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 ORIGINAL ARTICLE

Therapeutic Recommendations for the Treatment of Toenail Onychomycosis in the US

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ABSTRACT

Background: Onychomycosis affects around 14% of individuals in North America and Europe and is undertreated. Treatment is challenging as toenail growth can take 12–18 months, the nail plate may prevent drug penetration, and disease recurrence is common. National guidelines/consensus documents on onychomycosis diagnosis and treatment were last published more than 5 years ago and updated medical guidance is needed.

Methods: This document aims to provide recommendations for the diagnosis and pharmaceutical treatment of toenail onychomycosis following a roundtable discussion with a panel of dermatologists, podiatrists, and a microbiologist specializing in nail disease.

Results: There was a general consensus on several topics regarding onychomycosis diagnosis, confirmatory laboratory testing, and medications. Onychomycosis should be assessed clinically and confirmed with microscopy, histology, and/or culture. Terbinafine is the primary choice for oral treatment and efinaconazole 10% for topical treatment. Efinaconazole can also be considered for off-label use for maintenance to prevent recurrences. For optimal outcomes, patients should be counseled regarding treatment expectations as well as follow-up care and maintenance post-treatment.

Conclusions: This article provides important updates to previous guidelines/consensus documents to assist dermatologists and podiatrists in the diagnosis and treatment of toenail onychomycosis.

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INTRODUCTION AND PRIOR TREATMENT

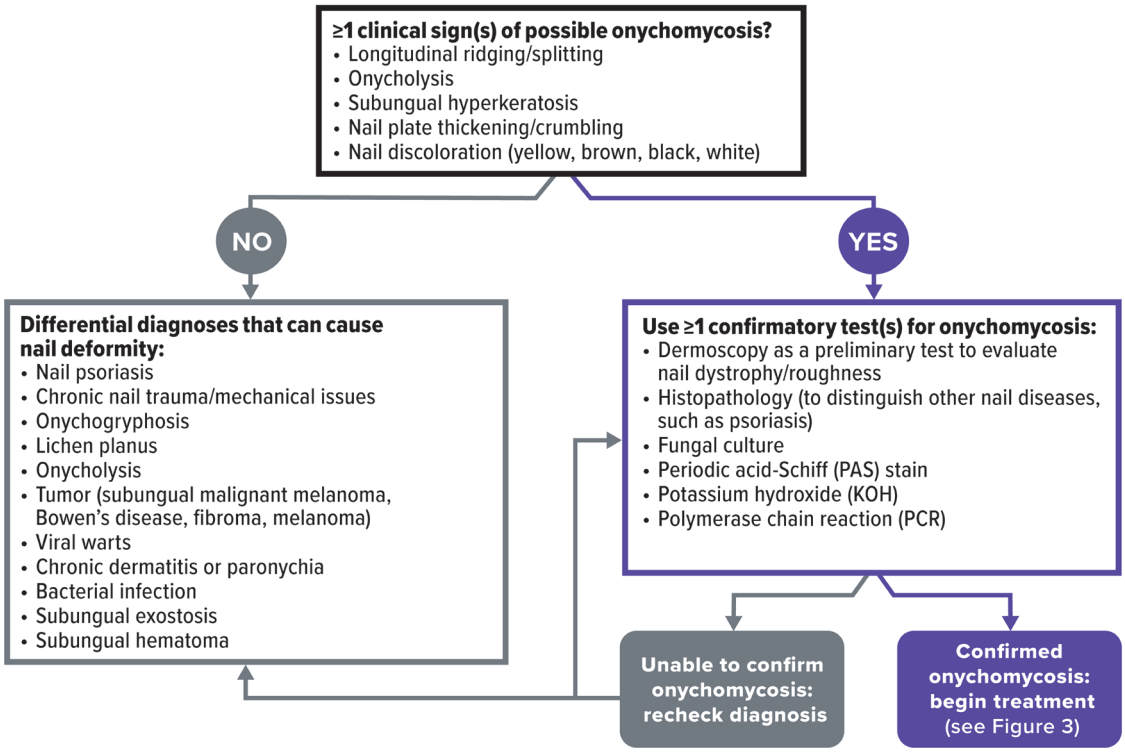
Onychomycosis—a fungal infection of the nail bed or plate caused by dermatophytes, non-dermatophyte molds, or yeasts—affects up to 14% of individuals in North America.[1,2] It is undertreated[3] and treatment is challenging as toenail growth can take up to 12 months or more,[4,5] the infection is frequently located under the keratinized nail plate,[6] and disease recurrence is common.[5] Oral medications are generally efficacious, but there are safety concerns such as drug-drug interactions, smell/taste disturbances, allergic reactions, or possible liver toxicity.[7,8] In addition, there may be evidence of recent emergence of antifungal resistance to terbinafine.[9,10]

