Update on Onychomycosis: Effective Strategies for Diagnosis and Treatment

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The Rationale for Renewed Attention to Onychomycosis

The Epidemiology, Etiology, and Pathophysiology of Onychomycosis

Diagnosis, Clinical Implications, and Complications of Onychomycosis

Current and Emerging Options in the Treatment of Onychomycosis

Promoting and Maintaining or Restoring Healthy Nails: Practical Recommendations for Clinicians and Patients

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Clinicians should be able to:

After participating in this continuing medical educational activity, physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives

After participating in this continuing medical educational activity, clinicians should be able to:

• List and describe the differential diagnosis of onychomycosis and the expert-recommended methods for establishing the diagnosis of this infection.

• Explain the benefits of early diagnosis and treatment of onychomycosis and the potential sequelae if this infection is untreated or is inadequately treated.

• Apply practice protocols for identifying patients with onychomycosis, particularly the elderly, patients with diabetes mellitus, and other high-risk populations.

• Integrate effective, office-based diagnostic tests into the workup of patients with symptoms of onychomycosis.

• Use currently available oral and topical medications to treat various patient populations.

• Evaluate the results of clinical studies on new and emerging treatments for onychomycosis.

Target Audience

This continuing medical education activity has been developed for dermatologists, family practice and internal medicine physicians, and other health care providers who treat diseases of the skin.

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Onychomycosis is a common problem that the average dermatologic practitioner encounters every day. Our experiences with this infection are as varied as the patients who present with onychomycosis.

All clinicians certainly have encountered patients with very mild, asymptomatic cases of onychomycosis of the toenails, about which the patient expresses little or no interest in treatment. Even those whose infection has progressed to yellowing, brittleness, and lifting of the nail plate in several toes may mention the condition inside their shoes only as an afterthought in a medical encounter for a different complaint. Patients who do seek medical attention for onychomycosis as their primary complaint usually do so because of one or more of the following: pain and discomfort, a secondary infection of the skin around the nail plate, unsightly appearance, or interference with normal function. Other patients come to the attention of clinicians because their nail disease is associated with other systemic diseases.

Few in our specialty today would consider the infection too trivial to treat, even in cases in which the clinical manifestations are, to all appearances, mainly cosmetic. Onychomycosis often is a progressive condition that warrants intervention.

Clinical Sequelae

The understanding of nail disease as an important medical condition is a relatively recent development. As Richard K. Scher, MD, noted in an editorial, “Nail disorders—One of dermatology’s last frontiers,” few articles appeared in the literature on this topic until the 1980s.1 This lack of attention can be attributed in part to underappreciation of the importance of infections of the nail and in part to the dearth of available effective modalities to treat these conditions.

The consequences of failure to treat include permanent damage to the nail plate and its attachments, the development of secondary infections with bacteria and other organisms, local spread of the infection (paronychia) or spread to other parts of the body, and transmission of the infection to others.2 For example, *Trichophyton rubrum*—the most common causative organism of both onychomycosis and tinea pedis—can be transmitted to the groin area as individuals step into and pull clothing up the legs. In addition, minor wounds on the legs may be colonized by fungal organisms in this manner, and secondary bacterial infections and cellulitis may result.

In addition, in elderly patients—in whom onychomycosis is highly prevalent—the infection may complicate any existing foot problems and may lead to decreased mobility.2 Any alterations in normal gait represent an increased risk for falls, and as the population continues to age—and as older persons live longer—both the individual and public health consequences are evident.

The adverse effects of onychomycosis on quality of life also must be considered. In addition to embarrassment and self-consciousness, untreated or ineffectively treated onychomycosis often interferes with social interactions (particularly intimate relationships) because of fear of contagion. Furthermore, adverse effects on job function or on new or continued employment is possible when onychomycosis of the toenails affects mobility and when infections of the fingernails interfere with a job that involves direct contact with the public (such as restaurant wait staff, health care workers, and retail sales).

Clearly, onychomycosis is an infectious disease of significant importance.

Conclusion

Clinicians need to know about how onychomycosis presents clinically, how to make a definitive diagnosis (which involves identifying the causative organism in each patient prior to initiating therapy), which treatments currently are available and how best to use them, and which new agents are now in clinical trials and may soon be options for therapy.

The purpose of the articles in this supplement is to offer a convenient compendium of current information in all of these areas for both clinician and patient.

References

The Epidemiology, Etiology, and Pathophysiology of Onychomycosis
Richard K. Scher, MD, * Phoebe Rich, MD, † David Pariser, MD, ‡ Boni Elewski, MD §

ABSTRACT The prevalence of onychomycosis in the United States is estimated to be at least 12%; prevalence increases with increasing age and is highest in individuals more than 65 years of age. *Trichophyton rubrum*, which also causes *tinea pedis*, is responsible for approximately 90% of cases of toenail onychomycosis. Risk factors include a family history of onychomycosis and previous injury to the nails, as well as advanced age and compromised peripheral circulation. Patients with compromised immune function may have an increased risk for onychomycosis and are susceptible to infection with less common dermatophytes and nondermatophyte organisms.

