Onychomycosis

Treatment and prevention of recurrence

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Learning objectives
After completing this learning objective, participants should be able to describe FDA-approved systemic therapies for treatment of onychomycosis; identify FDA-approved topical therapies for treatment of onychomycosis; list devices that are used or are in development for treatment of onychomycosis; and discuss techniques to prevent recurrence of onychomycosis.

Disclosures

Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Onychomycosis is a fungal nail infection caused by dermatophytes, nondermatophytes, and yeast, and is the most common nail disorder seen in clinical practice. It is an important problem because it may cause local pain, paresthesias, difficulties performing activities of daily living, and impair social interactions. The epidemiology, risk factors, and clinical presentation and diagnosis of onychomycosis were discussed in the first article in this continuing medical education series. In this article, we review the prognosis and response to onychomycosis treatment, medications for onychomycosis that have been approved by the US Food and Drug Administration, and off-label therapies and devices. Methods to prevent onychomycosis recurrences and emerging therapies are also described. (J Am Acad Dermatol 2019;80:853-67.)

Key words: booster therapy; ciclopirox; clinical cure; complete cure; efinaconazole; fluconazole; fungal nail infection; itraconazole; lasers; mycologic cure; onychomycosis; photodynamic therapy; plasma therapy; pulse dosing; tavaborole; terbinafine; treatment.

Abbreviations used:

ALA:	5-aminolevulinic acid
DLSO:	distal lateral subungual onychomycosis
FDA:	Food and Drug Administration
NDM:	nondermatophyte mold
PDT:	photodynamic therapy

OVERVIEW OF TREATMENT

The goals of onychomycosis therapy are to both eliminate the infecting fungal organism and restore the nail to its normal state as it grows. Patients should be counseled that this process can take some time because fingernails grow about 2 to 3 mm per month and toenails grow 1 to 2 mm per month. The US Food and Drug Administration (FDA) requires treatment efficacy endpoints that are based on clinical examination and negative cultures/stains for drug approvals.[1] Endpoints used in clinical trials include mycologic cure, clinical cure, and complete cure (Table I).[2] Patients should be counseled that a

From the Department of Dermatology, Weill Cornell Medicine, New York.
Funding sources: None.
Dr Scher has received honoraria from MOE Medical Devices, Epihealth, Medicxi, and Valeant. Dr Lipner has received grants for clinical trials from MOE Medical Devices.
Accepted for publication May 10, 2018.
Reprints not available from the authors.

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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.05.1260
Date of release: April 2019
Expiration date: April 2022

clinical cure may not be possible in some cases of severe onychomycosis, secondary nail disease, immunosuppression, or previous trauma with permanent damage to the nail matrix/bed.[3] The treatment for onychomycosis must be individualized based on the patient's degree of nail involvement, infecting organism, comorbidities, concomitant medications, cost, and preferences.

Prognosis and response to treatment

- Patient characteristics, nail findings, and infecting organisms contribute to response to antifungal therapy
- The Onychomycosis Severity Index can be used to predict response to antifungal therapy

Patient demographics, comorbidities, nail findings, and pathogenic organism(s) affect response to treatment and prognosis (Table II). Advancing age is associated with lower cure rates and is likely related to slow nail growth, poor circulation, and higher frequency of infection by nondermatophyte molds (NDMs) and mixed infections compared with younger individuals.[4-6] Patients with diabetes mellitus may have similar complete cure rates as nondiabetics,[41] but duration to complete cure is longer with higher recurrence rates.[32] Other negative prognostic nail findings are subungual hyperkeratosis >2 mm,[20-22] nail matrix involvement,[22,24] surface area covering >50% of the nail unit,[5,23] and two feet–one hand syndrome (Fig 1, *A-C*).[38,39] In addition, mixed infections (Fig 1, *D*),[28,29] yeasts, and NDMs have traditionally been harder to treat than dermatophytes.[31] A scoring system called the Onychomycosis Severity Index has been proposed as a method to objectively describe the extent and involvement of distal lateral subungual onychomycosis and then classify the affected nail as mild, moderate, or severe.[42] It may be useful in predicting response to onychomycosis therapy.

Systemic treatments approved by the FDA

- Oral terbinafine and itraconazole are approved by the FDA for the treatment of onychomycosis
- Because of higher cure rates with terbinafine and fewer drug interactions, terbinafine is usually preferred over itraconazole

Systemic medications are widely used to treat onychomycosis because of their accessibility, low cost, and high efficacy. Terbinafine and itraconazole are approved by the FDA and fluconazole is used off-label for onychomycosis therapy. Griseofulvin is rarely used because of long treatment durations and the higher risk of adverse events and lower cure rates compared with other medications.[43-47] Indications for oral therapy are shown in Table III.