For diagnosis and testing, prior guidelines and consensus publications on onychomycosis treatment have noted that in addition to clinical examination, confirmatory laboratory testing should be performed using one or more of the following: microscopic examination (eg, potassium hydroxide [KOH], periodic acid-Schiff test [PAS]), or fungal culture.[11-16] While polymerase chain reaction (PCR) techniques were considered useful for confirming diagnosis, they were deemed not cost effective enough for general use.[12-14,16]

For pharmaceutical treatments administered orally, terbinafine was considered first-line and was preferred over itraconazole.[1,12] While fluconazole is not approved for onychomycosis treatment in the US, it was considered an alternative to terbinafine or itraconazole.[12] Griseofulvin was generally not recommended due to low efficacy and high recurrence rates compared with other oral antifungal agents.[12] Oral medications were recommended for severe cases,[14,15] though some oral drugs were to be avoided or required caution when used in patients with certain comorbidities or concomitant medications.[1,12]

Topical medications (ciclopirox, tavaborole, efinaconazole) were recommended for pediatric patients[13,14] and adults with mild-to-moderate disease (20%–60%, <50%, or <65% involvement),[1,11,13-15] especially those taking concomitant medications or with other

FIGURE 1. Differential diagnosis decision tree.



contraindications to oral medications.[12,14,15] Combination treatments with an oral and topical therapy were recommended if the expected topical monotherapy response would be poor,[12] or if there was >50%–60% nail involvement, matrix involvement, or >3 nails involved.[1,14,15] Non-pharmaceutical treatments such as debridement alone, lasers, or photodynamic therapy were not recommended due to lack of efficacy and sparse data from clinical trials supporting their use.[12,14]

National guidelines and consensus documents on onychomycosis diagnosis and treatment were last published in 2014 (British[12]) and 2015 (Canadian[1])—around the time that both topical efinaconazole and tavaborole were first approved in the US in 2014. Since then, more data have become available for topical tavaborole and efinaconazole and both have received US approvals for use in pediatric patients (aged ≥6 years).[17,18] In addition, terbinafine resistance may be a growing issue.[10,19] As such, updated medical guidance is needed.

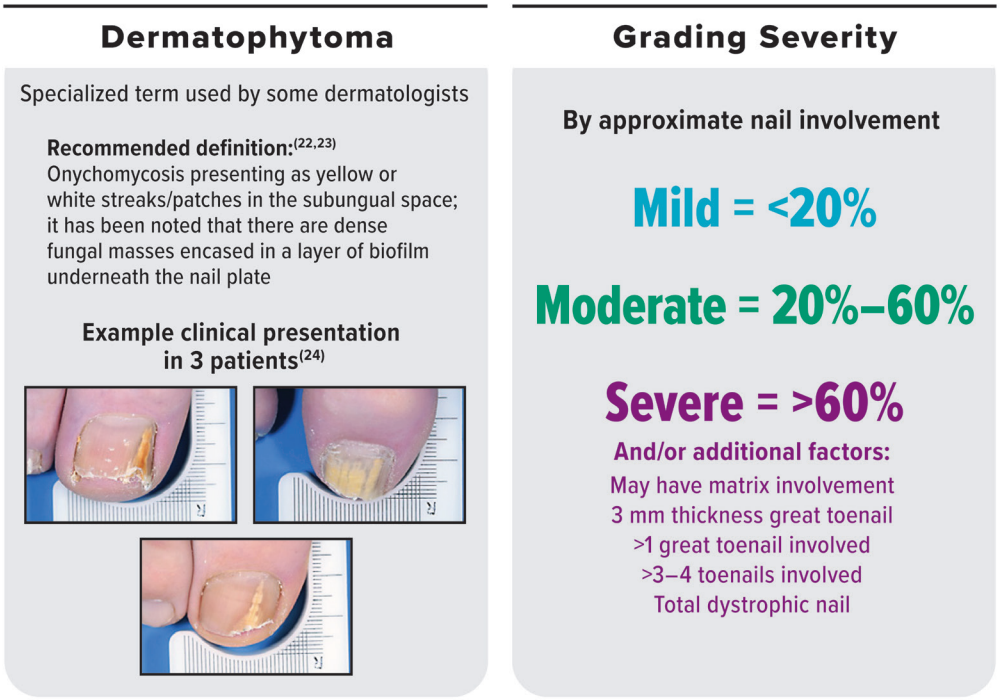
This document aims to provide recommendations for the diagnosis and therapeutic treatment of toenail onychomycosis following a roundtable discussion with the authors on March 15, 2021. Included in this article are a decision tree for choosing appropriate medications based on disease severity and patient characteristics, as well as a handout intended for patients on best practices to mitigate disease recurrence.

