A CME/CE CERTIFIED SUPPLEMENT TO

Family Practice News
Internal Medicine News

ORIGINAL RELEASE DATE: MARCH 2016
MOST RECENT REVIEW DATE: MARCH 2016
EXPIRATION DATE: FEBRUARY 28, 2018
ESTIMATED TIME TO COMPLETE ACTIVITY: 2.5 HOURS

# Onychomycosis:

## Diagnosis, Treatment, and Prevention Strategies



FACULTY

***Linda F. Stein Gold, MD***
Director of Dermatology Research
Department of Dermatology
Henry Ford Health System
Detroit, Michigan

***Theodore Rosen, MD***
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

Jointly provided by University of Louisville Continuing Education & Professional Development and Global Academy for Medical Education

Supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

# Onychomycosis: Diagnosis, Treatment, and Prevention Strategies

Original Release Date: **March 2016**
Most Recent Review Date: **March 2016**
Expiration Date: **February 28, 2018**
Estimated Time to Complete Activity: **2.5 hours**
Participants should read the activity information, review the activity in its entirety, and complete the online post-test and evaluation. Upon completing this activity as designed and achieving a passing score on the post-test, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail or you may print it out at that time. The online post-test and evaluation can be accessed at **http://tinyurl.com/onychosuppl16.**

Inquiries about CME accreditation may be directed to the University of Louisville CME & PD at cmepd@louisville.edu or (502) 852-5329.

## Accreditation Statements

Physicians: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Louisville and Global Academy for Medical Education, LLC. The University of Louisville is accredited by the ACCME to provide continuing medical education for physicians.

The University of Louisville Office of Continuing Medical Education & Professional Development designates this enduring material for a maximum of 2.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nurses:** This program has been approved by the Kentucky Board of Nursing for 3.0 contact hours through the University of Louisville Hospital, provider number 4-0068-7-16-895. The Kentucky Board of Nursing approval of an individual nursing education provider does not constitute endorsement of program content. Participants must complete the entire session, provide their license number, and complete the evaluation to receive contact hours.

## Target Audience

This journal supplement is intended for dermatologists, family practitioners, internists, nurse practitioners, physician assistants, and other clinicians who treat patients with onychomycosis.

## Educational Needs

For many years, the treatment of onychomycosis was frustrating for clinicians and patients alike, and the perceived futility of addressing fungal nail infections meant that many patients failed to seek treatment, and many others with suspected infections were neither definitively diagnosed nor treated. With the introduction of oral terbinafine in 1996 and the approval of the first topical agent in 1999, more effective control—if not cure—became possible, and clinicians showed increased interest in diagnosing and treating the condition. The introduction of two new topical agents in 2014 broadened the therapeutic options.

The optimum results with these agents require the correct diagnosis, which cannot be made reliably on visual inspection alone. To use antifungals most effectively, clinicians must test to confirm the presence of infecting organisms and, in appropriate cases, identify the species involved so that the most appropriate antifungal can be prescribed. Patient selection also is important: for example, the potential for drug-drug interactions with systemic antifungals must be considered, the presence of certain comorbid conditions may affect the choice of antifungal employed, and the patient's ability to adhere to the long treatment regimens required must be addressed.

Clinicians must remain up-to-date on these issues, and must be able to effectively and safely use the available antifungal, evaluate the emerging data on medications and devices now being investigated, and educate patients to improve adherence.

## Learning Objectives

After reading and studying this journal supplement, participants will be better able to:

- Establish or improve practice protocols for identifying patients with onychomycosis, particularly in special populations (eg, the elderly, pediatric patients, immunocompromised patients, patients with psoriasis, and those with diabetes mellitus).
- Discuss techniques, including obtaining good culture specimens, that permit more accurate diagnosis of the infecting organisms and the most appropriate choice of therapy.
- Explain the drug classes and mechanisms of action for the currently available therapeutic options, including differences in formulation and associated efficacy.
- More effectively use currently available oral and topical medications to treat various patient populations.
- Review and, if necessary, improve patient education materials designed to enhance patient adherence with the treatment regimen and to change habits that increase the chances of good long-term management of onychomycosis.
- Determine and help each patient recognize the realistic expectations for improvement in his or her individual case.
- Evaluate the results of clinical studies on new and emerging and available treatments for onychomycosis based on an understanding of possible differences in testing protocols (eg, inclusion or exclusion of patients with psoriasis or diabetes mellitus).

## Disclosure Declarations

As a provider accredited by the ACCME, the Office of CME & PD, School of Medicine, University of Louisville, must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All planners, faculty, reviewers, and other persons that affected the content of this CME activity were required to submit a financial disclosure form from which relevant conflicts of interest were determined. The persons below disclosed the following:

**Linda F. Stein Gold, MD,** Consultant: Anacor Pharmaceuticals Inc., Eli Lilly and Company, Galderma Laboratories, L.P., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sandoz, Taro Pharmaceutical Industries Ltd., and Valeant Pharmaceuticals North America LLC. Speaker: Galderma, LEO, Novartis, and Valeant. Grant Research/Support: Anacor, Galderma, GlaxoSmithKline, LEO, Novartis, Pfizer Inc., Sandoz, Taro, and Valeant.

**Theodore Rosen, MD,** Consultant: Anacor Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

**CME Reviewer:** Cindy England Owen, MD, Assistant Professor, Division of Dermatology, University of Louisville School of Medicine, has no relevant financial relationships to disclose.

**The CME & PD Staff and Advisory Board** have nothing to disclose with the exception of Douglas Coldwell, MD, Speaker: Sirtex, Inc.; Consultant: DFine, Inc.

**Global Academy for Medical Education Staff:** Sylvia H. Reitman, MBA, DipEd; Shirley V. Jones, MBA; Jenny Campano; and Joanne Still have no relevant financial relationships to disclose.

## Off-Label/Investigational Use Disclosure

This CME/CE activity discusses the off-label use of fluconazole for the treatment of onychomycosis. Also discussed are off-label, alternative dosing schedules for itraconazole, as well as the use in pediatric patients of medications approved for the treatment of onychomycosis in adults; currently, no medication is approved for the treatment of onychomycosis in pediatric patients.

Jointly provided by University of Louisville Continuing Medical Education & Professional Development and Global Academy for Medical Education

Supported by an educational grant from **PharmaDerm, a Fougera Pharmaceuticals company**

# *Onychomycosis:*
## Diagnosis, Treatment, and Prevention Strategies

**Reprinted from *Seminars in Cutaneous Medicine and Surgery.***

The manuscript was originally published as a supplement to *Seminars in Cutaneous Medicine and Surgery*, Vol. 35, No. 3S, March 2016. It has been reviewed and approved by the faculty as well as the Editors of *Seminars in Cutaneous Medicine and Surgery*.

The Faculty acknowledge the editorial assistance of Global Academy for Medical Education, LLC, and Joanne Still, medical writer, in the development of this supplement.

This continuing medical education (CME/CE) supplement was developed from a satellite symposium held at the Skin Disease Education Foundation's 16th Las Vegas Dermatology Seminar™, Friday, November 6, 2015, in Las Vegas, Nevada. Neither the Editors of Internal Medicine News and Family Practice News nor the Editorial Advisory Board nor the reporting staff contributed to its content. The opinions expressed are those of the faculty and do not necessarily reflect the views of the accredited provider, the supporter, or the publisher.



Global Academy for Medical Education

# Table of Contents

# Introduction

**Linda F. Stein Gold, MD**
Director of Dermatology Research
Henry Ford Health System
Detroit, Michigan

**Theodore Rosen, MD**
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

Onychomycosis recently has become more widely recognized as a medical condition having importance well beyond the cosmetic appearance of nails. Failure to diagnose this infection accurately and treat it effectively may lead to medical sequelae such as permanent damage to the nail plate and its attachments, and the potential for secondary bacterial infections, as well as spread of the fungus locally and to other parts of the body and transmission of the infection to others. In addition, quality-of-life and psychosocial consequences cannot be overlooked. However, until the introduction of newer, more effective medications over the past 2 decades, most patients with onychomycosis remained undiagnosed and untreated or ineffectively managed.

The introduction of terbinafine in 1996 marked the beginning of a new era in the diagnosis and treatment of onychomycosis. The approval of the first topical antifungal for the treatment of this infection followed soon afterward; in 1999, the topical antifungal agent ciclopirox was approved by the US Food and Drug Administration (FDA).

Research focusing on a clearer understanding of the underlying infectious organisms subsequently led to the introduction of two new topical agents, efinaconazole and tavaborole, both approved by the FDA in 2014.

This educational supplement features highlights of a CME/CE independent satellite symposium, which was held on November 6, 2015, at Skin Disease Education Foundation's 16th Annual Las Vegas Dermatology Seminar. It reviews the efficacy and safety of onychomycosis treatments, provides an overview of the mechanisms of action of the available antifungal agents, addresses onychomycosis in special patient populations, and discusses strategies for improving patient adherence to recommended therapy and reducing the risk for recurrence of infection.

**Linda F. Stein Gold, MD**
Director of Dermatology Research
Henry Ford Health System
Detroit, Michigan

**Theodore Rosen, MD**
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

Publication of this CME/CE article was jointly provided by the University of Louisville and Global Academy for Medical Education, LLC with Skin Disease Education Foundation (SDEF) and is supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

Dr Rosen and Dr Stein Gold have received an honorarium for their participation in this activity. They acknowledge the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal supplement.