Table I. Endpoints used in clinical trials*

Endpoint	Definition
Mycologic cure	Negative potassium hydroxide microscopy and negative culture
Clinical cure	Clinically completely normal nail
Complete cure	Negative potassium hydroxide microscopy and negative culture and clinically completely normal nail (mycologic cure and clinical cure)

*Data from Gupta and Studholme.[2]

Terbinafine. Terbinafine, an allylamine, inhibits squalene epoxidase, with broad-spectrum activity against dermatophytes, with some activity against NDMs and *Candida* spp.[48,49] It is approved by the FDA to treat onychomycosis caused by dermatophytes and is dosed 250 mg daily orally for 6 weeks for fingernails and 12 weeks for toenails. Package insert mycologic cure rates are 79% and 70% and complete cure rates are 59% and 38% for fingernails and toenails, respectively (Table IV).[51]

The most common side effects are headache, gastrointestinal symptoms, and rash, which rarely require discontinuation of the medication. Less commonly, liver enzyme abnormalities and taste disturbances may occur.[51] Its bioavailability is similar if taken on an empty stomach or with a meal.[55] It is classified as FDA pregnancy category B,[51] and is excreted into breast milk.[55] Because of insufficient human embryotoxicity data, treatment of onychomycosis with terbinafine should be delayed until after delivery and breastfeeding. Clearance of terbinafine is reduced in patients with liver or renal dysfunction.[56] There are a limited number of drug–drug interactions with terbinafine (Table V),[51] and it does inhibit the CYP450 2D6 isozyme.[57,58]

Laboratory testing with terbinafine therapy is controversial. In a review of the Livertox database of the National Institutes of Health, PubMed, and EMBASE, 69 patients had symptomatic drug-induced liver injury, at a mean 30.2 days of therapy (range 5-84 days), with no cases detected through laboratory monitoring.[59] Because of rare idiosyncratic drug induced liver injury,[60-62] the FDA recommends measuring serum transaminases before initiating terbinafine therapy,[51] but recommendations on laboratory monitoring during therapy and frequency are lacking. Therefore, the decision to perform laboratory monitoring with

Table II. Features associated with poor prognosis to onychomycosis treatment

Patient characteristics	Comorbidities	Nail characteristics	Pathogenic organism
Advancing age[4-6]	Immunosuppression HIV[7-9] Hyper–immunoglobulin E syndrome[10] Cancer (AML,[11] ALL,[12] and non-Hodgkin lymphoma[13]) Solid organ transplantation (liver[14] and kidney[15,16]) Neutrophil defects[17] Steroid therapy[18,19]	Distal lateral subungual onychomycosis Subungual hyperkeratosis >2 mm[20-22] >50% of the nail surface area involved[5,23] Nail matrix involvement[22,24] Lateral nail disease[22,25-27]	Mixed bacterial and fungal infections[28,29]
History of nail trauma[20,22,23]	Peripheral vascular disease[30]	Proximal subungual onychomycosis	Mixed fungal infections[31]
Personal history of onychomycosis[20,22,23]	Uncontrolled diabetes mellitus[32]	Total dystrophic onychomycosis[23,33]	Yeasts[31]
		Dermatophytoma[34-36] Severe onycholysis[20,37] Two feet–one hand syndrome[38,39] Slow nail growth[22,30,40]	Nondermatophytes[31]

Fig 1. Poor prognostic factors for onychomycosis therapy. **A**, Left great toenail with subungual hyperkeratosis >2 mm and >50% surface area of the nail plate affected. **B**, Right great toenail with more than 50% of the surface area of the nail plate affected with involvement of the nail matrix. **C**, Two foot–one hand syndrome with involvement of the bilateral toenails and fingernails of the right hand. **D**, Right thumbnail with subungual hyperkeratosis and green discoloration of the nail plate with evidence of mixed infection with *Trichophyton rubrum* and *Pseudomonas aeruginosa*.

terbinafine therapy should be individualized based on the patient's medical history and concomitant medications.