Diagnosis, Testing, and Clinical Presentation

When diagnosing onychomycosis, careful assessment and testing must be performed as nail dystrophy can be induced by over 20 disorders[15] and there are many common conditions that can mimic onychomycosis.[20] Nail dystrophies due to nail psoriasis, chronic trauma, mechanical issues (toe overlaps, etc.), onychogryphosis, lichen planus, or other diseases that have a similar clinical appearance to onychomycosis should be ruled out (see Figure 1).[12,13,20]

In addition to identifying clinical signs, laboratory testing should be performed to identify the infecting organism and exclude any non-fungal conditions.[1,12] Preferred confirmatory testing methods may differ between dermatologists and podiatrists, but common options include clinical diagnosis in conjunction with one or more of the following: KOH with microscopy on nail subungual debris; fungal culture on subungual debris; and histopathology on nail clippings with PAS or Gomori methenamine silver staining. When obtaining subungual debris for KOH or culture, the most proximal involvement should be sampled via 2 mm curette or nail elevator; additionally, an attached nail bed is optimal for PAS samples. Dermoscopy can also be used to help confirm the diagnosis of onychomycosis and rule out other nail diseases and biomechanical issues. In addition, PCR may be performed for identification of the infecting organism. PCR may be costly and has high sensitivity,

FIGURE 2. Clinical presentation.



Dermatophytoma clinical presentation adapted from Wang et al., 2019.[24] Copyright© 2019 Karger Publishers, Basel, Switzerland.

so care must be taken to distinguish between contaminants and pathogens. Results may be corroborated with a fungal culture.

While onychomycosis diagnosis still requires in-person visits for nail sampling, telemedicine has been useful during the COVID-19 pandemic to limit face-to-face interactions and reduce spread of coronavirus.[21] Outside of the COVID-19 pandemic, however, telemedicine may be best for follow-up visits.

Typical clinical features of onychomycosis comprise one or more of the following: nail plate longitudinal ridging and/or splitting; onycholysis; subungual hyperkeratosis; nail plate thickening and/or crumbling; and nail discoloration (yellow, brown, black, or white).[13] Clinical patterns of onychomycosis are: distal lateral subungual (DLSO), superficial white, proximal subungual, endonyx, and total dystrophic; DLSO is the most common subtype.[20]

In addition to a standard clinical pattern, some patients may present with yellow or white streaks/patches in the subungual space (Figure 2); underneath the nail plate, it has been noted that there are dense fungal masses encased in a layer of biofilm. These have been referred to as *dermatophytomas* by some dermatologists,[22,23] though this term may be less commonly used by podiatrists and other clinicians. Presentation is not as well defined and there are limited data on treatment, as these patients are often excluded from clinical trials. While dermatophytomas are reportedly less responsive to oral antifungal therapy, topical efinaconazole 10% has been used successfully.[24]

Disease severity should be determined via percent nail surface area involvement, nail thickness, and number of nails involved. The authors-recommended onychomycosis severity definitions are shown in Figure 2.

Efficacy and Safety of Treatments and Medications

When treating onychomycosis, there are multiple endpoints that can be used to assess efficacy. Clinical trials typically use mycologic cure (negative KOH and negative culture), clinical cure (clinically completely normal nail), and complete cure (mycologic cure and clinical cure).[25] Physicians may be interested in mycologic cure as an objective endpoint, but in the clinic, both physicians and patients are most interested in clinical cure/clear nail.

Onychomycosis can be managed using surgery, devices, oral or topical medications, or combinations thereof. Nail debridement can be used as an adjunct with pharmaceutical treatments[13,14] while surgical nail avulsion is generally no longer recommended,[12] except in specific limited situations such as a single nail which is painful and/or not growing

properly. Photodynamic therapy, plasma, and over-the-counter treatments (eg, tea tree oil, mentholated vapor rub) are not FDA approved and while some have reported good efficacy, results would have to be corroborated in larger clinical trials before they can be broadly recommended.[14,26,27] Lasers are US FDA approved for *temporary* increase in clear nail; however, the FDA requires less stringent endpoints for device approvals and cure rates are typically lower than those of orals and topicals, and as such, they cannot be directly compared.[26]

Oral medications

In the US, there are three oral medications approved for adults for onychomycosis treatment: terbinafine (250 mg QD for 12 weeks)[7]; itraconazole (200 mg QD for 12 weeks)[8]; and griseofulvin (375 mg QD for at least 6 months).[28] These medications have also been used off label for children and dosed according to weight.[26] Fluconazole (eg, 150, 300, or 450 mg once-weekly for 6–12 months [adults][29]) is used off label in adults and children either when traditional medications fail or prior to using itraconazole.

