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Onychomycosis: Art and Science
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ORIGINAL ARTICLE

s96 **Onchomycosis: An Overview**

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Onychomycosis: An Overview

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ABSTRACT

Onychomycosis is a fungal infection of the nail unit, more common in toenails than in fingernails, and caused by a variety of fungi including dermatophytes, nondermatophyte molds, and *Candida*. There are 4 to 5 subtypes related to the method of fungal invasion of the nail unit, the most common being distal lateral subungual onychomycosis. Here the fungus enters the distal lateral part of the nail bed, the region of the hyponychium, often as an extension of tinea pedis. Hyperkeratosis occurs under the nail plate, resulting in detachment of the nail plate from the nail bed (onycholysis), with subungual thickening.

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INTRODUCTION

Onychomycosis is a fungal infection of the nail unit, more common in toenails than in fingernails,¹ and caused by a variety of fungi including dermatophytes, nondermatophyte molds, and *Candida*.^{2,3} There are 4 to 5 subtypes related to the method of fungal invasion of the nail unit, the most common being distal lateral subungual onychomycosis (DLSO) (Figure 1).^{4,5} Here the fungus enters the distal lateral part of the nail bed, the region of the hyponychium, often as an extension of tinea pedis. Hyperkeratosis occurs under the nail plate, resulting in detachment of the nail plate from the nail bed (onycholysis), with subungual thickening (Figure 1).

Practice Tip: No tinea pedis (recent or in the past), no onychomycosis.

Onychomycosis may occur without tinea pedis in only a couple of scenarios: if a pedicure has inoculated the fungus directly into the nail, or if the patient has used infected clippers. Older patients will often tell you that they don't have tinea pedis, until you ask them to take their socks off. They assume incorrectly that foot dryness is normal.

Practice Tip: If someone comes in with fingernail disease, look at his or her toenails, and vice versa.

We also need to look for dermatophytomas, yellow-orange streaks and patches that can extend the full length of the nail (Figure 2). Dermatophytomas are often seen in patients who

have been treated with oral antifungals. The nails clear up initially, but patients have a recurrence due to a cluster of fungi growing into a fungal abscess, which presents as a streak or patch under the nail. The presence of dermatophytomas is an important consideration when considering nail debridement.

Proximal subungual onychomycosis, a relatively uncommon subtype, occurs when the fungus invades under the cuticle or nail plate, and advances from the proximal to distal part of the nail.⁵ It occurs in individuals who are immunocompromised (it was originally reported as an early clinical marker for HIV infection),⁶ in transplant patients, and in others with primary or secondary immunodeficiency. It is difficult to treat until the immunosuppression has resolved. It may also arise secondary to trauma.⁵

White superficial onychomycosis is less common than DLSO, representing about 10% of onychomycosis cases.⁷ The superficial nail plate or dorsal aspect is usually involved initially. It is most commonly caused by *Trichophyton mentagrophytes* and several nondermatophyte molds (such as *Fusarium*, *Aspergillus*, and *Acremonium spp.*). The nail feels rough but may become soft and crumbly where the fungus has attacked,⁸ and it can be scraped off with a scalpel. Eventually the nail becomes totally dystrophic.⁹

Candida onychomycosis is rare and only affects immunosuppressed patients. It typically invades the entire nail plate and is associated with paronychia. *Candida* can be a primary invader of the nail in a rare condition called chronic mucocutaneous onychomycosis, in which the patient has an immune deficiency that allows candida to invade the nails and mucous membranes.

FIGURE 1. a) Distal lateral subungual onychomycosis **b)** leading to onycholysis.

Endonyx onychomycosis differs from DLSO because of the absence of nail-bed hyperkeratosis and onycholysis, and is usually caused by *Trichophyton soudanense*. This fungus is not found in the United States.

Practice Tip: About half of all abnormal nails are caused by fungal pathogens.

Some investigators have reported mixed infections, although the true incidence and significance of mixed infections has not been entirely established.¹⁰ Dermatophytes are generally the primary pathogen, as there are only few nondermatophytes that digest keratin – *Scytalidium dimidiatum* and *Scytalidium hyalinium*, for example. Other organisms get into the nail plate once it has been broken down by the primary pathogen. According to the group's collective experience, there is an increase in the incidence of nondermatophyte molds (especially in more tropical regions) and mixed infections. This could be one reason why current antifungal therapy is less effective in some patients.