Itraconazole. Itraconazole, a triazole, inhibits lanosterol 14α-demethylase,[63] and has broader spectrum activity than terbinafine, with efficacy against dermatophytes, NDMs, and *Candida* spp.[64] It is approved by the FDA to treat fingernail and toenail onychomycosis caused by dermatophytes.[47,52,65,66] The approved dosing regimen is 200 mg day for 12 weeks for toenails and 2 treatment pulses of 200 mg twice daily for 1 week separated by 3 weeks without treatment for fingernails.[52] The package insert complete cure rate and mycologic cure rates are 47% and 61% for fingernails and 14% and 54% for toenails (Table IV).[52]

The most common side effects are headache, upper respiratory tract infection, diarrhea, abdominal

Table III. Indications for oral and topical treatment of onychomycosis

Indications for oral therapy	Indications for oral or topical therapy	Indications for topical therapy
Proximal subungual onychomycosis	Superficial onychomycosis	Contraindications to oral therapy
DLSO affecting >50% of the surface area of the nail plate with matrix involvement and nail plate thickness >2 mm	DLSO affecting <50% of the surface area of the nail plate without matrix involvement and nail plate thickness < 2 mm	More severe cases in combination with systemic medications or debridement*
>3 or 4 nails affected	Up to 3 or 4 nails affected	For prevention of recurrences or reinfection*
Poor compliance, visibility, and flexibility		
Poor prognostic factors		

DLSO, Distal lateral subungual onychomycosis.
*Theoretical uses of topical therapy that need additional study.

pain, hypertriglyceridemia, and elevated transaminases.[65] Bioavailability is maximal with a full meal[66] but poor with elevated gastric acidity.[67] Rare side effects include hepatic injury[68] and peripheral neuropathy. Itraconazole has many important drug interactions as a potent inhibitor of CYP3A4 (Table V).[52,69,70] It is contraindicated in patients with ventricular dysfunction, including congestive heart failure.[52,71] Itraconazole is classified as a pregnancy category C drug and should be avoided during pregnancy and for 2 months before planning pregnancy.[52,72] Because it is excreted into human milk,[52] treatment with itraconazole should be delayed until after breastfeeding is completed.

A recent Cochrane Review of oral antifungal agents for toenail onychomycosis showed that terbinafine was likely more effective than azoles in achieving clinical cure, with no difference in adverse events or recurrence rates.[73]

Off-label systemic treatments

- Fluconazole is an alternative off-label systemic treatment for onychomycosis with broad-spectrum antifungal coverage
- Terbinafine may be dosed in pulses with similar cure rates to continuous dosing
- Treatment of onychomycosis in children is off-label, with terbinafine and itraconazole considered first-line therapies

Fluconazole. Fluconazole, another triazole, inhibits lanosterol 14α-demethylase and is approved for the treatment of onychomycosis in Europe, but its use is off-label in the United States. Its coverage includes dermatophytes, *Candida* spp., and some NDMs. One advantage of administering fluconazole over itraconazole is that its absorption is not dependent on food or gastric pH.[74] In a double-blind randomized study (n = 362), complete cure rates for toenails at 12 months were 37%, 46%, and 48%, in subjects receiving 150, 300, or 450 mg once per week, respectively, with a low recurrence rate of 4% at 6 months after treatment.[75] The recommended dosing for onychomycosis is 150 mg weekly until the entire nail grows out (6-9 months for fingernails, 12-18 months for toenails; Table IV).[76] This long treatment course is necessary because of its short residual concentration in the nails.[77]

The most common side effects are headache, nausea, rash, abdominal pain, and elevation of transaminases.[78] It is rarely associated with liver injury or failure, which is more common in immunosuppressed individuals. Fluconazole is a potent inhibitor of CYP2C9 and moderate inhibitor of CYP3A4, and therefore caution must be taken with concomitant medications (Table V). When taken for >1 dose, it is classified as FDA pregnancy category D because of case reports of fetal anomalies in humans.[53,54] Fluconazole is secreted into human milk, and treatment with fluconazole for onychomycosis should be delayed until breastfeeding has ceased.

Terbinafine pulse dosing. Pulse-dose therapy with terbinafine is not approved by the FDA for the treatment of onychomycosis but has been studied in clinical trials and may be used off-label for this purpose. It may be preferred by some physicians and patients to limit cost and adverse effects.[79] A number of pulsed regimens have been shown to be as effective as continuous terbinafine regimens in attaining complete cure. For example, 1 intermittent regimen—2 cycles of 250 mg per day of terbinafine for 4 weeks on and 4 weeks off—had the greatest efficacy of all pulse regimens, with mycologic and complete cure rates comparable to that of 250 mg per day terbinafine for 12 continuous weeks.[80]

Booster therapy. Booster or supplemental therapy is defined as treatment with additional therapy after the original full antifungal course. It has been suggested to improve cure in patients with