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The reported prevalence of onychomycosis in the United States varies considerably, as no scientifically rigorous, large epidemiologic studies have been done to date. The prevalence varies according to patient population (including age, family history, comorbid conditions) and also depends on variables such as geography and climate. The authors concur that the median figure probably is 10% to 12% or higher.1,2 However, it also should be noted that onychomycosis is rare in children (less than 1%)2 and increases in prevalence with increasing age (the prevalence in the geriatric population has been estimated at 60%).1

Etiology and Pathophysiology

The causative organisms in most cases of onychomycosis are dermatophytes. (The term “tinea unguium” often is used interchangeably with onychomycosis; however, tinea unguium applies only to cases of onychomycosis caused by dermatophyte fungi.) Dermatophyte organisms are ubiquitous and are found in soil (geophilic), animals (zoophilic), and humans (anthrophiophilic). Species of three genera are anthropophilic: *Trichophyton*, *Microsporum*, and *Epidermophyton*. These are keratinophilic organisms, and, as such, they invade keratinized tissues, including the stratum corneum, the hair, and the nails.

The most common organisms found in onychomycosis (Table on page S3) are *Trichophyton rubrum*, which is responsible for an estimated 90% of infections, and *Trichophyton mentagrophytes*, which is implicated most commonly in the balance of cases.1 Not surprisingly, onychomycosis of the toenails typically occurs in individuals who have concurrent tinea pedis infections (“athlete’s foot”), also caused by *T. rubrum*. *Microsporum* spp and *Epidermophyton floccosum* (the only *Epidermophyton* species found in humans) are unusual causes of onychomycosis in the United States.

A number of other organisms also may be involved in nail infections, including some yeasts—especially *Candida* spp, which most commonly occur in fingernails and most often are seen in tropical regions—and some nondermatophyte molds (such as *Fusarium* and *Aspergillus* spp).1 Although these occur much less frequently than do the dermatophyte infections, it is important to be aware that yeasts and non-dermatophyte molds may be present, particularly in certain
groups of patients (see the section, “Special Patient Populations,” below). Candida spp and nondermatophyte molds tend to be more difficult to treat effectively, and earlier identification of these organisms and prompt initiation of therapy may improve outcomes.

Certain factors are known to increase the risk for developing onychomycosis. Individuals who perspire heavily or whose occupations or recreational activities expose them to humid, moist environments are at increased risk. In such persons, footwear that crowds the toes or prevents adequate air circulation—and, therefore, evaporation of excess moisture—compounds the problem.

Individuals with a previous history of nail injury or previous infection are particularly susceptible under these conditions. Also, the risk for onychomycosis is increased with participation in occupations, sports, or exercise in which chronic minor trauma to the toes is sustained. In addition, practices such as walking barefoot in public places where moisture is an integral part of the environment (eg, swimming pools, spas, gyms, locker rooms) are common sources of transmission of causative organisms. Another frequent source of onychomycosis is nail salons; disinfection regimens for clippers, scissors, and other instruments are not always effective (even if rigorously followed), and emery boards retain dust from person to person and may be a source of organism transmission.

Onychomycosis also is a topic of concern among several special patient populations: individuals with compromised peripheral circulation, the elderly, those with diabetes, persons with a family history of onychomycosis, those with compromised immune function, and possibly also patients with psoriasis and pediatric patients.

### Special Patient Populations

#### Compromised Peripheral Circulation

Impaired circulation from any cause—for example, diabetes, vascular disease, or advanced age—is associated with an increased risk for onychomycosis as well as with a diminished response to therapy. Poor circulation is associated with a decrease in nail growth rate, which increases the risk for colonization by dermatophytes and other organisms. Patients with poor peripheral circulation may need higher dosages of systemic medications and/or may require a longer course of therapy than do individuals with good circulation.

#### Advanced Age

Onychomycosis is among the most common infections that affect older individuals. Elewski and Charif report that approximately 40% of elderly patients have onychomycosis. The presence of arthritis and other conditions that affect physical flexibility contributes to the increased prevalence of onychomycosis in this population. Gait changes and circulatory problems contribute to the development of corns, calluses, and bunions, and minor repeated trauma to the toes is common. It is difficult for many older individuals to exercise careful hygiene of the feet and nails, increasing susceptibility to colonization by infectious organisms.

Many older patients have one or more conditions—such as diabetes and peripheral vascular compromise—that contribute to an increased risk for onychomycosis and can represent potential impediments to a good therapeutic response. As in patients with poor circulation, slower nail growth increases the risk for onychomycosis in older individuals. The reduction in nail growth rate ranges from about 40 to 60% in persons more than 65 years of age; nail growth can slow even more as age increases.

Finally, slower drug metabolism, which occurs with aging, may interfere with effective systemic therapy for onychomycosis. In addition, many older patients take multiple medications, so the possibility of interactions with systemic antifungal agents must be considered.

#### Diabetes

Some controversy exists as to whether individuals with diabetes are more susceptible to onychomycosis than are those without diabetes and whether the treatment of those with diabetes is more difficult than the treatment of those without diabetes. Less debatable is the observation that onychomycosis is more prevalent in patients with diabetes than in patients without the condition. There is no question, however, that onychomycosis makes patients with diabetes more susceptible to secondary infection and that nail infections contribute to the development of cellulitis and...
phlebitis. In addition, patients with diabetes tend to have onychomycosis from atypical organisms, particularly yeasts, than do those without diabetes, and infections with these organisms often are more difficult to treat than those caused by dermatophytes.