Aditya Gupta: "We do not fully understand the significance of a mixed infection. It could be that if you kill off the dermatophyte, the nondermatophyte is going to go away anyway. There is a lot to learn."¹¹

A definite diagnosis of onychomycosis is made by looking for the presence or absence of fungal elements using potassium hydroxide (KOH) preparation or a periodic acid-Schiff (PAS) stain, and identification of the fungi with a culture or polymerase chain reaction analysis. Most experts would use KOH and do a fungal culture. Many dermatologists would use a PAS stain because it is less subject to interpretive errors than fungal cultures; but it is more expensive.

Only about half of dystrophic nails are attributed to fungi, the rest are attributed to something else such as trauma, psoriasis,

FIGURE 2. Examples of dermatophytoma indicative of onychomycosis.

or onychogryphosis. A number of mimickers of onychomycosis are shown in Table 1.

Practice Question: You treat a patient with onychomycosis for 3 months with oral terbinafine, assuming it is a dermatophyte infection after a positive PAS stain, and it is not getting better. Why?

The group felt there could be a number of possibilities to investigate in this patient. There could be a secondary problem such as psoriasis, or a nondermatophyte or mixed infection. Or perhaps the infection is terbinafine-resistant? It is possible the infection was so severe that it caused some permanent destruction of the nail matrix. In addition, the group pointed out some important aftercare issues to consider. For example, is the patient fully compliant with the drug regimen? Are they properly cleaning their clothes and footwear, and avoiding exposure to places with high rates of infection such as gym floors?

The prevalence of onychomycosis is increasing; judging by studies over the last 20 years, it has increased from 2% to 14%. It is more common in men and in those with advancing age.¹²⁻¹⁵ In Cleveland we found that 50% of patients over 70 years of age had onychomycosis.¹³ It is relatively uncommon in children.¹⁴

Practice Tip: Women and younger patients are more inclined to seek treatment in contrast to the prevalence data. If you have one person in the family with onychomycosis, there may be others. Ask so that you don't miss a big population and are able to stop further spreading.

Psoriasis is a risk factor, particularly in dermatophyte onychomycosis.¹⁶ A 27% prevalence of onychomycosis was reported in

TABLE 1.

Conditions That can Mimic Onychomycosis

Psoriasis (the most common)

Lichen planus

Bacterial infections

Onychogryphosis

Traumatic onychodystrophies

Pachyonychia congenita

Yellow nail syndrome (rare)

Phlebitis

Toenail cellulitis

Contact dermatitis

Nail-bed tumors

Idiopathic onycholysis

psoriatics when the toenail was clinically abnormal, with 13% pedal onychomycosis in psoriatics overall.¹⁷

Practice Tip: Psoriasis is a major risk factor for developing dermatophyte onychomycosis.

Other coexisting conditions include tinea pedis. A history of circulatory disease is an important predisposing condition.

Practice Question: Are we seeing more onychomycosis because of increased awareness and increased reporting?

The group felt that onychomycosis is becoming more common for a number of reasons: people are living longer and are also generally more concerned about their health, with the result that there are a greater number of milder cases presenting compared with 20 years ago.

David Pariser: "When you do full body skin exams you find it all the time. Many patients don't even know they have onychomycosis, or, if they do, it doesn't bother them."

Practice Question: Should we treat all patients who have onychomycosis?

We don't treat all cases of onychomycosis because we don't go out of our way to tell patients they have it; but if they do come in with it, do we treat them?

The group identified situations where we need to treat patients with onychomycosis (Table 2). They felt that onychomycosis is

TABLE 2.

High Priority Treatment Needs in Onychomycosis

Diabetic mellitus

Primary or secondary immunodeficiencies

Peripheral arterial disease

Symptoms (pain)

Fingernail involvement

Spreading to hands and other body parts

History of phlebitis

Inflammatory tinea pedis, cellulitis, connective tissue disease

an important problem that should be properly diagnosed and treated, especially if it is symptomatic or bothersome; but that physicians must also recognize extenuating circumstances such as cost.