Linda F. Stein Gold, MD, *Consultant*: Anacor Pharmaceuticals Inc., Eli Lilly and Company, Galderma Laboratories, L.P., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sandoz, Taro Pharmaceutical Industries Ltd., and Valeant Pharmaceuticals North America LLC. *Speaker*: Galderma, LEO, Novartis, and Valeant. *Grant Research/Support:* Anacor, Galderma, GlaxoSmithKline, LEO, Novartis, Pfizer Inc., Sandoz, Taro, and Valeant.

Theodore Rosen, MD, *Consultant*: Anacor Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Address reprint requests to: Linda F. Stein Gold, MD, 2360 Heronwood Drive, Bloomfield Hills, MI 48302; lstein1@hfhs.org.

# Understanding Onychomycosis: Resolving Diagnostic Dilemmas

Linda F. Stein Gold, MD*


## Abstract

No scientifically rigorous, large, prospective studies have been done to document the true prevalence of onychomycosis; the reported rates vary mainly by climate and by population, but the overall prevalence in the United States is estimated to be at least 10%. Advanced age and diabetes are the most commonly reported risk factors for onychomycosis. The differential diagnosis of onychomycosis is lengthy, and visual inspection alone is not sufficient for a definitive diagnosis—direct microscopic examination of a wet-mount preparation with 10% to 20% potassium hydroxide is the first-line diagnostic test.



## Key Words

Dermatophyte; onychomycosis; *Trichophyton rubrum*

Semin Cutan Med Surg 35(suppl 3):S48-S50



**TABLE 1. Risk Factors for Onychomycosis**

- Tinea pedis[4,5]
- Nail trauma[5]
- Diabetes[6-8]
- Psoriasis[9]
  - 18% in a systematic review of the literature[10]
  - 28% in a prospective study of hospitalized patients with psoriasis[11]
- Advanced age[12-15]
- Peripheral vascular disease[5]
- Compromised immune function[16]
- Personal/family history of onychomycosis[17]

Onychomycosis prevalence estimates vary widely; based on the available studies, the overall prevalence of onychomycosis is probably at least 10% to 12%, possibly higher.[1-3] The vast majority of cases of onychomycosis involve dermatophyte molds, particularly *Trichophyton rubrum*, which accounts for 90% of infections, and *T. mentagrophytes*. *Candida* species cause between 10% and 20% of onychomycosis, and a small number of cases can be attributed to nondermatophyte molds, such as *Acremonium, Fusarium,* and *Scopulariopsis* spp.[1-3]

## Risk Factors for Onychomycosis

Despite the lack of more exact epidemiologic data, climate, population, and other risk factors can be helpful in narrowing the diagnosis in patients with nail symptoms. Onychomycosis is more common in hot, humid regions and is less commonly seen in temperate or cold, dry climates. Other environmental risk factors include public areas where individuals may walk barefoot—pools, spas, gym locker rooms, and hot tubs. In addition, increasing age is a risk factor: it is clear that onychomycosis is uncommon in pediatric patients, whereas its prevalence in geriatric populations is estimated to be as high as 60%.[3]

A number of medical conditions also are associated with an increased risk for onychomycosis (**Table 1**), including several comorbid conditions: diabetes, psoriasis, peripheral vascular disease, tinea pedis, and diseases that adversely affect immune function.[4-17] Among these, diabetes is the most common—up to one-third of patients with diabetes also have onychomycosis.[6-8]

Patients with psoriasis also are at increased risk for onychomycosis. In one review of the literature, Klaassen et al[10] reported that about 18% of patients with psoriasis have onychomycosis, and Méndez-Tovar and colleagues[11] found onychomycosis in 28% of hospitalized patients.

Tinea pedis increases the risk for nail infection (**Figure 1**). Although such coinfections are not among the most common, when onychomycosis is suspected, examination should be done for signs of tinea pedis between the toes (interdigital distribution) and on the soles of the feet (moccasin distribution). Individuals who share a residence with a patient who has onychomycosis also should be asked about and, if possible, examined for fungal infections of both nail and skin. This is particularly important in cases of pediatric onychomycosis or recurrent nail infections. Onychomycosis is uncommon in young children in general but is more common among children whose parents or older siblings have onychomycosis or tinea pedis. In patients with recurrent in-

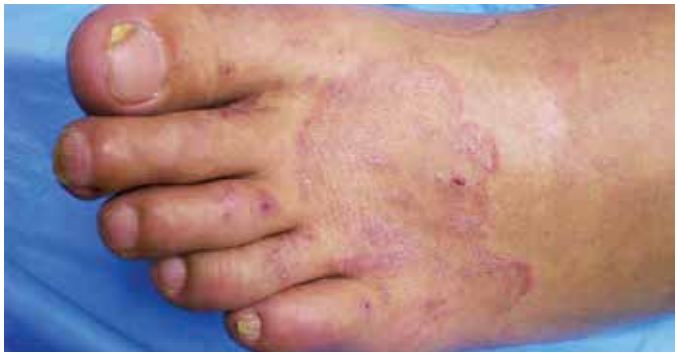
* Director of Dermatology Research, Henry Ford Health System, Detroit, Michigan.

Publication of this CME/CE article was jointly provided by the University of Louisville and Global Academy for Medical Education, LLC, with Skin Disease Education Foundation (SDEF) and is supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

Dr Stein Gold has received an honorarium for her participation in this activity. She acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal supplement.

Linda F. Stein Gold, MD, *Consultant*: Anacor Pharmaceuticals Inc., Eli Lilly and Company, Galderma Laboratories, L.P., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sandoz, Taro Pharmaceutical Industries Ltd., and Valeant Pharmaceuticals North America LLC. *Speaker*: Galderma, LEO, Novartis, and Valeant. *Grant Research/Support*: Anacor, Galderma, GlaxoSmithKline, LEO, Novartis, Pfizer Inc., Sandoz, Taro, and Valeant.

Address reprint requests to: Linda F. Stein Gold, MD, 2360 Heronwood Drive, Bloomfield Hills, MI 48302; lstein1@hfhs.org.



■ **FIGURE 1. Onychomycosis and Tinea Pedis.** When onychomycosis is suspected, the skin should be inspected for signs of tinea pedis. The reverse is also true—if a patient complains of symptoms of athlete's foot, the toenails should be examined for evidence of onychomycosis. Photo courtesy of Theodore Rosen, MD.

fections, other individuals in the household who have untreated tinea pedis may be a source of chronic reinfection.

In addition, any type of nail trauma can increase the risk for onychomycosis, as damage to the nail plate—and, consequently, disruption of the plate from the nail bed—allows introduction of potentially pathogenic organisms.

## Differential Diagnosis

Although onychomycosis is a common nail disease, it is important to note that 50% of cases of nail disease can be attributed to causes other than fungus or yeast infections.[18] As shown in **Table 2**, a number of other conditions can mimic onychomycosis, including other infections or diseases and trauma.[18-21] Because discoloration, brittleness, and other signs of nail dystrophy are common to many clinical entities, visual inspection alone is not sufficient to establish a diagnosis of onychomycosis (**Figure 2**); objective diagnostic techniques should be used.

## Diagnostic Techniques

The first-line diagnostic technique for onychomycosis is direct microscopy of a carefully prepared specimen of affected subungual tissue in 10% to 20% potassium hydroxide (KOH). For a more definitive diagnosis—ie, identification of the infecting organism(s)—a culture or histopathologic techniques (periodic acid–Schiff [PAS] stain or polymerase chain reaction [PCR] testing) may be considered. An overview of these recommended diagnostic techniques is provided below. [For a more detailed discussion of onychomycosis presentations, mycology, and diagnostic testing, the reader is referred to the comprehensive article published by Elewski.[3]]

### Potassium Hydroxide Preparation: Examination and Culture

Microscopic examination of a specimen prepared with 10% to 20% KOH is a readily accessible technique for determining whether fungal organisms are present in a sample; however, proper sampling is essential to its value as a first-line diagnostic tool.

To obtain a good subungual sample, it is necessary to trim back the nail to access the moist debris that lies behind the dry, flaky material at the end of the distal nail. After trimming, the nail and surrounding tissue should be cleaned thoroughly to prevent bacterial contamination of the sample. In obtaining a sample, a curette may be more helpful than a blade to minimize bleeding and patient discomfort.

■ **TABLE 2. Differential Diagnosis of Onychomycosis[18-21]**

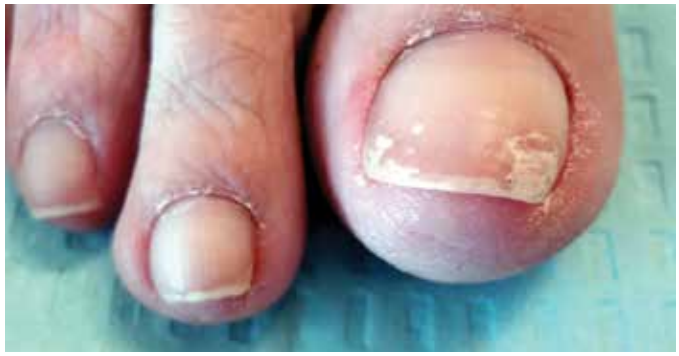
- Nail trauma
- Psoriasis
- Lichen planus
- Paronychia
- Bacterial infection
- Pachyonychia congenita
- Nail bed tumors (squamous cell carcinoma) and verrucae
- Yellow nail syndrome
- Alopecia areata
- Contact/atopic dermatitis
- Idiopathic onycholysis
- Twenty-nail dystrophy (trachyonychia)
- Nail changes associated with systemic disease or nail cosmetics

### Mycologic Culture

A mycologic culture can be considered if onychomycosis is suspected but KOH findings are negative, or to identify the specific organism when hyphae, spores, or other fungal structures are seen on direct microscopy. The results usually are available in 4 to 6 weeks; meanwhile, therapy can be initiated, if indicated.