Family History
Good evidence demonstrates that a family history of onychomycosis predisposes individuals to nail infection. It is likely that a genetic predisposition exists, but it is also probable that transmission of the causative organism(s) is increased among family members living in the same household. For the same reasons, a family history of onychomycosis is associated with recurrence of nail infections after treatment and almost always is associated with pediatric onychomycosis.

Compromised Immune Function
Immunocompromised patients can be problematic both in terms of susceptibility and because they are susceptible to invasion by less common organisms—that is, unusual dermatophytes and nondermatophyte microbes. Candida albicans, which is implicated predominantly in fingernail infections, may be acquired by direct contact with a lesion caused by the same organism. Interestingly, Candida species do not produce the enzymes necessary to effectively invade keratin in healthy individuals. It is seen primarily in immunocompromised hosts who already have onycholysis, which creates a warm, moist, dark environment underneath the nail plate. It can also sometimes cause paronychia.

Individuals with HIV/AIDS also have a higher susceptibility and may have the proximal white subungual type of onychomycosis. In addition, the number of medications these patients must take on a daily basis makes the prescription of yet another systemic medication an issue to be carefully considered.

Psoriasis
Nail psoriasis very closely resembles onychomycosis, particularly in toenails. Several studies have shown that in almost 30% of individuals with psoriasis who have abnormal toenails, a dermatophyte organism can be cultured from the nail. Treatment for onychomycosis in these cases will clear the dermatophyte infection, but the portion of the nail affected by psoriasis will not improve. About 5% of patients have nail involvement as their initial presentation of psoriasis. Therefore, psoriasis should be considered as a possible diagnosis—or concomitant diagnosis—in patients with onychomycosis.

Pediatric Patients
A prevailing myth from years past was that children do not get onychomycosis. More recent observation and evidence demonstrates that children do indeed acquire the infection; the prevalence is very low, now estimated at less than 1%, although it may be increasing. In general, pediatric patients who develop onychomycosis have a family history of the infection. Therefore, an examination of the nails of adolescent and adult family members is warranted whenever a child presents with signs or symptoms of onychomycosis.

Systemic therapy for onychomycosis in children is not approved by the US Food and Drug Administration, although terbinafine, fluconazole, and itraconazole are used commonly for treating fungal infections in pediatric patients. Recently, Gupta and Paquet proposed dosing regimens, based on the patient’s weight, for children with either fingernail or toenail onychomycosis.

Conclusion
Onychomycosis is a common infection that requires appropriate diagnosis and treatment. In most patients, the causative organism is a dermatophyte—usually T. rubrum—that is readily and easily treatable. Patients in some special populations are at higher risk for infections with nondermatophyte fungi and yeasts. Nail infections with these organisms may have a protracted course and may be difficult to eradicate. Treatment in such patients may be complicated by the presence of systemic illnesses that require the use of multiple potent systemic medications.

References
onychomycosis is defined as a fungal infection of the nail unit (Figure 1): the nail plate, nail bed, and periungual tissue. The most common culprits in immunocompetent patients are *Trichophyton rubrum* (90% of cases) and *Trichophyton mentagrophytes* (most of the remaining 10% of cases).1 Less commonly, yeasts and nondermatophyte molds may be causative organisms, particularly in certain patient populations, such as patients with diabetes, the elderly, and immunocompromised individuals. (For further discussion in this supplement, see Scher et al.2) Onychomycosis caused by dermatophytes is significantly more common in toenails than in fingernails; the opposite is true of *Candida* infections, which are significantly more common in fingernails than in toenails.3

Physical Examination

The physical examination should include careful inspection of all fingernails and toenails. The extent of involvement (the number of nails and the percentage of involvement of each nail unit) should be noted.

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**Figure 1. Nail Anatomy** The *nail plate* (consisting of keratin) forms in the *matrix* and is attached to the *nail bed* as it grows. Although the distal portion of the matrix is typically visible (as the *lunula*) in the thumb and forefinger, it is concealed under the *proximal nail fold* in the rest of the fingers and the toes. The *proximal nail fold* covers and adheres to the *base of the nail*; the distal portion of the proximal fold is the *cuticle*. *Lateral nail folds* form soft tissue boundaries at the sides of the nails.

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Richard K. Scher, MD, is an advisor/consultant to Valeant.
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The clinical features of onychomycosis (Table 1) include nail bed hyperkeratosis with subsequent separation of the nail plate from the nail bed (onycholysis), the presence of subungual debris, and nail plate dyschromia. Individuals with onychomycosis also may experience associated inflammation and tenderness of the nail bed or periungual tissue. Concomitant tinea pedis infection (also caused by *T. rubrum*) is extremely common in patients with toenail onychomycosis.

