact of nail polish on efficacy been assessed, nor is it contraindicated.

Because toenail growth progresses from proximal to distal, newly formed nail plate replaces diseased nail, a process that can take 12 to 18 months.[39] Clinical trial data suggest that tavaborole and efinaconazole must be applied daily to the toenails for at least 48 weeks. Some patients may require treatment for considerably longer because of slow toenail growth, disease severity, or for other reasons. It is not known whether longer treatment regimens with tavaborole or efinaconazole would produce better efficacy results; however, higher cure rates after longer follow-up periods have been reported with other agents.[40–42]

It is important that patients recognize that cure may not translate to a completely clear nail.[43] Poor adherence with any long-term chronic therapy is well documented.[44] A number of post hoc analyses with efinaconazole have been carried out to better identify prognostic factors for treatment success. Gender[45] and disease severity[46] were significant influencers of complete cure over the duration of the studies; female patients and those with milder disease may see results much quicker in clinical practice, whereas male patients and those with moderately severe disease may require a longer treatment course, or combination therapy with oral antifungals. Although male patients are more difficult to treat, reasons are unclear. They tend to seek help for more advanced disease and suffer more nail trauma, and their toenails tend to be thicker. The reduced rate of growth and thickness of the nail may be factors in more severe disease, although it may be that these patients just require longer treatment courses.

Tinea pedis is an important causative factor for onychomycosis, and better results are seen when any coexisting tinea pedis is also treated.[47] In addition, managing tinea pedis is critical to minimizing disease recurrence.

Onychomycosis remains a common, progressive, and difficult disease to manage successfully. Early diagnosis and treatment are important irrespective of risk factors or comorbidities.[48] A multidirectional approach to drug delivery may broaden the utility of topical therapies, such as efinaconazole in the treatment and greater clinical experience will help to guide management practice.

Table 1
Efficacy results from recent clinical trials with efinaconazole and tavaborole in mild to moderate onychomycosis

	Efinaconazole Clinical Studies[31]				Tavaborole Clinical Studies[30]			
Cure	Efinaconazole (n = 656)	Vehicle (n = 214)	Efinaconazole (n = 580)	Vehicle (n = 201)	Tavaborole (n = 399)	Vehicle (n = 194)	Tavaborole (n = 396)	Vehicle (n = 205)
Complete (%)	17.8	3.3	15.2	5.5	6.5	0.5	9.1	1.5
Mycologic (%)	55.2	16.8	53.4	16.9	31.1	7.2	35.9	12.2

Complete cure and mycologic cure rates after 48 weeks' daily therapy, 4-week follow-up data ($P<.001$ for all active data vs respective vehicle data).

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