### Histologic Evaluation

Histologic evaluation of a sample of nail clippings using PAS stain also can be ordered to identify the infecting organism. In contrast to culture, the results of PAS studies are available in 1 to 2 days. Moreover, PAS results are more specific than fungal culture findings. This superior sensitivity was demonstrated in a study of 100 consecutive cases of suspected onychomycosis in which direct



■ **FIGURE 2. White Superficial Onychomycosis.** Several clinical signs, including erythema and swelling of the nail folds, make visual inspection alone an unreliable diagnostic method. This patient has white superficial onychomycosis, confirmed by diagnostic testing. Photo courtesy of Theodore Rosen, MD.

microscopy and fungal culture results were negative. Mayer and colleagues[22] showed that 38 patients (38%) had positive fungal elements when the nail clippings were processed with hematoxylin, eosin, and PAS.

PCR testing also has been shown to be more sensitive than PAS in detecting the presence of mycologic organisms compared with direct microscopy with KOH or culture. In one study that compared the positivity rates with KOH/microscopy, culture, and PCR, the investigators reported rates of 10%, 29%, and 40%, respectively.[23] The results of PCR testing usually are available in about 3 days.

## Conclusion

The accurate diagnosis and early treatment of onychomycosis is important to the preservation and function of the nail plate in patients with early disease and to the prevention of progressive destruction and deformity in patients with long-standing disease. In addition, onychomycosis represents a reservoir of fungus that can seed the skin of other areas of the body, and can be transmitted to others with whom the patient comes in contact. Effective therapy is available.

## References


1. Ghannoum MD, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol.* 2000;43:641-648.
2. Heikkilä H, Stubb S. The prevalence of onychomycosis in Finland. *Br J Dermatol*. 1995;133:699-703.
3. Scher RK, Rich P, Pariser D, Elewski B. The epidemiology, etiology, and pathophysiology of onychomycosis. *Semin Cutan Med Surg.* 2013;32(2 suppl 1):S2-S4.
4. Pleacher MD, Dexter WW. Cutaneous fungal and viral infections in athletes. *Clin Sports Med.* 2007;26:397-411.
5. Elewski B. Onychomycosis: Pathogenesis, diagnosis, and management. *Clin Microbiol Rev.* 1998;11:415-429.
6. Tan JS, Joseph WS. Common fungal infections of the feet in patients with diabetes mellitus. *Drugs Aging.* 2004;21:101-112.
7. Gupta S, Koirala J, Khardori R, Khardori N. Infections in diabetes mellitus and hyperglycemia. *Infect Dis Clin North Am.* 2007;21:617-638.
8. Winston JA, Miller JL. Treatment of onychomycosis in diabetic patients. *Clin Diabetes*. 2006;24:160-166.
9. Rich P, Griffiths CE, Reich K, et al. Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year. *J Am Acad Dermatol*. 2008;58:224-231.
10. Klaassen KM, Dulak MG, van de Kerkhof PC, Paasch MC. The prevalence of onychomycosis in psoriatic patients: A systematic review. *J Eur Acad Dermatol Venereol.* 2014;28:533-541.
11. Méndez-Tovar LJ, Arévalo-López A, Domínguez-Aguilar S, et al. Onychomycosis frequency in psoriatic patients in a tertiary care hospital [in Spanish]. *Rev Med Inst Mex Seguro Soc*. 2015;53:374-379.
12. Smith ES, Fleischer AB Jr, Feldman SR. Demographics of aging and skin disease. *Clin Geriatr Med.* 2001;17:631-641.
13. Elewski B, Charif MA. Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions. *Arch Dermatol.* 1997;133:1172-1173.
14. Htew TH, Mushtaq A, Robinson SB, Rosher RB, Khardori N. Infection in the elderly. *Infect Dis Clin North Am.* 2007;21:711-743.
15. Abdullah L, Abbas O. Common nail changes and disorders in older people: Diagnosis and management. *Can Fam Physician.* 2011;57:173-181.
16. Gupta AK, Taborda P, Taborda V, et al. Epidemiology and prevalence of onychomycosis in HIV-positive individuals. *Int J Dermatol.* 2000;39:746-753.
17. Piraccini BM, Sisti A, Tosti A. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol.* 2010;62:411-414.
18. Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. *Br J Dermatol.* 2003;149(suppl 65):1-4.
19. Allevato MA. Diseases mimicking onychomycosis. *Clin Dermatol.* 2010;28:164-177.
20. Cockerell C, Odom R. The differential diagnosis of nail disease. *AIDS Patient Care*. 1995;9(suppl 1):S5-S10.
21. Daniel CR III. The diagnosis of nail fungal infection. *Arch Dermatol.* 1991;127:1566-1567.
22. Mayer E, Izhak OB, Bergman R. Histopathological periodic acid-Schiff stains of nail clippings as a second-line diagnostic tool in onychomycosis. *Am J Dermatopathol*. 2012;34:270-273.
23. Luk NM, Hui M, Cheng TS, Tang LS, Ho KM. Evaluation of PCR for the diagnosis of dermatophytes in nail specimens from patients with suspected onychomycosis. *Clin Exp Dermatol*. 2012;37:230-234.

# Antifungal Drugs for Onychomycosis: Efficacy, Safety, and Mechanisms of Action

**Theodore Rosen, MD*, and Linda F. Stein Gold, MD†**

**Abstract**

In 1996, oral terbinafine joined itraconazole and fluconazole on the short list of systemic medications that could be used to treat onychomycosis (although fluconazole was not approved for this indication by the US Food and Drug Administration [FDA], it was commonly used for this purpose). In 1999, ciclopirox was the first topical treatment to be FDA approved. The addition of the topical antifungal agents efinaconazole and tavaborole in 2014 expanded the roster of medications available to more effectively manage onychomycosis in a wide range of patients, including those for whom comorbid conditions, concomitant medications, or patient preference limited the use of systemic antifungals.

**Keywords**

Candidiasis; ciclopirox; efinaconazole; dermatophytosis; fluconazole; itraconazole; onychomycosis; tavaborole; terbinafine

Semin Cutan Med Surg 35(suppl 3):S51-S55


In selecting an antifungal agent to treat onychomycosis, clinicians must consider several factors: efficacy, side effect profile, drug-drug interactions, and the presence of comorbid diseases and conditions. This article focuses on the efficacy, safety, and drug-drug interactions associated with the systemic and topical medications used in the treatment of onychomycosis. [The third article in this supplement, "Concepts in Onychomycosis Treatment and Recurrence Prevention: An Update," on pages 13-16, addresses the topic of onychomycosis comorbidities in detail.]

* Professor of Dermatology, Baylor College of Medicine, Houston, Texas.

† Director of Dermatology Research, Henry Ford Health System, Detroit, Michigan.

Publication of this CME/CE article was jointly provided by the University of Louisville, and Global Academy for Medical Education, LLC, with Skin Disease Education Foundation (SDEF) and is supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

Dr Rosen and Dr Stein Gold have received an honorarium for their participation in this activity. They acknowledge the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal supplement.

Linda F. Stein Gold, MD, *Consultant*: Anacor Pharmaceuticals Inc., Eli Lilly and Company, Galderma Laboratories, L.P., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sandoz, Taro Pharmaceutical Industries Ltd., and Valeant Pharmaceuticals North America LLC. *Speaker*: Galderma, LEO, Novartis, and Valeant. *Grant Research/Support:* Anacor, Galderma, GlaxoSmithKline, LEO, Novartis, Pfizer Inc., Sandoz, Taro, and Valeant.

Theodore Rosen, MD, *Consultant*: Anacor Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Address reprint requests to: Theodore Rosen, MD, 2815 Plumb, Houston, TX 77005; vampireted@aol.com.

## Systemic Therapy: Efficacy Rates

Clinical trials have established the efficacy of terbinafine, itraconazole, and fluconazole in dermatophyte infections, using the FDA standard of complete cure—ie, negative mycology (both direct microscopy of a potassium hydroxide [KOH] wet-mount preparation and negative culture where shown in red wet-mount preparation and negative culture) and normal nail plate appearance as the end point (**Table 1**).

Terbinafine has been the drug of choice since its introduction in 1996. The initial clinical trials comparing terbinafine with itraconazole showed that terbinafine was more effective. Those studies demonstrated a 38% complete cure rate using what became the FDA-approved dosage regimen for oral terbinafine—250 mg/day for 12 weeks.[1,2] Subsequently, Evans and colleagues[3] investigated the use of pulsed dosing of terbinafine, using either three or four pulses of 250 mg/day (ie, 1 week of daily treatment followed by 3 weeks off, repeated either once or twice). The reported cure rates were 49% for the three-pulse regimen and 54% for the four-pulse regimen. Pulsed dosing of terbinafine is not approved by the FDA.