### Table 1. Clinical Signs of Onychomycosis (Toenails or Fingernails)

- Onycholysis
- Debris under the nail plate
- Subungual hyperkeratosis
- Discoloration (usually nontransparent white or yellow discoloration; less frequently, brown pigmentation)
- Destruction of all or part of the nail plate

Several patterns of nail plate invasion have been described. The most common of these is invasion of the nail plate from the hyponychium (distal-lateral-subungual onychomycosis) (Figure 2). In the presentation known as proximal subungual onychomycosis (Figure 3), the organisms invade the proximal nail bed via the cuticle. This is an unusual presentation in immunocompetent individuals; the presence of proximal subungual onychomycosis should raise the index of suspicion for an underlying cause of immunosuppression. Superficial white onychomycosis is characterized by direct invasion of the nail plate surface, causing leuconychia and crumbling of the plate (Figure 4).

**Chronic mucocutaneous candidiasis** is a presentation that is caused by *Candida albicans*, which affects the entire nail unit. Normally, *Candida* cannot invade the nail plate in immunocompetent patients. *Candida* may be a secondary invader in onycholysis and chronic paronychia (Figure 5).
Laboratory Confirmation of Clinical Diagnosis

The diagnosis of onychomycosis should be confirmed prior to institution of treatment. A diagnosis of onychomycosis often has been made based on clinical impressions alone, particularly in cases of mild infections limited to partial involvement of one or only a few nails and especially when topical therapy—rather than systemic therapy—is prescribed. However, this is no longer considered the ideal practice, given what is now known about the potential clinical sequelae of onychomycosis, the importance of selecting the most appropriate treatment, and the possibility of misdiagnosis of nail disease from other causes (such as immune dysfunction or psoriasis).

Exogenous substances can cause nail dystrophy that can mimic onychomycosis. Nail polish can stain the nail yellow, and other products, such as self-tanning cream, can stain the nail plate brown. Exposure to a number of substances can cause changes in nails that resemble infectious processes. In addition, physiologic changes occur with aging that resemble fungal dystrophy.

Finally, certain systemic medications are known to induce nail changes. For example, antineoplastic drugs may cause onycholysis, and sun exposure during tetracycline therapy may cause photo-onycholysis. Retinoids may cause nail brittleness.

In children, the differential diagnosis includes several uncommon clinical conditions (Table 3). However, a history of onychomycosis and/or tinea pedis in the family or other household members suggests a dermatophyte infection.

<table>
<thead>
<tr>
<th>Table 2. Differential Diagnosis of Onychomycosis in Adults</th>
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<tr>
<td>• Psoriasis</td>
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<td>• Nail trauma</td>
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<tr>
<td>• Contact irritants</td>
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<td>• Lichen planus</td>
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<tr>
<td>• Neoplasms</td>
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<tr>
<td>• Bacterial infection</td>
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<tr>
<td>(Pseudomonas aeruginosa, Proteus mirabilis)</td>
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<tr>
<th>Table 3. Differential Diagnosis of Onychomycosis in Children</th>
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<tr>
<td>• Psoriasis</td>
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<tr>
<td>• Congenital malalignment of large toenail</td>
</tr>
<tr>
<td>• Subungual exostosis</td>
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<tr>
<td>• Subungual warts</td>
</tr>
<tr>
<td>• Subungual hematoma</td>
</tr>
<tr>
<td>• Paronychia secondary to finger sucking</td>
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<td>• Parakeratosis pustolosa</td>
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The goal of onychomycosis treatment is to eradicate the causative organism. Elimination of the fungus generally restores the appearance of the nail in most cases. However, patients should not expect to see normal-appearing nails until after the fungi are eliminated and until the damaged nail has grown out—a process that, for fingernails, may take 6 months or more from the time effective treatment is initiated and, for toenails, 12 to 18 months. Toenails grow at the rate of about 1 to 2 mm per month and fingernails grow faster, at the rate of 2 to 3 mm per month; however, nail growth rate peaks during the teenage years and decreases with advancing age.

Some onychomycosis infections, especially those involving the nail matrix, may produce permanent scarring of the matrix, and, thus, the nail may never appear normal even after the infection is completely eradicated (Figure 1).

The definition of “complete cure,” as defined by the US Food and Drug Administration (FDA) for the evaluation of clinical trial results, is negative results on potassium hydroxide (KOH) preparation and on fungal culture, as well as a completely normal appearance of the nail. In clinical practice—and for practical purposes—most cures will be defined by the absence of fungus on KOH preparation and possibly, but not always, by a completely normal nail (Figure 2). Realistically, patients who have had long-standing infections or chronic onychomycosis are likely to have sustained damage to the nail matrix or subungual area so that, despite the clearance of infectious organisms, new nail growth may be permanently discolored and dystrophic, and some onycholysis (lifting of the nail plate) may persist. Furthermore, nails may be thickened, discolored, and dystrophic for reasons other than mycotic infection—as is
common, for example, in elderly patients who have age-related changes in the nails or onychogryphosis, or even in patients with inflammatory disorders such as psoriasis.

**Systemic Therapy**

Systemic antifungal therapy options currently include itraconazole, terbinafine, and fluconazole. A summary of systemic antifungal agents and cure rates can be found in Tables 1 and 2. A meta-analysis of studies involving these medications demonstrated low risk for side effects in immunocompetent patients.²

Fluconazole is not approved by the FDA for this indication, although it is approved for fingernail and toenail onychomycosis in other countries. It was originally tested in dosages of 150 mg/week, 300 mg/week, and 450 mg/week for up to 9 months or until clearance of the nail.³ In an FDA study, clinical cures were seen in 48% of patients who received 450 mg/week, 46% of those who received 300 mg/week, and 37% of those who received 150 mg/week.³ However, probably a dosage of 200 mg or 400 mg once weekly is effective, and once-weekly dosing is convenient for patients on multiple medications and the elderly. Fluconazole can be taken with or without food; the drug must be avoided in pregnant women. Drug interactions are via CYP2C9.