Table IV. Oral medications used for the treatment of onychomycosis

Drug	Mechanism of action	Indication	Adult dosing	Pediatric dosing[50]	Mycologic cure rate	Complete cure rate	Common side effects	Rare side effects
Terbinafine[51]	Inhibits squalene epoxidase in ergosterol biosynthesis pathway	Fingernail and toenail onychomycosis due to dermatophytes	250 mg daily for 6 weeks for fingernails and 12 weeks for toenails	<20 kg: 62.5 mg/day, 20-40 kg: 125 mg/day, >40 kg: 250 mg/day for 6 weeks for fingernails and 12 weeks for toenails	Fingernails: 79%; toenails: 70%	Fingernails: 59%; toenails: 38%	Headache, gastrointestinal symptoms, rash, liver enzyme abnormalities, taste disturbance, and visual disturbance	Liver injury, liver failure, depressive symptoms, severe neutropenia, thrombocytopenia, agranulocytosis, pancytopenia, anemia, hearing loss, angioedema, allergic reactions, Stevens–Johnson syndrome, toxic epidermal necrolysis, and systemic lupus erythematosus
Itraconazole[52]	Inhibits lanosterol 14α-demethylase in ergosterol biosynthesis pathway	Fingernail and toenail onychomycosis due to dermatophytes	200 mg twice daily one week per month for 2 months for fingernails and 200 mg daily for 12 weeks for toenails	5 mg/kg/day for one week per month, 2 months fingernails, 3 months toenails	Fingernails: 61%; toenails: 54%	Fingernails: 47%; toenails: 14%	Headache, rhinitis, upper respiratory tract infection, diarrhea, abdominal pain, hypertriglyceridemia, and elevated liver function enzymes	Liver injury, liver failure, leukopenia, neutropenia, thrombocytopenia, peripheral neuropathy, congestive heart failure, pancreatitis, allergic reactions, Stevens–Johnson syndrome, toxic epidermal necrolysis and menstrual disorders, and erectile dysfunction
Fluconazole[53,54] (off-label)	Inhibits lanosterol 14α-demethylase in ergosterol biosynthesis pathway	Not approved by the FDA for the treatment of onychomycosis; off-label for treatment of fingernail and toenail onychomycosis	150 mg once per week for 6-9 months for fingernails and 12-18 months for toenails	3-6 mg/kg once per week for 12 weeks, fingernails and 26 weeks for toenails	—	—	Headache, nausea, vomiting, rash, abdominal pain, diarrhea, and elevation of transaminases	Liver injury, liver failure, anaphylaxis, QT prolongation, torsade de pointes, seizures, leukopenia, neutropenia, agranulocytosis, thrombocytopenia, chloestasis, Stevens–Johnson syndrome, toxic epidermal necrolysis, and taste disturbance

FDA, US Food and Drug Administration.

Table V. Drug interactions with systemic medications used to treat onychomycosis

Drug	Contraindicated with	May alter plasma concentration of
Terbinafine[51]		Tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers, antiarrhythmics class 1C (eg, flecainide and propafenone), monoamine oxidase inhibitors type B, desipramine, dextromethorphan, cyclosporine, and caffeine
Itraconazole[52]	Cisapride, midazolam, nisoldipine, terfenadine, felodipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol, lovastatin, simvastatin, eletriptan, ergot alkaloids, ergometrine, ergotamine, methylergometrine, and methadone	Tolbutamide, glyburide, glipizide, digoxin, disopyramide, carbamazepine, rifabutin, busulfan, docetaxel, vinca alkaloids, alprazolam, diazepam, verapamil, atorvastatin, cerivastatin, cyclosporine, tacrolimus, sirolimus, indinavir, ritonavir, saquinavir, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, fluticasone, trimetrexate, warfarin, cilostazol, eletriptan, and fentanyl
Fluconazole[54]	Terfenadine (≥400 mg/d), cisapride, and pimozide	Tolbutamide, glyburide, glipizide, phenytoin, cyclosporine, rifampin, theophylline, terfenadine (<400 mg/d), astemizole, rifabutin, voriconazole, tacrolimus, midazolam, triazolam, alfentanil, amitriptyline, nortriptyline, carbamazepine, nifedipine, isradipine, amlodipine, felodipine, cyclophosphamide, fentanyl, halofantrine, atorvastatin, simvastatin, fluvastatin, losartan, methadone, nonsteroidal antiinflammatory drugs, prednisone, saquinavir, zidovudine, sirolimus, vinca alkaloids, vitamin A, and warfarin

onychomycosis with slow growing nails, nail plates >2 mm in thickness, lateral involvement, disease affecting >75% of the surface area of the nail plate, nail matrix involvement, or immunosuppression.[81,82] This booster dose is an additional 4 weeks of terbinafine or itraconazole given 6 to 9 months after the initiation of antifungal therapy.[83] This time frame is considered the ideal "window of opportunity" based on pharmacokinetic data.[84]