Itraconazole, at a dosing schedule of 200 mg/day for 12 weeks, has been reported to yield a cure rate of 14%.[4] The results of clinical trials of pulsed dosing of itraconazole in patients with fingernail onychomycosis—a complete cure in 47% of patients—led to FDA approval of a regimen of two pulses of 400 mg/day for this indication (ie, 1 week of treatment followed by 3 weeks off, repeated once).[3] Studies of pulsed dosing of itraconazole in patients with toenail onychomycosis yielded efficacy rates of 23% for three pulses and 26% for four pulses.[3] Although not approved by the FDA for this indication, pulsed dosing of itraconazole frequently is used to treat toenail onychomycosis.

Fluconazole is not FDA approved for onychomycosis, but it is used quite commonly to treat both fingernail and toenail fungal infections. The typical regimen is a single weekly dose of 150 to 450 mg, for at least 6 months. Scher and colleagues[5] reported efficacy rates of 37% with 150 mg/week, 46% with 300 mg/week, and 48% with 450 mg/week.

In addition, Gupta and colleagues[6] reviewed other clinical trials that examined the efficacy of these medications with some smaller or noncontrolled trials yielding higher efficacy rates than those seen in the phase III trials. Although none of these medications is FDA approved for onychomycosis caused by *Candida* species, clinical studies have demonstrated that these oral antifungals do have some efficacy.[6]

## Systemic Therapy: Safety

Oral antifungal agents generally are considered safe, but the prescribing information for each medication should be considered with respect to individual patient characteristics, and careful atten-

**TABLE 1. Systemic Antifungals: Efficacy in Phase III Pivotal Trials**

| Medication/Regimen | Complete Cure Rates | Comments |
|---|---|---|
| **Terbinafine** | | Pulsed dosing of terbinafine is not FDA approved. |
| 250 mg/day x 12 weeks[1] | 38% | |
| 250 mg/day x 1 week/month[2] | | |
| Repeated for 3 pulses | 49% | |
| Repeated for 4 pulses | 54% | |
| **Itraconazole** | | |
| 200 mg/day x 12 weeks[3] | 14% | Approved regimen for toenail onychomycosis, with/without fingernail involvement. |
| 400 mg/day x 1 week/month[2] | | This regimen is not approved for either toenail or fingernail onychomycosis. |
| Repeated for 3 pulses | 23% | |
| Repeated for 4 pulses | 26% | |
| **Fluconazole[4]** | | Fluconazole is not FDA approved for use in onychomycosis. |
| 150 mg/week | 37% | |
| 300 mg/week | 46% | |
| 450 mg/week | 48% | |

tion should be paid to recommendations for baseline and follow-up testing and clinical monitoring.

For example, terbinafine has been associated with hepatic failure, and the prescribing information recommends that liver function tests be performed both at baseline and periodically during treatment. Other adverse events previously reported with the use of terbinafine include taste and smell disturbances that may become permanent, depression, severe neutropenia, and skin diseases such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and lupus erythematosus–like illness.[1]

The prescribing information for itraconazole contains cautions about heart failure, other cardiac effects, including life-threatening arrhythmias, and sudden death (especially when itraconazole is used concomitantly with certain cytochrome P450 inhibitors—see "Drug-Drug Interactions" below). Hearing loss has been reported with the use of this medication, and hepatotoxicity rarely has been reported to occur as early as the first week of treatment.[4] Moreover, in vitro drug resistance has been demonstrated with this and the other azole drug, fluconazole.[4,7]

In addition to in vitro drug resistance, fluconazole use has been associated with hepatotoxicity, significant skin diseases, and prolongation of the QT interval on electrocardiogram. Fluconazole also has been associated with congenital defects, and its use should be avoided during the first trimester of pregnancy.[7]

## Drug-Drug Interactions

No drug interactions have been reported with the use of any of the topical antifungal agents approved for the treatment of onychomycosis.

A number of drug-drug interactions—many of which are theoretical—are listed for each of the systemic antifungal medications (**Table 2**). The prescribing information for each of these medications should be consulted before choosing an oral antifungal. A detailed description of the mechanisms by which these interactions may occur is beyond the scope of this article, so one or two illustrative examples have been chosen for terbinafine, itraconazole, and fluconazole.

Terbinafine, which is metabolized by the cytochrome p450 (CYP450) enzyme 2D6 (CYP2D6), may interact in particular with drugs that are also metabolized by CYP2D6.[1] Although the class of beta-blockers is listed in the prescribing information, not all beta-blockers may interact to the same degree. Metoprolol—the most commonly prescribed beta-blocking agent in the United States—is the most likely drug in this class to interact with terbinafine. Terbinafine may inhibit the metabolism of metoprolol, resulting in excess systemic levels of metoprolol and a risk for bradycardia, low blood pressure, and, possibly, cardiogenic shock.[8]

Itraconazole is metabolized by the CYP3A4 enzyme, a characteristic it shares with several other medications.[4] One interaction of note is itraconazole's inhibition of metabolism of statin drugs, particularly simvastatin and lovastatin; this action can result in rhabdomyolysis. In addition, a potentially fatal interaction can occur when itraconazole is given concomitantly with opioids, particularly methadone; the combination is associated with a high likelihood of a fatal arrhythmia.[9]

Fluconazole has been widely studied and demonstrated to be effective against onychomycosis, and, although it is not FDA approved for this indication, it is widely used for treating this infection. Potential interactions include antiarrhythmic drugs, antipsychotics, and antihistamines[7] (although the most problematic among these, terfenadine, is no longer marketed).

However, not on the list derived from the fluconazole prescribing information is an interaction that has been demonstrated recently with tofacitinib—a medication currently approved for rheumatoid arthritis, well studied and likely to be approved for psoriasis and psoriatic arthritis, and being used investigationally in alopecia areata. Fluconazole inhibits tofacitinib's metabolism and, therefore, may lead to gastrointestinal disturbances, such as severe diarrhea. Furthermore, inhibition of tofacitinib's metabolism may

potentiate tofacitinib-related infections, particularly pharyngitis, sinusitis, and bacterial infections; some of these infections may be severe.[10]

## Topical Agents: Efficacy and Safety

Currently, three topical agents are approved for the treatment of onychomycosis: ciclopirox 8% solution, efinaconazole 10%, and tavaborole 5%. No systemic adverse events have been reported with these topical agents, and the incidence of serious local reactions generally is quite low. Because the pivotal studies of these agents were not conducted using standardized protocols, each medication must be considered on its own merits in determining which topical agent to choose for an individual patient. The efficacy rates from the pivotal trials of these three agents are listed in **Table 3**.

### Ciclopirox

Ciclopirox has antifungal, antibacterial, and anti-inflammatory effects. The lacquer is painted on the nail plates of the affected nails daily for 48 weeks. It has demonstrated good fungicidal activity in vitro against the dermatophytes *Trichophyton rubrum, T. mentagrophytes*, and *Epidermophyton floccosum*; *Candida* spp; and the nondermatophyte molds *Scopulariopsis brevicaulis*, *Aspergillus* spp, and *Scytalidium hyalinum*.[6]

The phase III pivotal trial protocol included patients between the ages of 18 and 70 years, with distal subungual onychomycosis of at least one great toenail (target nail) and positive KOH examination and culture for dermatophytic onychomycosis. Involvement of the target nail was no less than 20% and no greater than 65%. The lacquer was painted once daily on the entire nail plate of the target nail(s), along with approximately 5 mm of adjacent skin, the hyponychium, and the accessible ventral surface of the nail plate. The lacquer was removed once weekly with an alcohol wipe. In addition, subjects were required to report each month for professional trimming and debridement of the nails.[11] The guidelines for use specified in the prescribing information for ciclopirox include weekly removal of the lacquer and regular visits to a health care professional for debridement.[12]

In the two phase III pivotal trials, the complete cure rates reported were 5.5% and 8.5%.[12]

### Efinaconazole

Efinaconazole is an azole drug with good potency against *T. rubrum, T. mentagrophytes*, and *C. albicans*. The formulation has a low surface tension, causing a "wicking" action that draws the medication around the nail. Studies of in vivo penetration showed that daily application of 10% and 5% solutions to all 10 toenails for 28 days demonstrated high levels of nail deposition and low systemic exposure to efinaconazole and its metabolite.[13]

In two parallel, 52-week, phase III, multicenter trials of efinaconazole,[14] a total of 1,655 subjects were randomized, in a 3:1 ratio, to receive either efinaconazole or placebo. Included were subjects between 18 and 70 years of age with mild to moderate onychomycosis affecting 20% to 50% of at least one great toenail, with at least 3 mm of uninfected nail as measured from the proximal nail fold, and a nail plate thickness no greater than 3 mm. Nail trimming, to any extent, was permitted but not required.

