Concepts in Onychomycosis Treatment and Recurrence Prevention: An Update

Theodore Rosen, MD*

n **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(supp3):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. 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 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.

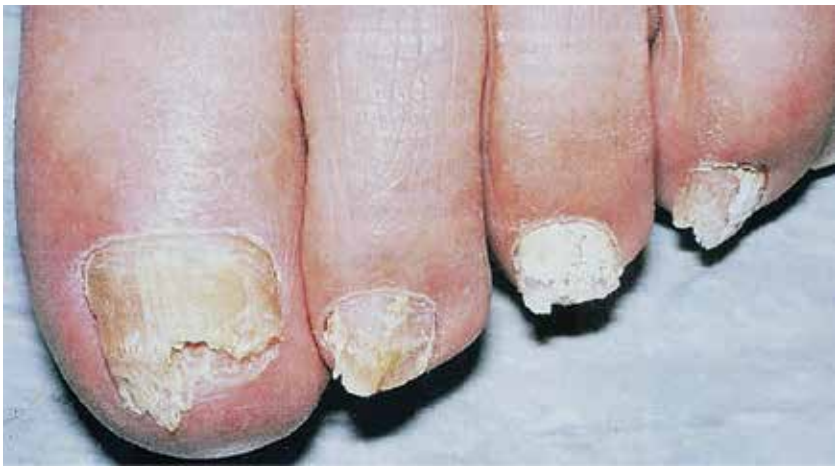
Patients should understand that the changes to nails that are associated with aging—such as dystrophy and discoloration—and that are not related to onychomycosis will persist after successful treatment (Figure).[6]

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, such as secukinumab, which may increase the risk for yeast infections.[11]

 1085-5629/13$-see front matter
DOI: 10.12788/j.sder.2016.010



n **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 diabetic patients with 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 that patients can log in to.

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 S62).

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 three 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(10 suppl):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(3 suppl):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(4):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(10):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(2):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(2):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.