Systemic treatment of onychomycosis in children. There are no systemic therapies approved by the FDA for the treatment of onychomycosis in children; however, oral terbinafine, itraconazole, and fluconazole are often used off-label in clinical practice (Table IV).[85] In a systematic review of 26 studies (5 clinical trials), oral treatment of onychomycosis (ie, terbinafine, itraconazole, fluconazole, and griseofulvin) resulted in an overall 70.8% complete cure rate with a favorable safety profile.[86] While there are no US guidelines for systemic treatment of onychomycosis in children, The British Association of Dermatologists recommends terbinafine or itraconazole as first-line treatment, with the former preferred over the latter.[60] Fluconazole is recommended as a second-line agent in the case of contraindications or poor tolerance to first-line drugs.[60] Griseofulvin can also be considered a second-line drug because of its long treatment course and low efficacy.[60]

Topical treatments approved by the FDA

- Ciclopirox 8% nail lacquer is approved by the FDA for the treatment of fingernail and toenail onychomycosis with some data on off-label use in children
- Efinaconazole 10% solution and tavaborole 5% solution are newer therapies approved by the FDA for toenail onychomycosis with favorable efficacy

Topical therapy is often desirable because of the low risks of systemic side effects and drug—drug interactions and the avoidance of laboratory monitoring. Designing effective nail topicals has been challenging because of often inadequate penetration of the nail plate,[71] accompanying hyperkeratosis, and immune privilege.[87] There are no strict guidelines for the use of topical monotherapy, and well-accepted uses are shown in Table III.[88,89] Treatment efficacy is enhanced by treating early[90,91] and treating concurrently for tinea pedis.[92,93] One important limitation in using the newer topical medications is their high cost (eg, efinaconazole 4 mL, $577.36; tavaborole 4 mL, $608.66).[94]

Ciclopirox. Ciclopirox, a hydroxypyridone, chelates trivalent cations, thereby inhibiting metal-dependent enzymes.[95,96] It has broad-spectrum coverage against dermatophytes, *Candida* spp., some NDMs, and Gram-positive and -negative bacteria.[97] Ciclopirox 8% nail lacquer was approved by the FDA for the treatment of mild to moderate

onychomycosis of fingernails and toenails without lunula involvement in immunocompetent patients caused by *Trichophyton rubrum* in 1999. Weekly clipping and monthly in-office debridement is recommended for better efficacy. For toenails, package insert mycologic cure rates are 29% to 36% and complete cure rates are 5.5% to 8.5% (Table VI).[98] While it is classified as FDA pregnancy category B,[98] because of a lack of human embryotoxicity data and because it is unknown whether it is excreted into breast milk, treatment should be delayed in pregnant and breastfeeding women. Adverse effects were localized and included burning, periungual erythema, and application site reactions.[98]

Efinaconazole. Efinaconazole, a triazole, inhibits lanosterol 14α-demethylase and is active against dermatophytes, NDMs, and *Candida* spp. both in vitro and in vivo. Efinaconazole 10% solution was approved by the FDA in June 2014 for the treatment of toenail fungus caused by *T rubrum* and *Trichophyton mentagrophytes*, with package insert mycologic cure rates of 53.4% to 55.2% and complete cure rates of 15.2% to 17.8% (Table VI).[99,101] Efinaconazole was shown to penetrate human cadaver nails coated with nail polish[102]; however, there have been no studies evaluating its efficacy in onychomycosis patients, and the current formulation degrades nail polish.[103] It is classified as pregnancy category C because of embryotoxicity in rats[101] and should be avoided in pregnant women. While it is unknown whether it is excreted into human milk, it was found in the milk of nursing rats who were given repeated subcutaneous doses,[101] and therefore it should be avoided in breastfeeding women. Adverse effects were limited to application site reactions and ingrown toenails.[101]

Tavaborole. Tavaborole is a benzoxaborole and it inhibits protein synthesis through fungal aminoacyl transfer RNA synthetase.[104] It has broad-spectrum antifungal activity against dermatophytes, NDMs, and yeasts. Tavaborole 5% solution was approved by the FDA in July 2014 for the treatment of toenail onychomycosis caused by *T rubrum* and *T mentagrophytes.*[104] Mycologic cure rates were 31.1% and 35.9% and complete cure rates were 6.5% and 9.1% (Table VI).[100] Tavaborole does not damage nail polish,[103] was shown to penetrate human cadaver nails with nail polish,[105] and inhibits the growth of *T rubrum* in the presence of polish in an ex vivo model,[106] but efficacy data in onychomycosis patients are lacking. It is labeled as pregnancy category C. Since there is no human embryotoxicity data and it is unknown whether it is secreted into human milk, caution must be taken with pregnant and breastfeeding women. Side effects are local with the most common being, exfoliation, erythema, and dermatitis.[100,107]