Terbinafine has shown higher complete and mycologic cure rates than itraconazole in adults (Table 1); the greater efficacy of terbinafine versus oral azoles (including itraconazole) was confirmed with moderate quality evidence in a 2017 Cochrane review.[30] Griseofulvin requires a longer treatment time, has lower efficacy, and has higher relapse rates versus itraconazole and terbinafine.[12] Finally, while fluconazole may not be as effective as other orals,[31] once-weekly dosing may be more convenient for some patients.[12] In terms of safety, itraconazole has black box warnings in patients with cardiac dysfunction.[8] Furthermore, all oral medications have known drug-drug interactions (some more extensive than others) and are contraindicated in certain populations, including those with liver disease; as such, a patient's concomitant medications and comorbidities must be assessed prior to determining treatment (see *Recommended Medications* section). The same Cochrane review above determined that the adverse event risk was similar between terbinafine and azoles (moderate quality evidence) and higher in griseofulvin than azoles or terbinafine (low to moderate quality).[30]

Topical medications

There are three topical medications approved in the US for both adults and children: ciclopirox 8% nail lacquer (patients aged ≥12 years)[32]; tavaborole 5% solution (≥6 years)[18]; and efinaconazole 10% solution (≥6 years).[17] All three require once-daily application for 48 weeks; ciclopirox also requires regular nail filing and debridement. While head-to-head comparisons are difficult to make across studies, efinaconazole has demonstrated the highest complete and mycological cure rates for topicals (Table 1). Furthermore, these efficacy findings were confirmed with moderate to high quality evidence in a 2020 Cochrane review of clinical studies in adults.[33] This review also determined that efinaconazole had a lower risk of adverse events (high quality evidence) than ciclopirox (low quality) or tavaborole (moderate quality).

A meta-analysis examining efficacy of topical and oral medications in adult onychomycosis showed that mycologic cure rate with terbinafine was superior to topicals.[31] When comparing data from phase 3 adult clinical trials, complete cure rates with topicals were numerically lower than oral treatments, through efinaconazole had higher mycologic cure rates versus itraconazole (Table 1). It is important to note, however, that comparisons are challenging for drugs approved nearly two decades apart, particularly since the onychomycosis being treated today may be different from when oral treatments were first approved in the US in the 1990s. In addition, there are differences in clinical trial design and patient demographics and characteristics.

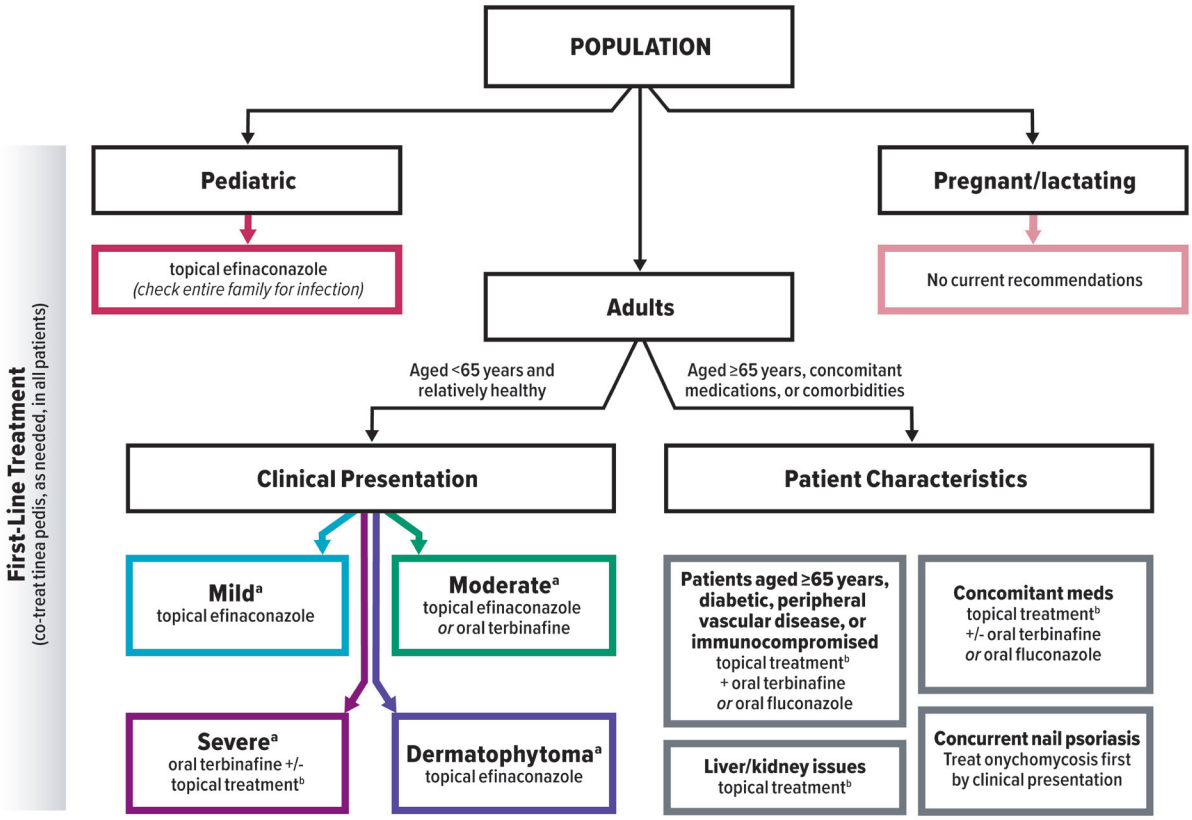
TABLE 1.