Ralph Daniel: "If not treated, onychomycosis can spread elsewhere and it can lead to cellulitis. It can also pose a major problem in diabetics. The thick nails can break the skin if they rub against another part of the leg at night."¹⁸

Phoebe Rich: "Sometimes the most challenging patient is a woman aged about 35 years, perfectly groomed and dressed, who has the tiniest amount of onychomycosis but is disproportionately bothered by it because she cannot stand not having perfect toenails. At the other extreme is the little old man who has had horrible onychomycosis for decades but couldn't care less about it. It all depends how much it bothers the patient."

Boni Elewski: "Some people are really fixated on their toes, despite having so many other potentially more serious problems. When their life is out of control, this seems like one thing they can potentially control."

Onychomycosis is an infectious disease that deserves prompt and appropriate care.⁴ Treatment options include systemic and topical agents. Two oral treatments (terbinafine and itraconazole) are approved by the US Food and Drug Administration (FDA) for 3 months daily treatment.^{19,20} Pulsed itraconazole is only approved for the treatment of fingernail onychomycosis, and fluconazole is not FDA-approved at all for this indication. Complete cure rates with these oral agents are 38%, 14%, and 37% to 48%, respectively (Table 3).²¹⁻²⁴

TABLE 3.**Reported Complete Cure Rates in Onychomycosis²¹⁻²⁴**

Oral Antifungal	Complete Cure Rates
Itraconazole 200mg/d, 12 weeks (PI)	14%
Itraconazole (LION study week 72)	25% – 3 pulses 28% – 4 pulses
Terbinafine 250mg/d, 12 weeks (PI)	38%
Terbinafine (LION study week 72)	49% – 12 weeks treatment 54% – 16 weeks treatment
Fluconazole, once weekly	150 mg – 37%, 300 mg – 46%, 450 mg – 48%

PI, Prescribing Information.

Efinaconazole 10% solution is a new topical treatment for onychomycosis.²⁵ The non-lacquer-based formulation spreads over, around, and under the nail with no build-up. The alcohol-based formulation and physicochemical properties of efinaconazole afford good penetration through the nail plate, with access to the nail bed by wicking into the air gap and spreading over the infection site.²⁵ Efinaconazole has a broad spectrum of activity against dermatophyte, nondermatophyte, and yeast species.²⁶ In clinical trials of mild to moderate onychomycosis, mycologic and complete cure rates are comparable to those seen with oral itraconazole, and greater than those reported with topical ciclopirox lacquer (Figure 3).²³ The clinical utility of efinaconazole 10% solution is likely underestimated in clinical studies. Complete cure rates in onychomycosis studies (where efficacy is assessed at week 52) are affected by the slow growth of the toenail; it may take 78 weeks or longer for the disease-affected appearance of the nail to grow out.^{27,28,29} Efficacy continues to rise steeply at week 52, and it would be interesting to extend treatment duration to 18 months, as others have suggested.³⁰

The group felt that addressing patient expectations is important. Patients want to be cured and have high expectations, but most patients are more satisfied with a certain degree of improvement than physicians might demand. The group believes that efinaconazole will be an important primary medication for those patients for whom effective topical treatment would be ideal, but they would also consider using efinaconazole in combination with an oral agent, or with adjunct therapies such as lasers and debridement.

Ralph Daniel: "At the present time I treat almost all the patients I see who have onychomycosis. I initially treat them with an oral medication, and I treat some with orals and topicals. After this treatment I continue indefinitely with topical therapy to reduce relapse and reinfection. With the superior efficacy of efinaconazole over other topical therapies, I use efinaconazole as my topical of choice."

TABLE 4.**Ideal Candidates for Topical Antifungals**

Children
Contraindications
Elderly/polypharmacy
Pregnancy
Fear/intolerance to oral therapies
White superficial onychomycosis/mild/moderate infection
Nondermatophyte infection
Relapse and reinfection prevention
Mild disease

Practice Question: How should we treat our patients with onychomycosis?