Table VI. Topical medications approved by the US Food and Drug Administration for the treatment of onychomycosis

Therapy	Mechanism of action	Treatment course	Application	Complete cure	Mycologic cure
Ciclopirox 8% nail lacquer[98]	Inhibition of cytochromes, involved in oxidative damage, affects nutrient uptake, synthesis of proteins, and nucleic acids	Fingernails: daily for 24 weeks; toenails: daily for 48 weeks	Brush applicator applied daily to the nail plate and its undersurface, hyponychium, and 5 mm of the surrounding skin for 1 week. Lacquer removed with alcohol weekly. Nail trimmed and filed. Monthly clipping/debridement by physician recommended	5.5% and 8.5% (48 weeks)	29% and 36% (48 weeks)
Efinaconazole 10% solution[99]	Inhibits fungal lanosterol 14α-demethylase in the ergosterol biosynthesis pathway	Fingernails: no indication; toenails: daily for 48 weeks	Brush applicator applied to the nail plate and its undersurface, nail folds, and hyponychium	17.8% and 15.2% (48 weeks)	55.2% and 53.4% (48 weeks)
Tavaborole 5% solution[100]	Inhibition of fungal aminoacyl transfer RNA synthetase	Fingernails: no indication; toenails: daily for 48 weeks	Glass-pointed tip dropper applied to the nail plate and under the nail tip	6.5% and 9.1% (48 weeks)	31.1% and 35.9% (48 weeks)

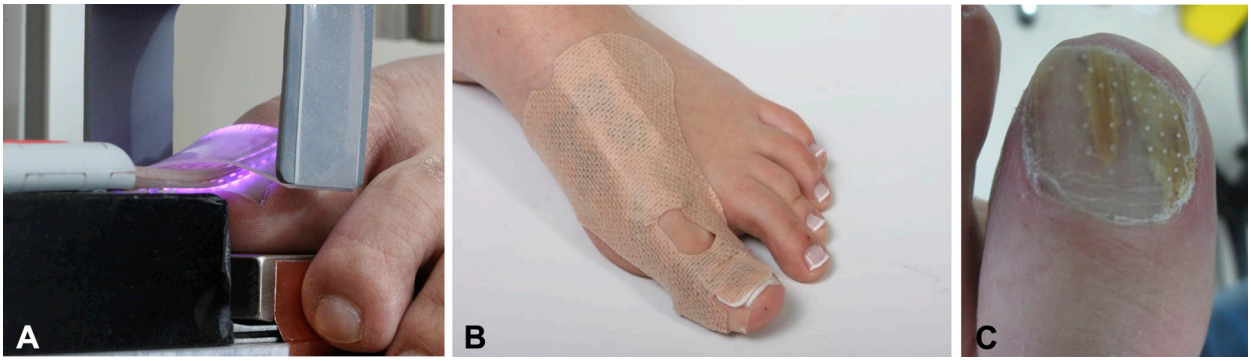

Fig 2. Device-based treatments in development for onychomycosis. **A**, Left great toenail treated with plasma patch application. **B**, Iontophoresis patch containing topical terbinafine applied to the left great toenail. A power supply is attached via electrodes to increase delivery of antifungals to the site of infection. **C**, Nail drilling. Nail plate with multiple 0.4-mm holes created using a microcutter. Terbinafine 1% spray was then applied to the nail plate daily. Photographs courtesy of MOE Medical Devices (*A*), Dr Avner Shemer (*B*) and Total Foot Health, Salisbury, UK (*C*).

Topical treatment of onychomycosis in children. Theoretically, topical medications would be successful in children because of the presumed easy penetration of their thin, fast-growing nails. However, onychomycosis therapies approved by the FDA are only approved for use in adults, and there are limited data documenting the use of these topical medications in children. Nevertheless, topical medications are often used off-label in pediatrics in children who have few nails involved, <50% of the nail plate surface area affected with no matrix involvement, or those with a contraindication to oral therapy.[108,109] In a randomized, double-blind, vehicle-controlled trial evaluating ciclopirox lacquer versus vehicle in 2- to 16-year-olds (n = 40), 77% of patients in the ciclopirox arm achieved mycologic cure at 32 weeks.[109] It may also be beneficial to combine topical therapy with systemic therapy for improved efficacy. In a systematic review of 26 studies, higher complete cure rates were seen with combined systemic and topical therapies (80.8% [16/20]) compared with systemic treatment alone (70.8% [107/151]).[86] While cure rates with efinaconazole or tavaborole would be expected to be higher than with ciclopirox based on the data in the adult population, to date there are no reports documenting use of the newer topical medications in children. One important consideration is that topical therapy requires adherence for long periods of time (48 weeks for toenails), which must be weighed with the patient's age and maturity level.