Efficacy of Pharmaceutical Treatments Approved in the US for Onychomycosis

Term used in Publication	Definition/Criteria	Pediatric Participants			Adult Participants				
		Topical			Oral		Topical[a]		
		Efinaconazole 10%[44]	Tavaborole 5%[45]	Ciclopirox 8%[46]	Itraconazole 200 mg[8]	Terbinafine 250 mg[7]	Efinaconazole 10%[47]	Tavaborole 5%[18]	Ciclopirox 8%[32]
	Treatment duration	48 weeks	48 weeks	32 weeks	12 weeks	12 weeks	48 weeks	48 weeks	48 weeks
	Assessment	week 52	week 52	week 32	week 52	week 48	week 52	week 52	week 48
Complete Cure, %	Negative fungal culture + negative KOH + 0% target nail involvement	40.0	8.5	--[b]	22.3	38.0	17.8; 15.2	6.5; 9.1	5.5; 8.5
Mycologic Cure, %	Negative fungal culture + negative KOH	65.0	36.2	--	44.0	70.0	53.4; 55.2	31.1; 35.9	29.0; 36.0
Negative fungal culture only		88.3	87.2	77.1[c]	--	--	--	--	--

Note: Excludes griseofulvin as it is rarely prescribed and fluconazole, which is used off-label.
[a]Two studies. [b]This endpoint was not evaluated; negative fungal culture + 0% target nail involvement was 34.2%. [c]Was termed "mycologic cure" in the publication but did not include KOH examination.
--, not applicable/data not provided; KOH, potassium hydroxide.

FIGURE 3. Decision tree on therapeutic recommendations for the treatment of confirmed onychomycosis.



Treatment Failure

Terbinafine failure

- Reassess and retest to confirm initial onychomycosis diagnosis
- Send sample for susceptibility testing after one month off terbinafine treatment:
  - Low MIC → second course of terbinafine + topical for maintenance[b]
  - High MIC → oral fluconazole +/- topical treatment

Topical treatment failure

- Reassess and retest to confirm initial onychomycosis diagnosis
- Adjunctive debridement
- Add oral treatment (terbinafine or fluconazole)

Maintenance

To prevent onychomycosis recurrence in the long-term

- Topical antifungal creams could be added
- In patients treated with orals: extended dosing at initial treatment +/- pulse or booster dosing 6–9 months after initial treatment
- Continued treatment with topicals such as efinaconazole, perhaps indefinitely (once-daily to once-weekly maintenance treatment)
  - Combination use of 2 drugs with different MOAs may minimize resistance
- Educate patients on strategies to prevent recurrence; use of printed materials may be beneficial (see Figure 5)
- Follow-up visit with patients after completion of initial treatment (3–6 months after oral; 1 year after topical)
- If recurrence occurs, give a second course of initial treatment

These are topline recommendations for treatment. All patient characteristics—including age, disease duration/severity, clinical presentation, concomitant medications, and comorbidities—must be taken into consideration when making treatment decisions, particularly for patients with more complex presentation.
For all treatments, check prescribing information for potential drug-drug interactions and contraindications.
[a]See definition in Figure 2.
[b]Efinaconazole preferred due to higher rates of complete cure and mycologic cure versus other topical treatments.
MIC, minimum inhibitory concentration; MOA, mechanism of action.

Recommended Medications

The authors all agreed that treatment should be individualized for each patient based on nail involvement (number, surface area, thickness), infecting organism, patient characteristics (including comorbidities), current medications, biomechanics, cost/availability/accessibility based on insurance, and patient preference.[26] A decision tree to provide practical guidance on therapeutic recommendations in onychomycosis treatment has been developed by the authors (Figure 3). Therapeutic recommendations by drug are also detailed in Figure 4.