**TABLE 2. Systemic Antifungals: Potential Drug-Drug Interactions**

| |
|---|
| **Terbinafine[1]** |
| • Beta-blockers |
| • Antiarrhythmics |
| • Tricyclic antidepressants |
| • Selective serotonin reuptake inhibitors (SSRIs) |
| • Monoamine oxidase inhibitors (MAOIs) |
| **Itraconazole[4]** |
| • Antiarrhythmics |
| • Statins |
| • Antihypertensives |
| • Benzodiazepines |
| • Opioids |
| • Antipsychotics |
| • Vasoconstrictors (ie, migraine therapy) |
| **Fluconazole[7]** |
| • Antiarrhythmics |
| • Antipsychotics |
| • Antihistamines |
| • Tofacitinib[10] (fluconazole inhibits tofacitinib's metabolism) |

The cure rates in the efinaconazole pivotal trials were 15% and 18%.[14,15]

### Tavaborole

Tavaborole represents a new class of antifungal agent. It is a low-molecular-weight, boron-containing compound that specifically targets fungal protein synthesis.[16] In preclinical studies, tavaborole demonstrated excellent and rapid penetration through the nail plate and into the nail bed.[17]

The inclusion criteria for the two parallel, phase III pivotal trials of tavaborole had several of the same or similar inclusion criteria as the pivotal trials of the other two topical antifungals: laboratory-confirmed onychomycosis of at least one great toenail; nail involvement of between 20% and 60%; at least 3 mm of uninvolved nail, as measured from the proximal nail fold; and nail thickness of 3 mm or less.[18]

However, these tavaborole studies differed from the ciclopirox and efinaconazole trials in three important respects, which should

**TABLE 3. Topical Antifungals: Efficacy in Phase III Pivotal Trials**

| Medication | Complete Cure Rates* |
|---|---|
| Ciclopirox 8%[12] | 5.5% and 8.5% |
| Efinaconazole 10%[15] | 15% and 18% |
| Tavaborole 5%[16] | 6.5% and 9.1% |

**Regimens:** All of these medications are approved for daily application for 48 weeks.

*Results of two phase III trials, respectively.

be considered when comparing cure rates. First, in the tavaborole studies, no upper age limit was established (whereas the upper age limit in the other two studies was 70 years). Second, in the tavaborole studies, the medication was to be applied without debridement. Third, the final nail trimming prior to the final assessment allowed no less than 1 mm of growth at the distal edge of the target nail(s); in the other studies, the nail could be trimmed to the distal edge of the nail, which could affect the grading results.

The complete cure rates in the tavaborole pivotal trials were 9.1% and 6.5%.[16,18]

## Mechanisms of Action

The antifungal activities of the medications used to treat onychomycosis vary by class (**Figure**). The systemic agents itraconazole and fluconazole and the topical agent efinaconazole are in the azole class—specifically, in the triazole category. Triazoles work by inhibiting 14α-demethylase of the P450 enzyme, blocking conversion of lanosterol to ergosterol in fungal cells; ergosterol is essential to fungal cell growth.[4,7,15]

Terbinafine, in the allylamine class, also inhibits ergosterol biosynthesis, but at a different point in the pathway. Rather than affecting P450 and lanosterol-converting enzymes, the allylamines inhibit squalene oxidase, resulting in lethal fungal cell membrane changes.[1]

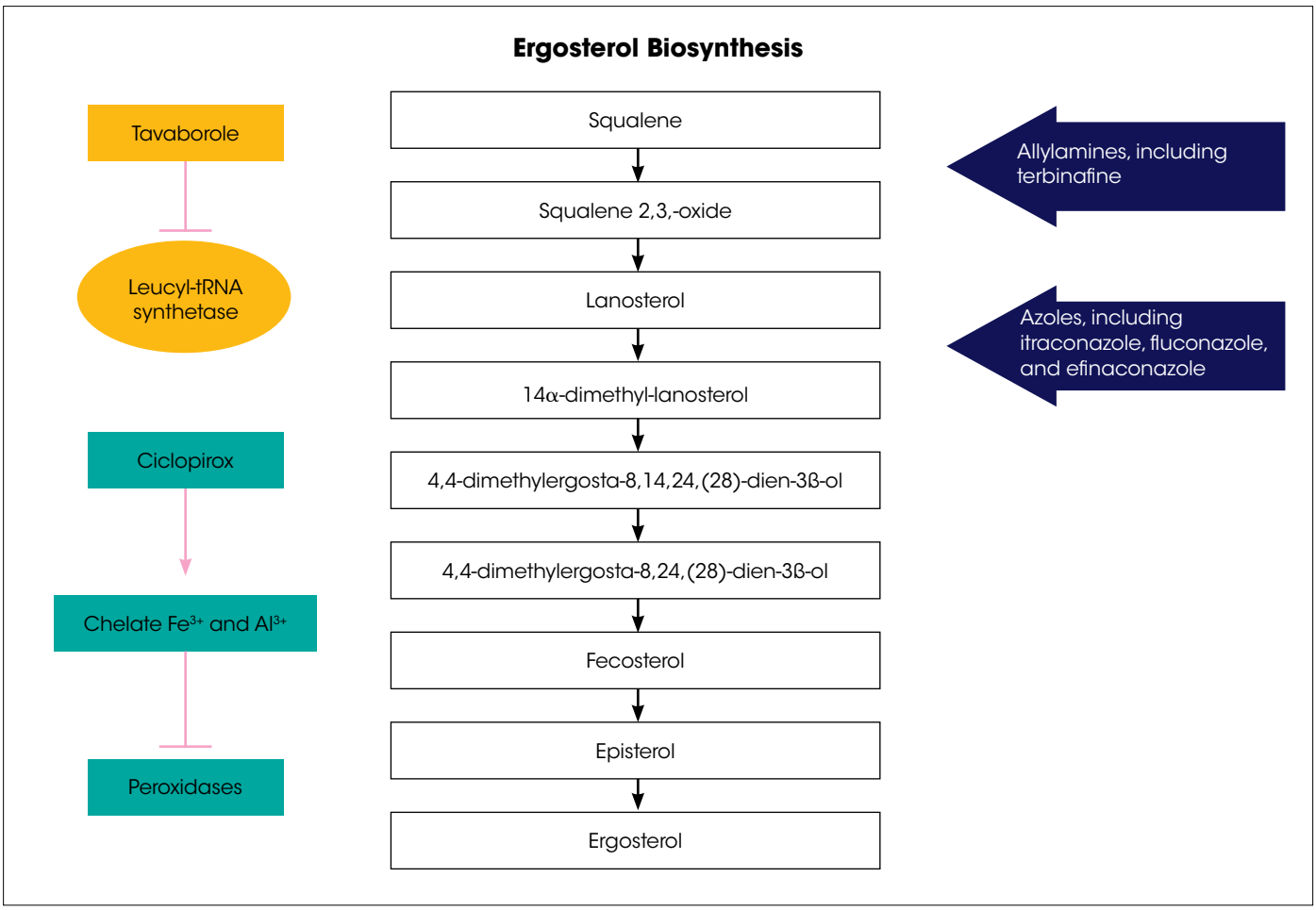
Ciclopirox is a synthetic antifungal agent. Its mechanism of action has not been clearly established but seems to involve both the inhibition of the metal-dependent enzymes responsible for the degradation of peroxides within the fungal cell as well as upregulation of fungicidal reactive oxygen formation within the fungal cytoplasm.[19,20]

Tavaborole's mechanism of action is thought to involve inhibition of the enzyme leucine aminoacyl-transfer ribonucleic acid synthetase. Tavaborole is active against *T. rubrum* and *T. mentagrophytes*, the two species most commonly found in onychomycosis. No resistance to tavaborole has been observed.[16]

Efinaconazole shows in vitro activity against *T. rubrum* and *T. mentagrophytes*. No clinically significant evidence of drug resistance to efinaconazole has been reported.

## Conclusion

In the pivotal trials for antifungal therapy for onychomycosis, the FDA-mandated criterion for efficacy is "complete cure." This is defined as negative results on both direct microscopic examination of samples prepared with 10% to 20% KOH and on mycologic culture, plus a substantially clinically improved nail (although not necessarily 100% normal appearance). In contrast, what might be called "effective treatment" is marked by a negative culture (re-




■ **FIGURE. Antifungal Medications: Mechanisms of Action**
Source: Theodore Rosen, MD.

gardless of the result of microscopic KOH examination, as a false-positive test may occur when nonviable hyphae are present), and substantial clinical improvement in the appearance of the nail.

In some patients, particularly those with early disease and little or no nail discoloration or deformity, a complete cure may be a realistic expectation. In those with infection of longer duration and a moderate degree of discoloration and deformity, a good result—ie, a clinical cure—is resolution of the infection, documented on direct microscopy and culture, and an appreciable improvement in the appearance of the nail. Effective treatment should be the baseline goal for the majority of patients. Resolution of infection, documented by a negative culture, and substantial improvement in nail appearance are achievable benchmarks in most cases, assuming that the medication chosen is effective against the infecting organism(s) and that the patient uses the treatment as prescribed.