Laser therapy

- Lasers are approved by the FDA for "temporary increase of clear nail in patients with onychomycosis," not cure
- Since cure rates for laser treatment are lower than those for orals and topicals, lasers are not recommended as first-line therapy for onychomycosis

Devices are attractive alternative therapeutic options for the treatment of onychomycosis because they would theoretically overcome systemic side effects and adherence problems inherent with medications. It is important to note that approval by the FDA for medical devices to treat onychomycosis is different than approval for drugs. While drugs are required to meet the medical endpoints of mycologic and complete cure, devices instead must demonstrate an aesthetic endpoint of visual improvement.[1] Lasers likely exert their fungicidal effects via several mechanisms. Using the principle of selective photothermolysis, lasers have a photothermal effect on fungi, with chitin augmenting the heating effect.[110-112] Because a temperature of 50°C is necessary to achieve this fungicidal effect,[113,114] the use of pulse durations minimizes pain and reduces complications, including necrosis.[114,115] Absorption of energy by fungal chromophores xanthomegnin, chitin, and melanin have further fungicidal effects.[116-118] Maximal efficacy is obtained with pulse durations that are shorter than the thermal relaxation time of the target chromophore.[115] Penetration of the nail plate and targeting of fungi occurs at wavelengths of 750 to 1300 nm.[119] Short, long pulsed, and Q-switched neodymium-doped yttrium aluminum garnet lasers,[114,120-128] near infrared and dual wavelength diode lasers,[129,130] and fractional CO_2 lasers[131,132] have been used for the treatment of fungal nail infections with mixed results. It is also difficult to compare clinical trial data between lasers

Table VII. Risk factors for recurrence and strategies to prevent recurrence

Risk factors for recurrence[32,165]	Strategies to prevent recurrence[25,165-169]
Family history of onychomycosis or tinea pedis	Prompt treatment of tinea pedis in patient and family members
Occlusive footwear	Keeping feet cool and dry and avoiding the use of occlusive footwear
Frequent use of public gyms and swimming pools	Using flip flops in public gyms and swimming pools
Diabetes mellitus	Discarding or treating infected footwear (with topical antifungals, ultraviolet light, or ozone)
>50% nail involvement at baseline	Discarding or treating infected socks (washing with hot water)
Nail trauma	Avoidance of nail trauma by trimming nails short
Infecting organism (nondematophytes, mixed infections)	Use of prophylactic antifungals to feet and webs (perhaps indefinitely and possibly nails)
Previous onychomycosis therapy, duration of therapy, treatment success, and adherence	Careful choice of optimal onychomycosis therapy, counseling patient on expectations, and adherence

and oral and topical therapies for onychomycosis because of the vastly different endpoints used. A recent review compared laser-induced improvement rates to those of oral and topical onychomycosis therapies approved by the FDA that used medical endpoints (21 studies).[118] Laser treatment (2 studies) resulted in lower mycologic cure rates (11%)[118] than oral and topical therapies approved by the FDA (29-61%).[118]

Besides efficacy, other considerations in using lasers to treat onychomycosis are the number of sessions required and duration of treatment. Multiple treatments are typically performed with duration as long as 19 months.[118] In addition, laser therapy is not covered under most insurance plans, with an average cost of $400 to $1200 per treatment session.[120] Pain associated with laser treatment is also an important concern, with many patients experiencing significant discomfort during the procedure.[114] Based on the above issues and limited efficacy, laser therapy cannot currently be recommended as a first-line treatment of onychomycosis.