Itraconazole can be used to treat fingernail or toenail onychomycosis. It may be given according to either of two dosing schedules, for a duration of 2 to 3 months for fingernail infections and 3 to 4 months for toenail infections.⁴ Regimen 1 is 400 mg/day for 7 days for 1 week out of each month for 4 months. Regimen 2 is 200 mg/day continuously for 3 months. Regimen 1 (pulsed dosage) is not approved for treating toenail onychomycosis. The cure rate for Regimen 2 (continuous dosage) per the package insert is 14%.⁴ Evans and colleagues⁵ reported higher cure rates for pulsed (intermittent) dosing in the Lamisil vs Itraconazole in Onychomycosis (LION) study: 25% complete cure in three cycles; 28% complete cure in four cycles.

Itraconazole is a potent inhibitor of CYP3A4 and may result in serious cardiovascular events if used simultaneously with cisapride, pimozide, quinidine, or levomethadyl. It must be used with caution when treating onychomycosis in patients with congestive heart failure or other ventricular dysfunction. Ahmad and colleagues⁶ reported that itraconazole has a negative inotropic effect on the heart in healthy individuals.

Terbinafine is used at a dosage of 250 mg/day for 6 weeks for fingernails and for 12 weeks for toenails.⁷ Drake and colleagues⁸ reported a complete cure rate of 38% with 250 mg/day for 3 months and no significant difference in response between 12-week and 24-week treatment courses. In the LION study, Evans and colleagues⁹ found that terbinafine produced a 49% complete cure with a 12-week course and a 54% complete cure with a 16-week course.

Pulsed-dose therapy with terbinafine is not FDA approved. Tosti and colleagues¹⁰ noted that most studies show that continuous therapy of daily 250-mg dosing was more efficacious than 500 mg daily for 1 week followed by 3 weeks of no treatment.

**Topical Therapy**

Assuming reasonable efficacy could be assured, topical therapy would be the preferred methodology for onychomycosis to avoid systemic side effects and the need for laboratory monitoring. In addition, if adverse reactions occur from topical agents, the effect is site-specific and, as such,

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Table 1. Summary of Treatment Options for Onychomycosis

<table>
<thead>
<tr>
<th>A. Topical Therapy</th>
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<tr>
<td><strong>Fingernails and Toenails</strong></td>
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<tr>
<td>Ciclopirox 8%</td>
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<tr>
<td>Efinaconazole</td>
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<td>Tavaborole</td>
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<th>B. Systemic Therapy</th>
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<td><strong>Fingernails</strong></td>
</tr>
<tr>
<td>Fluconazole³</td>
</tr>
<tr>
<td>Itraconazole⁴</td>
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<tr>
<td>Terbinafine⁷</td>
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| **Toenails** |
| Fluconazole³ | 200 mg/week for 12 to 24 weeks |
| Itraconazole⁵ | 400 mg/day for 1 week/month, repeated for 3 or 4 months‡ |
| Terbinafine⁷ | 250 mg/day for 12 weeks |

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Image: Figure 2. Before and after successful systemic therapy. This patient presented with distal subungual onychomycosis. Note the distortion of the nail before treatment (left) and the resolution of onycholysis and discoloration after 4 months of systemic therapy (right). Photo courtesy of Phoebe Rich, MD.
generally is more acceptable to patients. However, no topical treatment has been approved as monotherapy to date. A summary of topical antifungal agents and cure rates can be found in Tables 1 and 2.

The development of topical therapy for onychomycosis presents unique challenges. First, to be effective, the drug must penetrate through the nail plate and reach the nail bed in sufficient quantities. This requires overcoming the unique properties of the nail plate—its thickness and relatively compact structure. The factors involved probably include the proper molecular weight, lipophilicity, and keratin-binding properties.

Ciclopirox 8% lacquer, which was approved by the FDA in 1999, is associated with a complete cure rate ranging from 5.5% to 8.5% but requires frequent nail debridement. In clinical studies, fewer than 12% of patients were able to achieve a clear or almost-clear nail.10

New and Investigational Topical Agents

A new topical agent, efinaconazole, currently pending approval by the FDA, will be the first topical triazole to become available for dermatologic use and the first new antifungal for onychomycosis to be introduced in more than a decade. Unlike ciclopirox, no debridement of nails is required.