## References


1. Lamisil® (terbinafine) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.
2. Drake LA, Shear NH, Arlette JP, et al. Oral terbinafine in the treatment of toenail onychomycosis: North American multicenter trial. *J Am Acad Dermatol.* 1997;37(5 pt 1):740-745.
3. Evans EGV, Sigurgeirsson B, for the LION Study Group. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. *BMJ*. 1999;318:1031-1035.
4. Sporanox® (itraconazole) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2014.
5. Scher RK, Breneman D, Rich P, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol.* 1998;38(6 pt 2):S77-S86.
6. Gupta AK, Paquet M, Simpson FC. Therapies for the treatment of onychomycosis. *Clin Dermatol.* 2013;31:544–554.
7. Diflucan® (fluconazole) [package insert]. New York, NY: Roerig, Division of Pfizer Inc; 2014.
8. Bebawi E, Jouni SS, Tessler AA, Frenette AJ, Brindamour D, Doré M. A metoprolol-terbinafine combination induced bradycardia. *Eur J Drug Metab Pharmacokinet*. 2015;40:295-299.
9. NoorZurani MH, Vicknasingam B, Narayanan S. Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy. *Drug Alcohol Rev*. 2009;28:688-690.
10. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2015;29:290-305.
11. Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. *J Am Acad Dermatol.* 2000;43(suppl 4):S70-S80.
12. Penlac® (ciclopirox) [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.
13. Jo Siu WJ, Tatsumi Y, Senda H, et al. Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. *Antimicrob Agents Chemother.* 2013;57:1610-1616.
14. 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;68:600-608.
15. Jublia® (efinaconazole) [package insert] Bridgewater, NJ: Valeant Pharmaceuticals North America, LLC 2015.
16. Kerydin® (tavaborole) [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2014.
17. Gupta AK, Daigle D. Potential role of tavaborole for the treatment of onychomycosis. *Future Microbiol.* 2014;9:1243-1250.
18. Elewski BE, Aly R, Baldwin SL, et al. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based anti fungal agent, for the treatment of toenail onychomycosis: Results from 2 randomized phase-III studies. *J Am Acad Dermatol.* 2015;73:62-69.
19. Belenky P1, Camacho D, Collins JJ. Fungicidal drugs induce a common oxidative-damage cellular death pathway. *Cell Rep.* 2013;3:350-358.
20. Subissi A, Monti D, Togni G, Mailland F. Ciclopirox: Recent nonclinical and clinical data relevant to its use as a topical antimycotic agent. *Drugs.* 2010;70:2133-2152.

# Concepts in Onychomycosis Treatment and Recurrence Prevention: An Update

Theodore Rosen, MD*

## Abstract

In considering therapy for onychomycosis, the most important factor to take into account is patient selection rather than treatment selection. Patients should be screened and evaluated for the extent of nail involvement, the amount of subungual debris, the degree of dystrophy, their ability and willingness to follow the regimen, and whether comorbidities are present that may affect the efficacy and/or safety of one or more therapies. Onychomycosis is a chronic disease with a high recurrence rate. Common-sense measures to reduce the risk for reinfection include patient education and a clinician-patient team approach to long-term management.

## Keywords

Dermatophytes; diabetes; geriatric patients; immunosuppression; onychomycosis; pediatric patients; psoriasis; treatment adherence

Semin Cutan Med Surg 35(suppl 3):S56-S59


A number of patient-specific factors must be considered in the context of onychomycosis treatment, and these fall into two main categories: age related and medically related. Both extremes of the age spectrum—pediatric and geriatric patients—have special problems and needs related specifically to age. (Note that no antifungal medication currently available is approved for treating onychomycosis in pediatric patients.) In addition, patients with onychomycosis may have medical comorbidities—including diabetes, psoriasis, immunosuppression (acquired or drug-related), and organ transplantation—that can affect treatment choices. In many of these patients, systemic antifungal therapy can be problematic, and topical therapy may be a better first-line choice.

* Professor of Dermatology, Baylor College of Medicine, Houston, Texas.

Publication of this CME/CE article was jointly provided by the University of Louisville and Global Academy for Medical Education, LLC, with Skin Disease Education Foundation (SDEF) and is supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

Dr Rosen has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal supplement.

Theodore Rosen, MD, *Consultant*: Anacor Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Address reprint requests to: Theodore Rosen, MD, 2815 Plumb, Houston, TX 77005; vampireted@aol.com.

## Age-Related Issues in Onychomycosis

### Pediatric Population

Among the pediatric population, onychomycosis is seen most commonly in those between 12 and 18 years of age; onychomycosis is uncommon in children under 12 years and is relatively rare in those under 6 years of age.[1-4] The proposed reasons for the low prevalence of onychomycosis in younger children include faster nail growth, better circulation, less trauma, less exposure to fomites (eg, in gyms or public pools), and a lower incidence of tinea pedis[5]; however, no scientific evidence exists to directly support these theories.

Pediatric patients who develop onychomycosis often have a family history of onychomycosis and/or tinea pedis (caused by *Trichophyton rubrum*). The probability is high that children who develop onychomycosis have a genetic predisposition to acquire the infection, and their risk for developing an active infection is increased by exposure to dermatophytes and other organisms—eg, wearing occlusive athletic footwear, walking through and showering in locker rooms without footwear, and sharing a household in which others have onychomycosis or tinea pedis.

### Geriatric Population

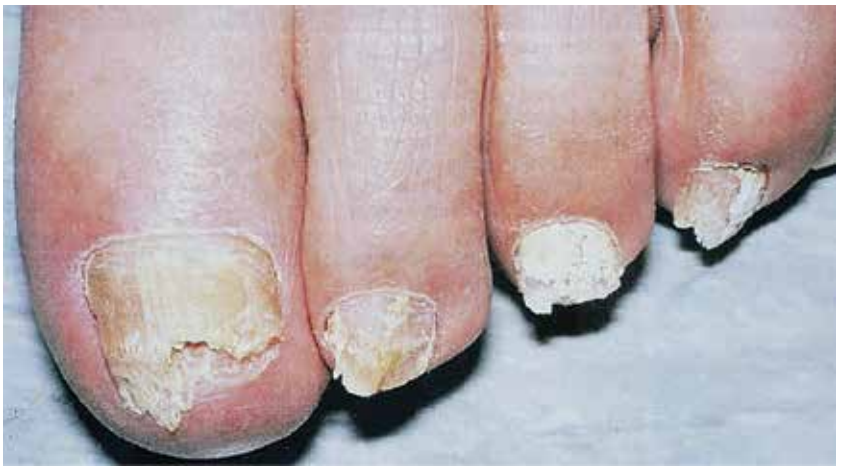
In geriatric patients, an increased risk for onychomycosis arises probably in association with multiple comorbidities, decreased circulation, and accumulated trauma to the nails. Approximately 40% of elderly patients have onychomycosis,[1] which may cause pain or affect gait, increasing the risk for falls in this population. Drug-drug interactions are of particular concern in older patients, who typically use several medications concomitantly. If it is physically possible for patients to apply topical antifungals—or if daily assistance is available for applying these medications—the use of yet another systemic medication can be avoided.

Patients should understand that the changes to nails that are associated with aging—such as dystrophy and discoloration—and that are not related to onychomycosis will persist after successful treatment (**Figure**).[6]

## Comorbidities

### Psoriasis

More than 82% of patients with psoriasis have nail abnormalities[7]; in an estimated 13% to 22% of cases, onychomycosis coexists with psoriatic nail involvement.[8] Thus, in a patient with psoriasis and nail involvement, clinicians should recognize the possibility of coexisting dermatophyte, candidal, or mixed dermatophyte/candidal infection,[7-10] and, if clinical signs are consistent with onychomycosis, consider obtaining a specimen for a mycologic culture. This is especially important in patients with psoriasis who are being treated with interleukin-17 inhibitors which may increase the risk for yeast infections.[11]



■ **FIGURE. Extensive Dermatophyte Onychomycosis.** Successful treatment will result in the eradication of the infection as well as improvement in the appearance of the nails. However, patients should have realistic expectations regarding the post-treatment cosmetic outcome. For example, this elderly patient has an extensive dermatophyte infection of long duration; the yellow discoloration is likely to have resulted, in part, from aging, and cannot be expected to resolve completely. Photo courtesy of Theodore Rosen, MD.

Two topical antifungal agents, efinaconazole and tavaborole, have demonstrated good in vitro activity against *Candida* species and nondermatophyte molds such as *Aspergillus* and *Fusarium* spp.[12] However, caution must be exercised when dealing with fungal pathogens, as in vitro susceptibility does not always correlate with in vivo efficacy.

### Diabetes

An estimated 46% of patients with diabetes have nail abnormalities, and about 50% of these abnormalities are due to onychomycosis[13]; thus, the prevalence of onychomycosis in this population may be as high as 20% to 30%.[14] Onychomycosis also increases the risk of diabetic foot syndrome,[15-17] a constellation of problems—diabetic neuropathy, macroangiopathy, and the combination of those conditions—which can lead to serious, limb- and life-threatening bacterial infections.

In patients with diabetes who develop onychomycosis, atypical organisms (especially yeasts) may be more commonly seen,[18] although some investigators have found no difference in the types of fungi in this patient population.[19] A mycologic culture is indicated to identify the offending organism in patients with diabetes who have signs and symptoms of onychomycosis. Efinaconazole and tavaborole have proven efficacy in this population in the pivotal trials.

Onychomycosis also is more common among patients undergoing hemodialysis treatment, not all of whom have diabetes and end-stage renal disease. An estimated 81% to 92% have nail abnormalities; 20% to 31% of these abnormalities are due to onychomycosis, for an onychomycosis prevalence of about 16% to 27% in this population.[20,21] Duration of hemodialysis is a significant predictor of onychomycosis.[20] The patterns of isolates in these patients seem to mimic what is seen in patients who are not on dialysis, ie, predominantly *T. rubrum* and, occasionally, *Candida* spp, and nondermatophyte molds.