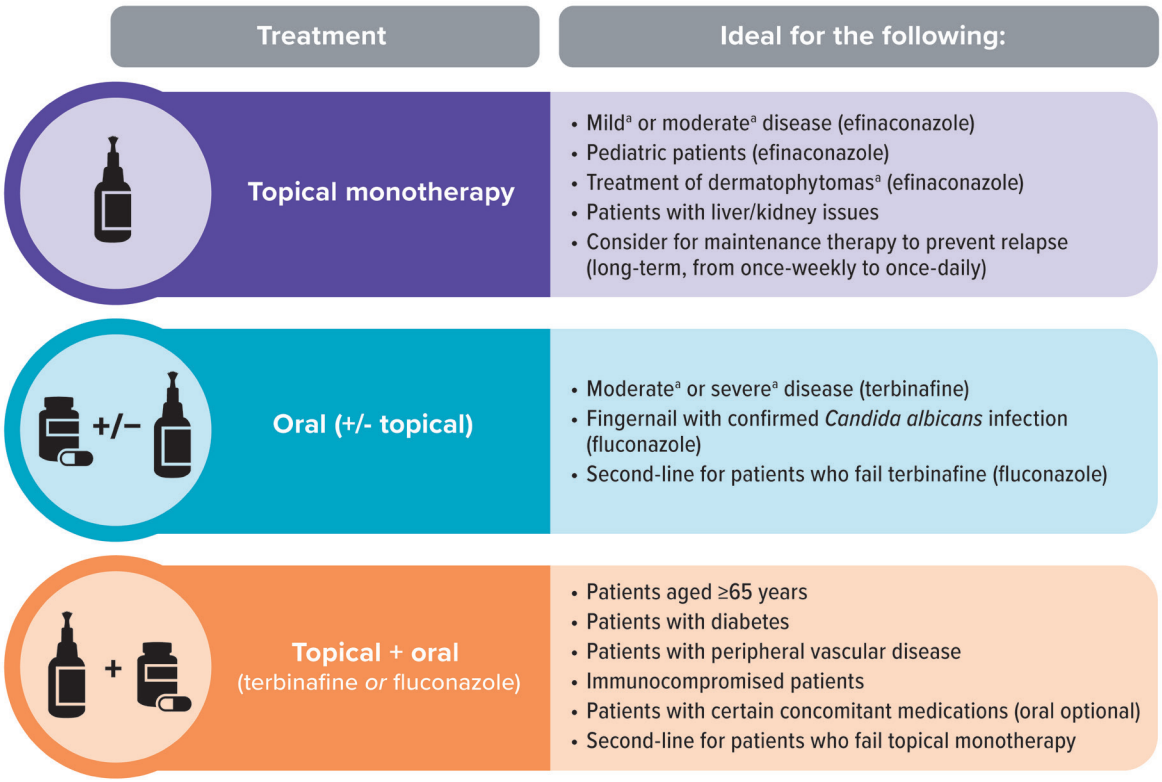
In general, the consensus was that for oral medications, terbinafine is most commonly used as first-line treatment, followed by fluconazole (can be used in patients for whom terbinafine is contraindicated). Itraconazole is generally avoided (black box warnings and frequent drug-drug interactions) and griseofulvin is rarely used (inferior efficacy). There had previously been little guidance on utility of laboratory monitoring.[34-36] It was agreed by the authors that a baseline liver profile may be needed in many patients to rule out pre-existing conditions, and that interval monitoring may not be necessary in young or healthy adult patients. For liver function testing, alanine aminotransferase (ALT) alone may be sufficient to capture transaminase changes and is cost-saving.[34]

Among topical products, authors agreed that efinaconazole is ideal as first-line medication in pediatric patients, patients with less severe disease, and those with dermatophytomas. A topical medication was also recommended for use in combination with terbinafine or fluconazole (particularly in older, immunosuppressed, diabetic, or severe patients) and can be considered as maintenance therapy to prevent relapse. To improve outcomes, concurrent tinea pedis should be treated in all patients receiving topical therapy for onychomycosis.[37]