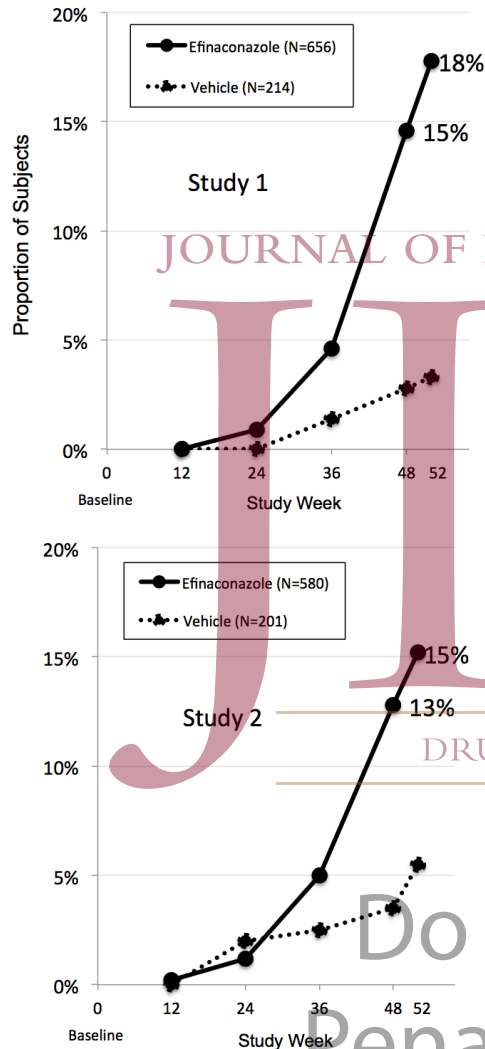
While the group does not treat every patient who has onychomycosis, the patient's view is a very important factor.

Richard Scher: "Terbinafine is treatment of choice for systemic therapy of onychomycosis. Ciclopirox has such poor efficacy. However, I would modify treatment if the patient has other medical conditions, or is on other drugs. I would increase the length of therapy in severe onychomycosis, and for diabetics."

Aditya Gupta: "The downside with oral treatments is their adverse effects, such as risk of hepatotoxicity, drug interactions, and the need to monitor the patient while on therapy. Another thing to bear in mind when treating onychomycosis is that in many cases it forms a dermatophytoma at some stage over the course of therapy, and this needs to be physically removed. We have done some work to show that ozone can be effective in disinfecting shoes."^{31,32}

Situations in which the group would consider use of an effective topical agent over an oral medication are summarized in Table 4.

What about adjunct therapy? Debridement may be helpful in some patients and some onychomycosis can actually be cleared just with debridement. Lasers may require extensive debridement to have any chance of working, but could be worth considering in patients who don't want to use an oral or topical treatment. However, in our experience, patients may have become 20% to 30% better in terms of the area of nail involvement, but none of them improved their scores when

FIGURE 3. Complete cure rates with efinaconazole 10% solution (intent to treat [ITT] population, last observation carried forward [LOCF]).²⁵**TABLE 5.****Reported Complete Cure Rates in Onychomycosis²¹⁻²⁴**

Patient Characteristic	Nail Characteristic	Organism
Immunosuppression	Subungual hyperkeratosis >2 mm	Nondermatophyte molds
Poor peripheral circulation	Significant lateral disease	Yeasts
Poorly controlled diabetes mellitus	Dermatophytoma (streak or patch)	Mixed bacterial/fungal infections
	>50% involvement	
	Slow rate of nail growth	
	Total dystrophic onychomycosis	
	Matric involvement	
	Long nail bed	

FIGURE 4. Example of an onychomycosis patient with a good prognosis.

we used the new classification system of severity. In vitro, we had to use the laser for 15 minutes at 50°C to kill *Trichophyton rubrum*. Above 41°C patients will not be able to tolerate the pain, so it is not practical.

Onychomycosis: Determining severity and prognostic outcome

Recently, a new classification system was proposed for grading the severity of onychomycosis,³³ its key objective being to establish a new, objective, simple system for defining mild, moderate, and severe onychomycosis using a numerical scale. The new classification system allows for standardization of the clinical assessment of nails in research studies, but is also clinically useful as an objective, easy to use tool for documenting severity of infection, likely prognostic outcome, and treatment response without using photographs.

The group identified a number of poor prognostic factors for the successful treatment of onychomycosis relating to the patient and nail characteristics, or the infecting organism (Table 5).³³

Practice Question: If mild disease is currently defined as >20% nail involvement, what do you do for patients who have less diseased nails but are still bothered by their onychomycosis?

The new classification system was an attempt to address this question, and defines severe onychomycosis as an infection that is unlikely to be cured with one course of an antifungal drug and may require multiple therapies. Mild disease was suggested as seldom seen, so hardest to quantify, but likely to respond to therapy. Moderate disease was defined as everything in between.