### Immunocompromise and Immunosuppression

Immunosuppression for any reason increases the risk for nail infections.[9] Approximately 40% of individuals with human immunodeficiency virus infection have nail abnormalities, about half of which are due to onychomycosis.[22] Patients with a CD4 count of 370 or less are highly susceptible to onychomycosis.[22]

The prevalence of onychomycosis in patients who have undergone solid organ transplantation is 10% to 13%, especially among those using cyclosporine or azathioprine post-transplant.[23,24] Similarly, patients receiving chemotherapy for cancer ("immunodisturbed" patients) also are at increased risk for onychomycosis. Onychomycosis in this patient population is most likely to occur in those who have a history of nail infection or tinea pedis prior to transplant surgery, and in those with a family history of these infections.

In these groups of individuals with impaired immunity, *Candida* spp and nondermatophyte molds are more common than in normal hosts. Patients who acquire such infections are at risk for potentially life-threatening fungemia. Clinicians should consider prophylactic use of topical treatments—efinaconazole and tavaborole have excellent minimum inhibitory concentrations against these organisms—in immunocompromised patients or those who are likely to be using long-term immunosuppressants (eg, post-transplant). (This is an unapproved indication for these medications, and no particular treatment regimens have been proposed.)

## Strategies for Adherence and Preventing Reinfection

The treatment of onychomycosis is both acute and long-term—and includes the use of medication and infection risk reduction strategies during the initial and any subsequent reinfection episodes, and, long-term, the continuation of risk reduction measures and vigilance for signs of recurrence of onychomycosis and/or tinea pedis, with prompt initiation of treatment.

Recurrence of onychomycosis is common because the propensity to develop these fungal infections in the first place is based largely on autosomal-dominant inheritance. Thus, patients who have had onychomycosis would do well to implement all reasonable measures to reduce the risk for reinfection. Patients should understand that although genetics cannot be changed, behavior can be modified.

### Clinician-Patient Team Effort

Adherence to onychomycosis treatment can be enhanced with measures such as phone calls, automated phone messages, postcards, and a website in which patients can log in.

### Attention to Footwear

Patients should absolutely avoid walking barefoot in public areas such as gyms, locker rooms, spas, and public showers and pools. An inexpensive pair of water shoes or rubber sandals can prevent exposure to fungi and other organisms.

If possible and practical, patients should consider discarding

shoes that have been worn prior to initiation of onychomycosis treatment. An alternative to discarding expensive or relatively new shoes is disinfection in an ozone cabinet (usually found in sports equipment stores) or with the use of ultraviolet C light-generating shoe inserts. These devices have been shown to be active against dermatophytes and *Candida* spp.[25-27] Other measures include alternating pairs of shoes daily (allowing fungus-promoting moisture to evaporate) and using medicated powder daily in shoes and socks.

### Application Instructions for Topical Antifungals

The instructions for applying the different antifungal agents should be simple and clear to patients (see "Using Topical Antifungal Medications: Instructions for Patients," page 17).

### Nail Polish and Topical Antifungals

Patients often ask whether they may use nail polish during their treatment with a topical antifungal. The use of nail polish is contraindicated during treatment with ciclopirox; however, recent studies demonstrate that the penetration and efficacy of efinaconazole and tavaborole are not affected when used over nail polish. The penetration studies of efinaconazole were performed with up to two coats of nail polish.[28] Tavaborole was studied with up to four coats of nail polish.[29] Advise patients who do want to use polish to test the tackiness of the polished nail surface before putting on socks, stockings, or shoes; color transfer has been seen with some polishes used with these topical antifungals. Thus, although nail polish does not affect the medications, the medications may affect the cosmetic aspects of nail polish.

### Great—But Realistic—Expectations

Because nails grow slowly, at an average of about 3 mm per month, patients should understand that although treatment may (and should) eliminate the infecting organism, the appearance of the affected nails will not improve until the nail plate grows out. Fingernails grow out in 3 to 6 months, but complete growth of toenails can take 9 to 18 months.

During this long treatment process, it helps to use or suggest methods for monitoring progress. Pictures taken at regular intervals—such as monthly—can be helpful, particularly if the clinician marks the proximal edge of clear nail, at the start of therapy. This allows the patient to more accurately gauge the growth of new nail.

Patients should be told that they can expect improvement in the appearance of the affected nails, but many factors—such as the age of the patient and the extent of infection—may affect the ultimate outcome. However, they must understand that the optimum results can only be expected if the recommended therapy is used in the manner directed and for as long as directed.

## Conclusion

Onychomycosis is a common fungal infection due principally to dermatophytes; *Candida* spp and saprophytic fungi account for a smaller number of cases. Comorbid diseases and conditions may affect the prevalence of onychomycosis, and may alter the clinical presentation as well as the causative organism(s).

Pediatric onychomycosis is uncommon, but the possibility of this diagnosis should not be overlooked, particularly in patients with family members who have onychomycosis and/or tinea pedis.

Treatment is feasible with both systemic and topical drugs; the newer topical agents, efinaconazole and tavaborole, have broad in vivo activity and can provide improved clinical efficacy.

The treatment goal of "complete cure"—ie, complete eradication of organisms and a totally normal appearance of the treated nail—used in clinical trials is a somewhat unrealistic expectation in real-world application.[6] Instead, treatment success—that is, eradication of the infection, improvement of the appearance of the nail, and, when pain is a symptom, resolution of discomfort—is a more reasonable and achievable, practical goal.

## References


1. Ghannoum MD, Hajjeh RA, Scher R, et al. A large-scale North American Study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol*. 2000;43:641-648.
2. Feldstein S, Totri C, Friedlander SF. Antifungal therapy for onychomycosis in children. *Clin Dermatol.* 2015;33:333-339.
3. Elewski B, Charif MA. Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions. *Arch Dermatol*. 1997;133:1172-1173.
4. Piraccini BM, Starace M. Nail disorders in infants and children. *Curr Opin Pediatr*. 2014;26:440-445.
5. Philpot CM, Shuttleworth D. Dermatophyte onychomycosis in children. *Clin Exp Dermatol*. 1989;14:203-205.
6. Rosen T. Assessment of dermatophytosis treatment studies: Interpreting the data. *J Drugs Dermatol*. 2015;14(suppl 10):S48-S54.
7. Larsen GK, Haedersdal M, Syeigaard EL. The prevalence of onychomycosis in patients with psoriasis and other skin diseases. *Acta Derm Venereol*. 2003;83:206-209.
8. Klaassen KM, Dulak MG, van de Kerkhof PC, Paasch MC. The prevalence of onychomycosis in psoriatic patients: A systematic review. *J Eur Acad Dermatol Venereol*. 2014;28:533-541.
9. Rich P, Jellinek N, Pariser DM. Management strategies for onychomycosis in special patient populations. *Semin Cutan Med Surg.* 2015;34(suppl 3):S54-S55.
10. Staberg B, Gammeltoft M, Onsberg P. Onychomycosis in patients with psoriasis. *Acta Derm Venereol*. 1983;63:436-438.
11. Mease PJ, McInnes IB, Kirkham B, et al; for the FUTURE 1 Study Group. Secukinumab inhibition of interleukin 17A in patients with psoriatic arthritis. *N Engl J Med*. 2015;373:1329-1339.
12. Gupta AK, Daigle D. Potential role of tavaborole for the treatment of onychomycosis. *Future Microbiol*. 2014;9:1243-1250.
13. Gupta AK, Konnikov N, MacDonald P, et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: A multicentre survey. *Br J Dermatol*. 1998;139:665-671.
14. Chang SJ, Hsu SC, Tien KJ, et al. Metabolic syndrome associated with toenail onychomycosis in Taiwanese with diabetes mellitus. *Int J Dermatol*. 2008;47:467-472.
15. Boyko EJ, Ahroni JH, Cohen V, et al. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: The Seattle Diabetic Foot Study. *Diabetes Care.* 2006;29:1202-1207.
16. Gupta S, Koirala J, Khardori R, Khardori N. Infections in diabetes mellitus and hyperglycemia. *Infect Dis Clin North Am*. 2007;21:617-638.
17. Tan JS, Joseph WS. Common fungal infections of the feet in patients with diabetes mellitus. *Drugs Aging.* 2004;21:101-112.
18. Winston JA, Miller JL. Treatment of onychomycosis in diabetic patients. *Clin Diabetes*. 2006;24:160-166.
19. Piérard GE, Piérard-Franchimont C. The nail under fungal siege in patients with type II diabetes mellitus. *Mycoses*. 2005;48:339-342.
20. Kuvandik G, Cetin M, Genctoy G, et al. The prevalence, epidemiology and risk factors for onychomycosis in hemodialysis patients. *BMC Infect Dis*. 2007;7:102.
21. Onelmis H, Sener S, Sasmaz S, Ozer A. Cutaneous changes in patients with chronic renal failure on hemodialysis. *Cutan Ocul Toxicol*. 2012;31:286-291.
22. Gupta AK, Taborda P, Taborda V, et al. Epidemiology and prevalence of onychomycosis in HIV-positive individuals. *Int J Dermatol.* 2000;39:746-753.
23. Dicle O, Parmaksizoglu B, Gurkan A, Tuncer M, Demirbas A, Yilmaz E. Skin infections in 401 renal transplant recipients in southern Turkey. *Exp Clin Transplant*. 2009;7:133-136.
24. Güleç AT, Demirbilek M, Seçkin D, et al. Superficial fungal infections in 102 renal transplant recipients: A case-control study. *J Am Acad Dermatol.* 2003;49:187-192.
25. Ghannoum MA, Isham N, Long L. Optimization of an infected shoe model for

the evaluation of an ultraviolet shoe sanitizer device. *J Am Podiatr Med Assoc*. 2012;102:309-313.
26. Gupta AK, Brintnell WC. Sanitization of contaminated footwear from onychomycosis patients using ozone gas: A novel adjunct therapy for treating onychomycosis and tinea pedis? *J Cutan Med Surg.* 2013;17:243-249.
27. Gupta AK, Brintnell W. Ozone gas effectively kills laboratory strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes* using an in vitro test system. *J Dermatolog Treat*. 2014;25:251-255.
28. Zeichner JA, Stein Gold L, Korotzer A. Penetration of (14C)-efinaconazole topical solution, 10%, does not appear to be influenced by nail polish. *J Clin Aesthet Dermatol*. 2014;7:34-36.
29. Vlahovic T, Merchant T, Chanda S, Zane LT, Coronado D. In vitro nail penetration of tavaborole topical solution, 5%, through nail polish on ex vivo human fingernails. *J Drugs Dermatol*. 2015;14:675-678.