Treatments in development

- Photodynamic and plasma therapies have been explored for the treatment of onychomycosis, but larger randomized trials are needed to determine their efficacy and practicality in the clinical setting

Photodynamic therapy. Photodynamic therapy (PDT) is a noninvasive treatment that combines light-based modalities with photosensitizers. It is approved by the FDA for the treatment of actinic keratoses and has been used off-label to treat onychomycosis.[133,134] Laser or visible light is used to excite a topically applied photosensitizing agent,[135] resulting in generation of reactive oxygen species and free radicals, which are cytotoxic to proliferating cells and have antimicrobial properties.[136-138] In vitro, PDT (methylene blue, 625-nm light source) was fungicidal to *T rubrum*.[139-141] To date, there have been 2 clinical trials and a number of case reports evaluating PDT for the treatment of onychomycosis.[133,134] In 1 study (n = 30), the clinical cure rate was 36.6% at 18 months.[133] In another study (n = 22), the mycologic cure rate was 100%, and the complete cure rates were 63.6% and 100% in patients with severe and mild to moderate onychomycosis, respectively.[134] Across the 6 published PDT onychomycosis studies, negative microscopy or culture was found in 67% of patients (n = 58).[133,134,142-145] Some disadvantages of PDT include the requirement for pretreatment with nail avulsion or urea, numerous sessions, and pain.[133,134] Well-controlled randomized clinical trials are needed to determine the true efficacy of PDT in treating onychomycosis.

Plasma therapy. Plasma therapy is also being investigated for the treatment of onychomycosis (Fig 2, *A*). Plasma is created in air by pulses of strong electric field that ionize air molecules, generating ozone, hydroxyl radicals, and nitric oxide, which have antifungal properties.[146] Thermal plasma causes extensive tissue heating, which could cause significant pain and damage to the nail unit. However, nonthermal plasma, with its small current and duration, does not produce substantial tissue heating. Nonthermal plasma, generated by surface microdischarge technology, inhibited growth of *T rubrum* in vitro,[147] was fungicidal to *T rubrum* in an in vitro–simulated nail model (M. F. Zemel, personal communication, May 2014), and inhibited growth of *T rubrum* in clinically infected human nail

plate (M. F. Zemel, personal communication, May 2014). The use of nonthermal plasma has been studied in a pilot study on 19 patients with toenail onychomycosis, with a clinical cure rate of 53.8% and a mycologic cure rate of 15.4%.[148] Larger trials are necessary to determine whether the treatment is effective and practical in treating onychomycosis in clinical practice (NCT02724384).

Other treatments. Numerous oral and topical therapies as well as devices are being investigated for the treatment of onychomycosis. Posaconazole, a broad-spectrum azole, was studied in a phase IIB trial and exhibited a greater complete cure rate (54.1%) in treating toenail onychomycosis at 200 mg daily for 24 weeks compared with terbinafine (250 mg daily for 12 weeks, 37%; not statistically significant).[149] VT-1161, an oral tetrazole, has in vitro antifungal activity against *T rubrum* and *T mentagrophytes*,[150,151] with limited potential drug–drug interactions by targeting CYP51.[152,153] A phase II randomized, double-blind study in patients with toenail onychomycosis has been completed (NCT02267356). ME1111 is a topical antifungal that inhibits succinate dehydrogenase in *T rubrum* and *T mentagrophytes*.[154] A phase II randomized, double-blind study in patients with toenail onychomycosis has been completed (NCT02022215). Iontophoresis (Fig 2, *B*), ultrasonography, and lasers are being studied to optimize antifungal drug delivery to the site of infection.[155-160] Nail drilling (Fig 2, *C*), which creates minute tunnels throughout the nail plate, is also being investigated to augment delivery and efficacy of topical antifungals to the site of infection.[161,162]

PREVENTION OF RECURRENCE

After treatment of onychomycosis, recurrences (ie, relapse [same infection after incomplete cure] or reinfection [same infection after complete cure]) occur at a rate of 20% to 25%.[4,163,164] In a retrospective chart review on patients with complete cure treated with oral terbinafine for toenail onychomycosis who then used a topical antifungal for prophylaxis (n = 320), the recurrence rate was significantly lower in patients receiving prophylaxis.[25] The ideal duration of prophylaxis is unknown, but may be required for life. Risk factors for recurrence[32,165] (some of which are modifiable) and strategies to prevent relapse/reinfection[25,165-169] are shown in Table VII.

In conclusion, onychomycosis is a highly treatable nail disorder and therapeutic options include oral and topical medications as well as devices. While medications used to treat fungal nail disease must meet medical endpoints, device approvals are less stringent and require aesthetic endpoints. The therapeutic landscape is rapidly evolving with new drugs and devices being investigated with novel mechanisms of action. Well-designed clinical trials are necessary to determine efficacy and establish optimal treatment guidelines.

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Answers to CME examination

Identification No. JB0419

April 2019 issue of the Journal of the American Academy of Dermatology.

Lipner SR, Scher RK. J Am Acad Dermatol 2019;80:853-67.

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