Efinaconazole is a solution, not a lacquer, so, unlike ciclopirox, efinaconazole does not need to be removed each week. The solution is applied on, under, and around the nail. In the pivotal clinical trials, efinaconazole yielded a mycologic cure in the range of 50%. Complete cure was seen in 15% of patients in one study and 18% of patients in the second phase III study. Cure classified as “almost complete” exceeded 20%.11

Currently in the research pipeline is topical tavaborole 5% solution. In the first of two phase III clinical trials recently completed, the primary end point of complete cure (both mycologic cure and a completely clear nail) was seen in 6.5% of patients versus 0.5% of patients treated with vehicle alone (P=0.001). In addition, a negative fungal culture was reported after 52 weeks of treatment in 87% of patients on tavaborole versus 47.9% of those in the vehicle group (P<0.001); at the same time point, a negative nail culture and “completely clear” or “almost clear” nail was seen in 24.6% of patients in the tavaborole group versus 5.7% in the vehicle group (P<0.001).12

Over-the-Counter (OTC) Treatments

A mention of nonspecific topical OTC and “folk” remedies is appropriate here. Many such remedies have been used—usually self-prescribed by patients—as monotherapy or in the belief that these agents will enhance the efficacy of prescription medications. Currently popular are tea tree oil and a camphor-containing ointment marketed as a chest rub. Many other substances have been used, including foot soaks with hydrogen peroxide or household chlorine bleach and applications of salicylic acid, as well as OTC solutions, creams, and ointments.

Evidence-based studies have not been done demonstrating that these agents are helpful, but there is some theoretical scientific basis for anecdotal claims of efficacy by patients—and by some clinicians—when these remedies have been
used diligently. Although they cannot be recommended on the basis of evidence of efficacy, most of these methods are neither harmful nor costly. Patients who choose to forgo prescription therapy for whatever reason should not be discouraged from trying these remedies for a time and told to reconsider definitive treatment if the infection does not clear or worsens.

### Mechanical Modalities

Nail avulsion and matrixectomy are seldom needed. These techniques may be appropriate if only one nail is affected and the infection does not respond to other treatments, as well as in cases of infections with nondermatophyte mold organisms. However, most patients have involvement of more than one nail. Occasionally, patients develop thickened dystrophic nails that are painful or interfere with proper ambulation. Such circumstances also may constitute an indication for surgical intervention.

Lasers, photodynamic therapy (PDT), and other methods have been used with varying degrees of success in treating onychomycosis. The laser devices approved by the U.S. FDA to date are the short-pulse neodymium-doped yttrium aluminum garnet (Nd:Yag) type, although other types currently are being studied; these include carbon dioxide, near infrared diode, and femtosecond infrared laser systems.

The exact mechanism of action of laser systems in onychomycosis has not been established. One early proposed mechanism was the direct action of heat on the infecting organisms, but recent in vitro studies show that laser-generated heat to a level required to kill *Trichophyton rubrum* is much higher than what would be tolerable; experiments with direct lasering of fungi have not affected the growth of fungal organisms. Others have suggested that the use of lasers may enhance the efficacy of other modalities. More likely mechanisms of action are the triggering of an immunologic effect or laser-induced denaturation of enzymes essential to fungal activity.

As the results of ongoing research provide additional insights regarding treatment regimens and patient selection along with longer-term evidence of efficacy, laser systems may become more widely used for treating onychomycosis.

The mechanism of action of PDT in dermatophytic onychomycosis has been established and involves eradication of the organism. No PDT system has been approved by the FDA for the treatment of onychomycosis, and it is not a practical therapeutic option. However, PDT may be useful in chronic cases that are refractory to other modalities, particularly when the causative organism is uncommon, such as a nondermatophyte mold.

Other devices and modalities continue to be developed and investigated, including the use of iontophoresis to enhance penetration of a topical medication through the nail plate.

### Preventing Recurrence

Reinfection with dermatophytic onychomycosis is common. It is difficult to know whether subsequent infection is a new infection or whether the original infection was not cleared completely and recurred after weeks, months, or years of dormancy. In either case, patients must understand that it is unlikely that one course of treatment will be all that is required over the long term.

However, it is important to emphasize that the risk for reinfection can be reduced by avoiding practices that expose the nails to infectious organisms and that create a milieu that encourages fungal colonization. See the patient handout in the article in this supplement by Pariser et al.

### Conclusion

Onychomycosis is a common problem that increases in prevalence with increasing age. Simple techniques are readily available for making an accurate diagnosis in all patients. The only prescription topical agent available has been ciclopirox 8% lacquer. A new topical agent, efinaconazole, currently pending approval by the FDA, provides better efficacy. Another topical agent, tavaborole, has shown good results in phase III studies to date. Systemic agents are highly effective for many patients but are contraindicated or otherwise inadvisable for some because of the potential for drug interactions or the presence of certain comorbidities.

### References

Guidelines for managing patients with onychomycosis were last published in 1996. In the absence of the availability of new medications since that time or of new data on existing agents that suggested the need for a change in the guidelines, an update has not been necessary. The management of onychomycosis is straightforward and can be summarized as follows:

- **Inspect clinically** and take a thorough personal and family history.
- **Consider the differential diagnosis.** Onychomycosis accounts for at least half of all cases of nail infection, particularly toenail infections. In patients who are not immunocompromised, psoriasis and lichen planus should be the first two considerations in the differential diagnosis.
- **Confirm the diagnosis** with a laboratory study: potassium hydroxide, periodic-acid Schiff stain, or fungal culture. (In the future, analysis by polymerase chain reaction may become widely available.)
- **Consider the treatment options.** If onychomycosis is confirmed, consider the available treatments. Factors to include are the site of disease (toenails or fingernails), the extent of disease, and the patient’s age, immune status, and concomitant conditions that may limit systemic choices or are likely to affect treatment efficacy, including severely thickened nails, compromised peripheral circulation, and the presence of diabetes mellitus. In addition, consider the patient’s health insurance coverage in the equation; some carriers will cover topical therapy only after a systemic treatment has been tried first.
- **Discuss your recommendations with the patient.** If the infection is limited to 50% or less of the nail plate of only one or a few toes, topical therapy is an option. Be clear about the cure rates associated with the proposed therapies. If systemic therapy is considered, discuss the potential side effects of the available systemic agents and inform the patient about any baseline and follow-up blood testing that will be required.
• Discuss realistic expectations for immediate and long-term treatment results. Patients must understand that one course of treatment may not produce the optimum result and that recurrence of onychomycosis is very common. It is also important to advise patients about the point in time that visible results can be expected (i.e., the rate of nail growth), and that clearance of an infection will be evident only as nails grow.

• Emphasize the role of preventive measures to avoid reinfection. For example, one of the most common ways that patients acquire infection with organisms such as *T. rubrum* is walking barefoot in pools, spas, gymnasiums, and locker rooms—areas where moisture is present and where fungi can thrive. Another common source of infection is the nail salon.

Individuals should bring their own nail clippers, files, and emery boards to the salon, and ensure that the technician washes the nail-soaking dish or pedicure tub with bleach between clients. Prompt treatment at the first signs of athlete’s foot infection can also reduce the recurrence of onychomycosis.

**Reference**

Onychomycosis Information for Patients

What is onychomycosis?
Nail fungus infection, called onychomycosis (ON-ick-co-my-CO-sis), usually affects the toenails but also may occur on the fingernails. Most cases of onychomycosis are caused by the same fungus that is responsible for athlete’s foot.

Nail infections most commonly affect the toenails. The fungus organisms usually invade the nail bed from the outside (distal) edge of the nail. Sometimes the nail plate itself is the original site of infection.

Who gets onychomycosis?
About 10% to 12% of people, overall, have onychomycosis. However, this is an average for the population. Actually, onychomycosis is more common in some groups of people than in others. For example, onychomycosis is seldom seen in children. When children get onychomycosis, it is usually because a teenager or adult in the household has athlete’s foot and onychomycosis. Also, onychomycosis is most common in older people; a large percentage of individuals more than 70 years of age have the infection.

People who tend to get athlete’s foot infections also have a higher risk for onychomycosis of the toenails. Injuries to the toes—even minor injuries—also can increase the chances of getting onychomycosis.

Onychomycosis is also more common in people with certain medical conditions: diabetes, psoriasis or other autoimmune disease, HIV/AIDS infection, and poor circulation in the feet and hands.

What are the signs and symptoms of onychomycosis?
The most common signs and symptoms of onychomycosis are:

- Brittleness of the nail(s)
- Change in nail shape
- Crumbling of the outside edges of the nails
- Debris trapped under the nail
- Loosening or lifting up of the nails at the outside edges
- Loss of luster and shine
- Thickening of the nail
- White or yellow streaks on the nail
- Proximal Nail Fold

These suggest the presence of an infection, but the proper treatment is chosen based on a firm diagnosis by a medical professional. The diagnosis can be made in the health care provider’s office by taking scrapings of the nail and examining the sample under a microscope to determine whether a fungus is present. The results of this test are immediate.

Sometimes the health care provider will decide that more involved testing is necessary, and he or she will send the sample for a culture. Laboratory identification of the infecting organism by culture can take several weeks. Your clinician will determine the best method in your case.

How is onychomycosis treated?
Prescription medications, either oral or topical (applied to the nail) offer the best chance to clear onychomycosis. Also available are non-drug therapies such as laser treatment. Your health care provider will discuss these with you and will make a treatment recommendation that is tailored to your needs.

Nonprescription over-the-counter products and “folk” remedies (such as tea tree oil and hydrogen peroxide) generally do not work. However, many people—including many health professionals—think they might help support the activity of the prescription medications and may help prevent the recurrence of onychomycosis later on.
Is treatment always effective?

There is no “quick fix,” and not every medication will work for everyone. About 50% of patients experience a clearance of the fungus with the first treatment. If your infection does not clear completely, your health care provider may recommend a different medication. It is important to follow these recommendations.

Remember, though, that nails grow slowly, and improvement can be seen only when the “new” nail grows in. For this reason, it may take several months to see clearing of onychomycosis. Fingernails grow faster than toenails, and nails in older individuals tend to grow more slowly than do those in younger people.

It is also important to remember that even if the fungus is cleared, it is common for it to return. This does not mean that medical treatment is useless; it means that onychomycosis tends to be stubborn and requires attention over the long term.

How can new infections be prevented?

The following tips can help prevent new infections:

At home:

• Throw away old shoes, particularly sneakers, running shoes, or other types of athletic shoes that you have used for exercise or sports.

• Use antifungal spray or powder in your shoes every day.

• Apply antifungal creams to your feet periodically to slow the growth of athlete’s foot fungus (which can then invade the nails).

• Treat all signs and symptoms of athlete’s foot immediately.

• Do not share tools used for manicures and pedicures.

• Do not use the same nail clippers and files on normal nails that are used on nails with a fungus infection.