## Using Topical Antifungal Medications: Instructions for Patients

Your clinician has prescribed one of these topical medications to treat your nail infection. The prescribed medication must be used every day, exactly as directed, and for 48 weeks.

### The goals of treatment are:

1. Resolution of the infection
2. Improvement in the appearance of the infected nail(s)
3. Resolution of discomfort.

Remember, nails grow slowly, at an average of about 3 mm each month—about the width of the edge of a nickel. The appearance of nails will not improve until the damage from the infection grows out. Fingernails grow out in about 3 to 6 months, but toenails can take 9 to 18 months to completely grow out.

Also, the newly regrown nails should look better than before, but not all patients see 100% improvement with any antifungal treatment—whether oral or topical. A number of factors can affect the appearance of nails following treatment and regrowth. Your clinician will explain what you can expect in your case.

### Ciclopirox

- Apply once daily to all affected nails (preferably at bedtime or 8 hours before washing).
- Apply over the previous coat.
- Using the applicator brush, apply evenly over the entire nail plate and under the tip of the nail.
- If the nail has lifted from the nail bed, also apply to the tissue under the nail.
- Every 7 days, remove lacquer with rubbing alcohol. Repeat this cycle for 48 weeks.
- A health care professional should remove unattached, infected nails as frequently as monthly.
- Do not use nail polish during treatment with this medication.

### Efinaconazole

- Apply to affected toenails, completely covering the toenail plate, the skin folds around the nail, and under the tip of the nail.
- If the nail has lifted from the nail bed, also apply to the tissue under the nail.
- Apply once daily for 48 weeks.
- You may use nail polish during treatment with this medication.

### Tavaborole

- Apply to entire nail plate and under the tip of each affected toenail.
- If the nail has lifted from the nail bed, also apply to the tissue under the nail.
- Apply once daily for 48 weeks.
- You may use nail polish during treatment with this medication.


Supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

FOR NOTES PURPOSES ONLY. MUST BE COMPLETED ONLINE.

# POST-TEST CME/CE QUESTIONS

## Onychomycosis: Diagnosis, Treatment, and Prevention Strategies

**Original Release Date:** March 2016 • **Most Recent Review Date:** March 2016

**Expiration Date:** February 28, 2018 • **Estimated Time to Complete Activity:** 2.5 hours; 3.0 contact hours

To get instant CME credits online, go to **http://tinyurl.com/onychosuppl16.** Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add cmepd@louisville.edu to your e-mail "safe" list. If you have any questions or difficulties, please contact the **University of Louisville School of Medicine Continuing Medical Education (CME & PD)** office at cmepd@louisville.edu.

**1. The genus of the most common causative organisms in onychomycosis is:**

a. *Aspergillus*
b. *Candida*
c. *Fusarium*
d. *Trichophyton*

**2. In pediatric patients with onychomycosis, always suspect a:**

a. Compromised immune system
b. Family history of tinea pedis
c. High blood glucose level, suggesting type 1 diabetes mellitus
d. Previous injury to the affected nail(s)

**3. Three of the antifungals are currently approved by the US Food and Drug Administration (FDA) for the treatment of onychomycosis. The exception is:**

a. Ciclopirox
b. Fluconazole
c. Itraconazole
d. Terbinafine

**4. In clinical trials of antifungal agents in onychomycosis, the FDA's requirement for a definition of "complete cure" is a negative result on a potassium hydroxide (KOH) preparation plus:**

a. Completely normal appearance of the target nail(s)
b. Negative results on fungal culture, as well as a completely normal appearance of the target nail(s)
c. Negative results on fungal culture, as well as clear or almost clear appearance of the target nail(s)
d. Negative results on fungal culture and periodic acid–Schiff stains, as well as a completely normal appearance of the target nail(s)

**5. Which one of the following statements is true with respect to drug-drug interactions in patients with onychomycosis who are being treated with antifungal medication?**

a. Fluconazole is the only systemic antifungal that is not associated with drug interactions
b. Itraconazole may inhibit the metabolism of a number of biologic medications used for the treatment of psoriasis
c. No drug interactions have been reported with ciclopirox, efinaconazole, or tavaborole
d. Terbinafine may interact with tofacitinib, one of the IL-17 inhibitors

**6. Patients who ask about using nail polish during treatment for onychomycosis should be advised that:**

a. Nail polish can make fungal infections worse and should not be used until nails are clear
b. Nail polish helps kill the infecting organisms, provided onychomycosis is confined to the nail plate
c. Nail polish may be used with efinaconazole and tavaborole, without affecting the efficacy of these topicals
d. Nail polish should not be used with any topical agent

**7. Which of the following is/are approved by the FDA for the "temporary increase of clear nail in onychomycosis"? (Choose one response.)**

a. All three FDA-approved topical medications: ciclopirox, efinaconazole, and tavaborole
b. Both of the FDA-approved systemic antifungal medications—itraconazole and terbinafine
c. Laser treatment
d. Photodynamic therapy

**8. The most frequently recommended, FDA-approved antifungal for treating pediatric onychomycosis in patients 6 to 11 years of age is:**

a. Any of the topical agents—ciclopirox, efinaconazole, or tavaborole
b. Itraconazole
c. Terbinafine
d. No antifungal is currently approved for pediatric use

**9. Of the following, the population with the largest prevalence of onychomycosis is:**

a. Patients with diabetes
b. Geriatric patients
c. Patients undergoing hemodialysis
d. Post-transplant patients

**10. Onychomycosis is a very common nail disease, but it's important to remember that causes other than fungal or yeast infections are responsible for an estimated ____ of nail diseases that must be considered in the differential diagnosis.**

a. 10%
b. 25%
c. 50%
d. 75%

**FOR NOTES PURPOSES ONLY. MUST BE COMPLETED ONLINE.**

# EVALUATION FORM

## Onychomycosis: Diagnosis, Treatment, and Prevention Strategies

**Original Release Date:** March 2016 • **Most Recent Review Date:** March 2016

**Expiration Date:** February 28, 2018 • **Estimated Time to Complete Activity:** 2.5 hours; 3.0 contact hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: **http://tinyurl.com/onychosuppl16.** If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

**Please indicate your profession/background:**

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow ☐ Researcher ☐ Administrator ☐ Student

☐ Other; specify _____

| **LEARNING OBJECTIVES:** *Having completed this activity, participants should be better able to:* | Strongly Agree | Agree | Somewhat Agree | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| Establish or improve practice protocols for identifying patients with onychomycosis, particularly in special populations (eg, the elderly, pediatric patients, immunocompromised patients, patients with psoriasis, and those with diabetes mellitus). | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Discuss techniques, including obtaining good culture specimens, that permit more accurate diagnosis of the infecting organisms and the most appropriate choice of therapy. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Explain the drug classes and mechanisms of action for the currently available therapeutic options, including differences in formulation and associated efficacy. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| More effectively use currently available oral and topical medications to treat various patient populations. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Review and, if necessary, improve patient education materials designed to enhance patient adherence with the treatment regimen and to change habits that increase the chances of good long-term management of onychomycosis. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Determine and help each patient recognize the realistic expectations for improvement in his or her individual case. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Evaluate the results of clinical studies on new and emerging and available treatments for onychomycosis based on an understanding of possible differences in testing protocols (eg, inclusion or exclusion of patients with psoriasis or diabetes mellitus). | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

**If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.**

_____

_____

**Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)**

☐ Implement a change in my practice/workplace.

☐ Seek additional information on this topic.

☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.

☐ Do nothing differently as the content was not convincing.

☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

**If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.**

_____

_____

**If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?**

☐ Yes. E-mail address: _____

☐ No. I don't plan to make a change.

**If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)?**_____

_____

| **OVERALL EVALUATION:** | Strongly Agree | Agree | Somewhat Agree | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| The information presented increased my awareness/understanding of the subject. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| The information presented will influence how I practice/do my job. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| The information presented will help me improve patient care/my job performance. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| The program was educationally sound and scientifically balanced. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Overall, the program met my expectations. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| I would recommend this program to my colleagues. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| **Linda F. Stein Gold, MD:** | | | | | |
| Author demonstrated current knowledge of the topic. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Author was organized in the written materials. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| **Theodore Rosen, MD** | | | | | |
| Author demonstrated current knowledge of the topic. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| Author was organized in the written materials. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

**What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?**

_____

_____

**Please provide additional comments pertaining to this activity and any suggestions for improvement.**

_____

_____

*The University of Louisville thanks you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patients' care.*

Global Academy for
Medical Education