An example of an onychomycosis patient with a good prognosis is shown in Figure 4. This patient has mild disease and would be a good candidate for oral therapy because there is

FIGURE 5. Examples of onychomycosis patients with a bad prognosis: **a)** thick nail (>5 mm) and tinea pedis scaling; **b)** spike or dermatophytoma with a small area involved.



only distal involvement. With 3 months terbinafine therapy, the nail will probably have grown out and be cured.

Antonella Tosti: "It is important to treat this patient because their onychomycosis is only going to get worse. They also have tinea pedis on the lateral fold."

Examples of patients with a poor prognosis are shown in Figure 5. In the first example, the nail is very thick and there is nail-bed dermatophytoma, in which the fungus grows under the nail. There is also tinea pedis scaling.

Ralph Daniel: "When you have persistent onycholysis and you don't treat the nail, it is more likely that the nail bed will cornify. It then becomes very difficult to get the nail to reattach, which is another important reason to treat because persistent nail disease can lead to a situation where the nail may never attach again."

In the second example there is not a lot of disease, but there is a dermatophytoma with lateral involvement. The patient would need to be treated with oral terbinafine until, with luck, the nail grew out.

Three additional examples of patients with a poor prognosis are shown in Figure 6. The first patient has a dermatophytoma patch and a fungal abscess, and would be very difficult to treat. The second patient also has a dermatophytoma with proximal nail involvement. In the third patient, the disease extends to the matrix and more than 75% of the nail is involved. A poor prognosis may occur with minimal involvement of the nail if there is lateral nail infection, matrix involvement, dermatophytoma, nondermatophyte infection, or the presence of adverse host factors (such as poor immune status, circulation issues, diabetic foot, or advanced age).

FIGURE 6. Additional examples of onychomycosis patients with a bad prognosis: **a)** with a patch or dermatophytoma; **b)** with proximal nail involvement; **c)** with matrix involvement and >75% nail involvement.



FIGURE 7. Difficult-to-treat nail.

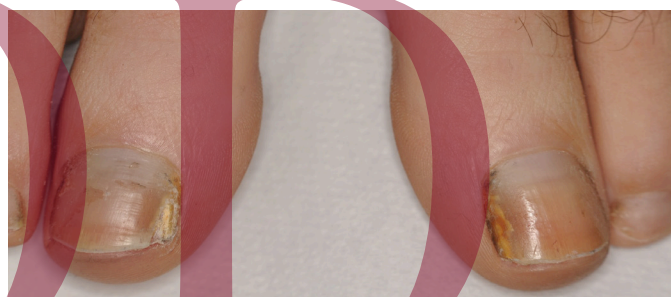


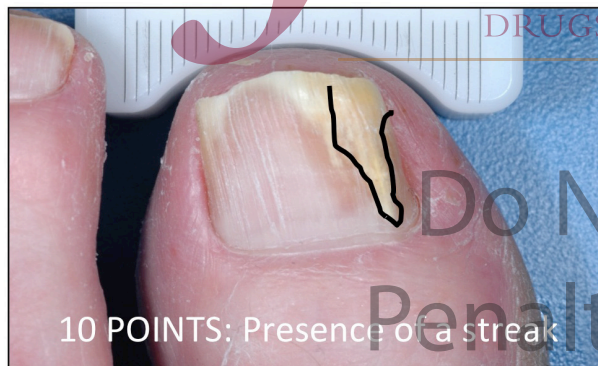
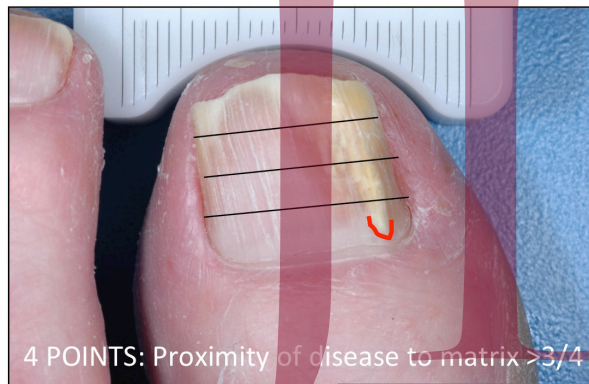
TABLE 6.