Treatment by severity or clinical pattern

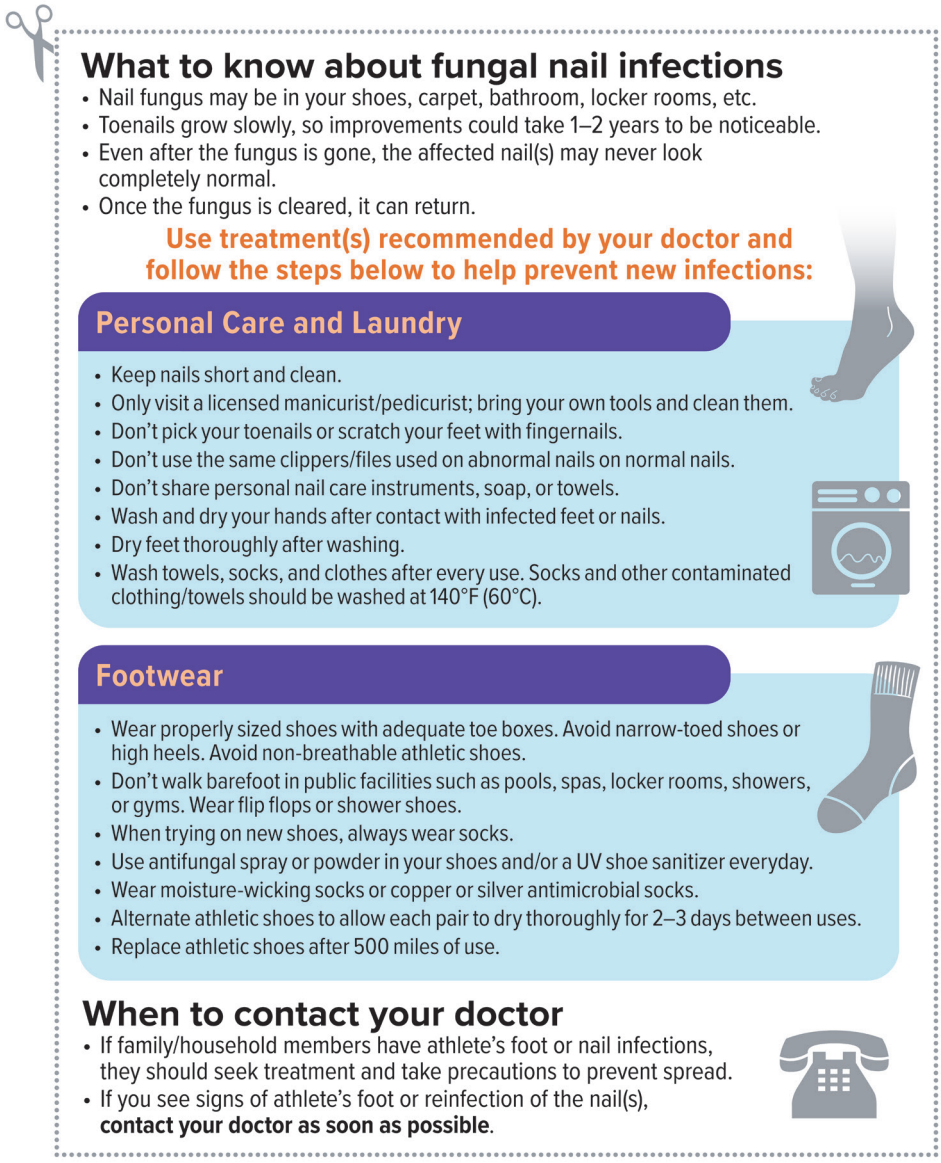
For treating patients with mild-to-moderate disease, topical efinaconazole or terbinafine are recommended as first-line therapy (Figure 3). For severe disease, defined in Figure 2, use terbinafine as a first-line oral with or without a topical. DLSO is the most common clinical pattern. As such, clinical trials typically exclude patients with other patterns, leaving a paucity of information regarding treatment efficacy in non-DLSO patterns.[1,12] Authors recommend all patterns be treated by severity following recommendations above. In the case of fingernail only infection with confirmed *Candida albicans*, treat with fluconazole first.

FIGURE 4. Therapeutic recommendations by drug.



These are topline recommendations for treatment. All patient characteristics—including age, disease duration/severity, clinical presentation, concomitant medications, and comorbidities—must be taken into consideration when making treatment decisions, particularly for patients with more complex presentation. For all treatments, check prescribing information for potential drug-drug interactions and contraindications.
Efinaconazole preferred for topical treatment due to higher rates of complete cure and mycologic cure versus other topical treatments.
[a]See Figure 2 for definitions.

FIGURE 5. Patient education handout.



Treatment of special populations

In pediatric patients, efinaconazole should be given as first-line monotherapy. If oral treatment is needed, use terbinafine. Additionally, other family members should be checked for onychomycosis or tinea pedis and treated as needed, as a child with infection is often indicative of other family members with infection. Patients aged ≥65 years or patients with diabetes, peripheral vascular disease, or compromised immune systems should be treated with a combination of a topical and either terbinafine or fluconazole. For patients taking concomitant medications, a topical with or without terbinafine or fluconazole is recommended dependent on disease severity, though drug-drug interactions must be checked. Patients with liver or kidney disease should be given a topical as first-line treatment; fluconazole can be used second-line with caution.[38] Patients with concurrent nail psoriasis should first be treated for onychomycosis by severity as noted above. In patients with dermatophytomas (defined in Figure 2), efinaconazole is the preferred treatment.[24] The authors make no recommendations on medications for pregnant or lactating patients as there are insufficient data on their safety.