• If you see signs of a nail infection, treat it immediately; do not wait until it has progressed.

• Wash and dry your hands thoroughly after contact with any fungal infection.

• Take proper care of your nails. Keep toenails trimmed and clean. Nails should be cut or filed straight across (not rounded or in a V shape).

• Wear properly fitting shoes with a wide enough toe box so that your toes are not cramped or hit up against the front of the shoe. (High heels and narrow-toed shoes cause trauma to the toes and can damage the natural skin seal between the nail itself and the skin underneath, allowing fungus to invade under the nail.)

• Make sure that household members with athlete’s foot infections receive treatment and take proper precautions to avoid spreading the fungus to others.

Outside the home:

• Do not walk barefoot in public facilities, such as around pools and in spas, locker rooms, and gyms. Wear water shoes or rubber sandals.

• Bring your own instruments (especially clippers and emery boards) to the nail salon.

• Make sure your manicurist/pedicurist washes the nail-soaking dish or pedicure tub with bleach between clients.
1. The type of organism implicated most commonly in onychomycosis cases in the United States are:
   A. Bacteria
   B. Dermatophytes
   C. Nondermatophyte molds
   D. Yeasts

2. Candida species are the most common cause of onychomycosis among:
   A. Children
   B. Elderly patients
   C. Immunocompromised patients
   D. Individuals with poor peripheral circulation

3. Pediatric patients who present with onychomycosis almost always have:
   A. Compromised immune function
   B. Diabetes
   C. Family history of tinea pedis
   D. Previous toenail injury

4. The most common presentation of onychomycosis is:
   A. Chronic mucocutaneous candidiasis
   B. Distal-lateral-subungual
   C. Proximal subungual
   D. Superficial white

5. The current standard method for identifying the causative organism in onychomycosis is:
   A. Nail culture
   B. Periodic-acid Schiff staining of nail plate samples
   C. Potassium hydroxide preparation of subungual debris
   D. Polymerase chain reaction analysis

6. Which one of the following statements concerning periodic-acid Schiff (PAS) staining is true?
   A. PAS staining showing septate hyphae is diagnostic
   B. PAS staining showing yeast forms only is not conclusive evidence of infection
   C. PAS staining alone does not confirm that organisms are present
   D. PAS staining ascertains the viability of organisms present

7. The definition of “complete cure,” as defined by the US Food and Drug Administration (FDA) for the evaluation of clinical trial results, is:
   A. Negative results on fungal culture, as well as a completely normal appearance of the nail
   B. Negative results on potassium hydroxide (KOH) preparation, as well as a completely normal appearance of the nail
   C. Negative results on potassium hydroxide (KOH) preparation and on fungal culture, as well as an almost completely normal appearance of the nail
   D. Negative results on potassium hydroxide (KOH) preparation and on fungal culture, as well as a completely normal appearance of the nail

8. All of the following currently are approved by the US Food and Drug Administration for the treatment of onychomycosis except:
   A. Ciclopirox
   B. Itraconazole
   C. Laser therapy
   D. Terbinafine pulse-dose therapy

9. The methods approved to date by the US Food and Drug Administration for the “temporary increase of clear nail in onychomycosis” are:
   A. Iontophoresis
   B. Laser systems
   C. Photodynamic therapy systems
   D. Topical therapy

10. A potent inhibitor of CYP3A4, must be used with caution when treating onychomycosis in patients with congestive heart failure or other ventricular dysfunction.
    A. Ciclopirox
    B. Fluconazole
    C. Itraconazole
    D. Terbinafine
EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential.

Please print.

Name: __________________________
Specialty: ______________________
Degree: □ MD □ DO □ PharmD □ RPh □ NP □ RN □ BS □ PA □ Other _______________________
Affiliation: ______________________
Address: _________________________
City: _____________________________ State: __________  ZIP: ______
Telephone: ________________________ Fax: _______________________
E-mail: __________________________
Signature: _________________________

CME CREDIT VERIFICATION
I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 2.5 CME credits will be issued for this activity.

COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

• Clinicians do not adequately treat onychomycosis. Many clinicians regard onychomycosis as a condition that is principally cosmetic in nature and therefore do not treat appropriately.
• Clinicians outside the podiatry specialty are not utilizing current literature on onychomycosis diagnosis and treatment. Because onychomycosis traditionally has been managed by podiatrists and, less so, by dermatologists, many clinicians in other specialties and general practice have considered definitive diagnosis and treatment of this infection to be outside the purview of their practices.
• Physicians are not identifying new medications and other therapeutic modalities for effective and safe treatment of onychomycosis.

Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?

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Please elaborate on your answer. __________________________________________________________

Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed on the left?

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Please elaborate on your answer. __________________________________________________________

Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?

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Please elaborate on your answer. __________________________________________________________

How certain are you that you will implement this change?

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What topics do you want to hear more about, and what issue(s) in your practice will they address? __________________________________________________________

Were the patient recommendations based on acceptable practices in medicine? ○ Yes ○ No

If no, please explain which recommendation(s) were not based on acceptable practices in medicine. __________________________________________________________

Do you think the articles were without commercial bias? ○ Yes ○ No

If no, please list the article(s) that was/were biased. __________________________________________________________

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