Top Tips for Minimizing Recurrence or Reinfection

- Treat nail and foot fungal infections in other family members
- Keep feet cool and dry; dry well after showering
- Wear flip flops and don't go barefoot in the gym
- Put antifungal powder in the shoes
- Consider using a topical antifungal indefinitely
- Don't use anyone else's clippers, and don't cut normal nails with the same clippers as abnormal nails
- Clean clippers with soap and water and alcohol/Clorox
- Don't go to pedicures or have footbaths, or wear other people's shoes

The patient shown in Figure 7 would be difficult to treat. Although there is only a small amount of overall involvement of the nail, there is a dermatophytoma spike. This is a good example of a patient with distal onycholysis who goes on to develop a spike. Once this occurs, the disease turns from mild to severe, and the time course could be only a few weeks. Onychomycosis is a progressive infection within the nail, and it may spread to other nails and to other people. In addition, there are a number of factors that cannot be ascertained from photographs such as patient factors (those mentioned above), culture results, and concomitant disease (eg, psoriasis).

The new classification system graded 3 key parameters – the area of onychomycosis involvement, the proximity of infection to the nail (depth of fungal penetration), and the fungal burden (whether dermatophytoma or subungual hyperkeratosis).

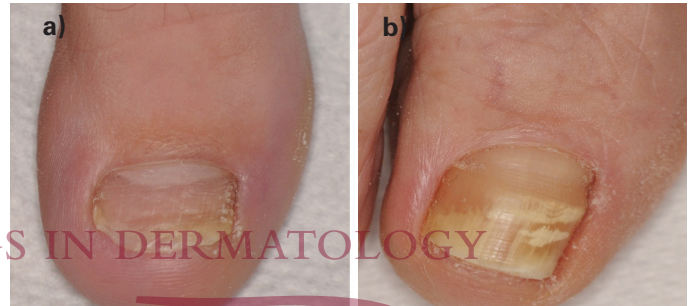
FIGURE 8. Calculation of Onychomycosis Severity Index.

Total Score = $3 \times 4 + 10 = 22$
(severe onychomycosis)

>2 mm were present). A score was determined by multiplying the area of involvement (6-point scale) by the proximity of the disease to the matrix (5-point scale) and adding 10 points if there was dermatophytoma and/or subungual hyperkeratosis present. A total score of 1 to 5 was defined as mild, 6 to 15 as moderate, and 16 to 35 as severe (Figure 8).

Examples of mild, moderate, and severe onychomycosis using the new scale are shown in Figure 9.

Practice Question: How can you minimize the likelihood of recurrence or reinfection?

FIGURE 9. Classification of severity: **a)** mild disease; **b)** moderate disease; **c)** severe disease.

The group discussed a number of strategies to minimize recurrence or reinfection (Table 6).³⁴

Ralph Daniel: "Nail and foot fungal

infections in other family members should be treated, feet should be kept cool and dry, feet should be dried well after showering, and flip flops should be worn in a gym rather than going barefoot. I also suggest antifungal powder in the shoes. I usually use a topical antifungal indefinitely to keep down the chance of relapse and reinfection. I tell them not to use anyone else's clippers or cut normal nails with the same clippers used for abnormal nails. Clippers should be cleaned with soap and water and alcohol/Clorox. Patients should not go to pedicures, have footbaths, or wear other people's shoes."

The group felt that in their experience recurrence or reinfection occurs more frequently than the literature suggests, and perhaps in as many as 50% of patients depending on how long they are followed up. Most of the group recommend using a topical antifungal such as efinaconazole 10% solution indefinitely to reduce the chance of relapse and reinfection, disinfecting shoes and socks, and minimizing high-risk behavior that could predispose patients to tinea pedis.

DISCLOSURES

The opinions expressed in this supplement are solely those of the authors. Dr. Elewski, Dr. Rich, Dr. Pariser, Dr. Scher, Dr. Daniel, and Dr. Gupta were advisors to Medicis, a division of Valeant Pharmaceuticals. Dr. Elewski, Dr. Rich, Dr. Pariser, and Dr. Gupta were all investigators in the efinaconazole 10% solution studies. All participants received an honorarium for their contribution to the roundtable discussion.

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PERMISSIONS

Permission required for Table 5 (Carney C, Tosti A, Daniel R, et al. A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. *Arch Dermatol*. 2011;147(11):1277-1282.) Permission required for Figure 3 (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.)

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