Combination medications

There was a consensus that, while more research is needed, combination treatment using two drugs with differing mechanisms of action is a possible strategy to minimize antifungal

resistance. Combination treatment may also be synergistic; an in vitro study found that efinaconazole in combination with an oral drug was the most advantageous,[39] though clinical studies are needed to confirm these results.

Treatment failure, recurrence, and maintenance

If a patient fails pharmaceutical treatment, reassess and retest to confirm initial diagnosis (Figure 3). Slightly different approaches are recommended in the event of treatment failure with an oral versus a topical. For terbinafine, a sample can be sent for susceptibility testing after one month off terbinafine; if minimum inhibitory concentration (MIC) is high, switch to fluconazole with or without a topical (treatment may need to be adjusted based on strain susceptibility). Since not all labs perform MIC testing, it is best to confirm test availability in advance. For topical treatment failure, consider adjunctive debridement or add an oral medication. To prevent recurrence: topical antifungal creams could be added; booster/pulsed dosing or extended dosing with an oral may be beneficial—particularly in older patients (tailor treatment duration to the patient); a topical such as efinaconazole can also be regularly applied after an oral regimen as maintenance treatment (off-label treatment ranging from once weekly to once daily; Figure 3). Though scientific evidence on topical maintenance treatments is limited, pharmaceutical treatment may be needed indefinitely to prevent recurrence. In case of recurrence with a topical or oral, give a second course of initial treatment.

Patient Education

It is important to manage patient expectations when treating onychomycosis. Toenails grow slowly, meaning optimal results can take 12–18 months.[40] Further, patients should be made aware that even after treatment they may never achieve a normal looking nail if there is toenail loss or they have a disappearing nail bed. Finally, clinical cure may not be possible, particularly in those with very long-term disease; in these patients an improved, better looking nail may be acceptable.

Another issue requiring patient education is the high recurrence rates of onychomycosis (6.5%–53%),[5] especially in athletes, older patients, or patients with long-term disease, diabetes, peripheral vascular disease, or a genetic predisposition.[5,41] It is recommended that physicians schedule follow-up visits 3–6 months after oral medications or one year after topical to check for recurrence and determine if treatment should be resumed or changed. Furthermore, a physical handout (see Figure 5) should be provided explaining follow-up care and maintenance, highlighting that long-term treatment is more than just pharmacologic (eg, personal care, footwear selection/care, laundry[42]). Patients should be advised to use an ultraviolet shoe sanitizer and/or copper or silver socks.[43] Antifungal powder added to shoes is also an option, although research regarding its efficacy is lacking.

For pediatric patients, parents or guardians should be asked to apply any topical treatment daily to ensure adherence. All family members should be checked for onychomycosis and tinea pedis and counseled regarding treatment and prevention.

CONCLUSION

This document aims to provide recommendations for the diagnosis and pharmaceutical treatment of toenail onychomycosis following a roundtable discussion with a panel of dermatologists, podiatrists, and a microbiologist. There was a general consensus on several topics regarding onychomycosis diagnosis, confirmatory laboratory testing, and medications. Onychomycosis should be assessed clinically and confirmed with microscopy, histology, and/or culture. Terbinafine is the primary choice for oral treatment and efinaconazole 10% for topical. Efinaconazole can be used for maintenance to prevent recurrence. For optimal outcomes, patients should be counseled regarding treatment expectations as well as follow-up care and maintenance post-treatment.

DISCLOSURES

Shari R. Lipner has served a consultant for Ortho Dermatologics, Hoth Therapeutics, and Verrica. Warren S. Joseph has served as consultant and speaker for Ortho Dermatologics. Tracey C. Vlahovic has served as investigator and speaker for Ortho Dermatologics. Richard K. Scher has nothing to disclose. Phoebe Rich has received research and educational grants from AbbVie, Allergan, Anacor Pharmaceuticals, Boehringer Ingelheim, Cassiopea, Dermira, Eli Lilly, Galderma, Janssen Ortho Inc., Kadmon Corporation, LEO Pharma, Merck, Moberg Derma, Novartis, Pfizer, Ranbaxy Laboratories Limited, Sandoz, Viamet Pharmaceutical Inc., Innovation Pharmaceuticals (Cellceutix), and Cutanea Life Sciences. Mahmoud Ghannoum has acted as a consultant or received contracts from Scynexis, Inc, Bausch & Lomb, Pfizer, and Mycovia. C. Ralph Daniel has provided clinical research support to Ortho Dermatologics and owns stock in Medimetriks Pharmaceuticals. Boni Elewski has provided clinical research support (research funding to University) for AbbVie, Anaptys-Bio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron, Sun Pharma, Ortho Dermatologics, Vanda; and as consultant (received honorarium) from Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, LEO Pharma, Lilly, Menlo, Novartis, Pfizer, Sun Pharma, Ortho Dermatologics, Verrica.

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