


# Updated Perspectives on the Diagnosis and Management of Onychomycosis

Julianne M Falotico<sup>1</sup>, Shari R Lipner<sup>2</sup> 

<sup>1</sup>Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA; <sup>2</sup>Weill Cornell Medicine, Department of Dermatology, New York, NY, USA

Correspondence: Shari R Lipner, Weill Cornell Medicine, Department of Dermatology, 1305 York Avenue, NY, NY, 10021, USA, Tel +1 646-962-3376, Fax +1 646-962-0033, Email sh19032@med.cornell.edu

**Abstract:** Onychomycosis is the most common nail disease encountered in clinical practice and can cause pain, difficulty with ambulation, and psycho-social problems. A thorough history and physical examination, including dermoscopy, should be performed for each patient presenting with nail findings suggestive of onychomycosis. Several approaches are available for definitive diagnostic testing, including potassium hydroxide and microscopy, fungal culture, histopathology, polymerase chain reaction, or a combination of techniques. Confirmatory testing should be performed for each patient prior to initiating any antifungal therapies. There are several different therapeutic options available, including oral and topical medications as well as device-based treatments. Oral antifungals are generally recommended for moderate to severe onychomycosis and have higher cure rates, while topical antifungals are recommended for mild to moderate disease and have more favorable safety profiles. Oral terbinafine, itraconazole, and griseofulvin and topical ciclopirox 8% nail lacquer, efinaconazole 10% solution, and tavaborole 5% solution are approved by the Food and Drug Administration for treatment of onychomycosis in the United States and amorolfine 5% nail lacquer is approved in Europe. Laser treatment is approved in the United States for temporary increases in clear nail, but clinical results are suboptimal. Oral fluconazole is not approved in the United States for onychomycosis treatment, but is frequently used off-label with good efficacy. Several novel oral, topical, and over-the-counter therapies are currently under investigation. Physicians should consider the disease severity, infecting pathogen, medication safety, efficacy and cost, and patient age, comorbidities, medication history, and likelihood of compliance when determining management plans. Onychomycosis is a chronic disease with high recurrence rates and patients should be counseled on an appropriate plan to minimize recurrence risk following effective antifungal therapy.

**Keywords:** onychomycosis, nail disease, fungal nail infection, diagnosis, management, treatment, recurrence

## Introduction

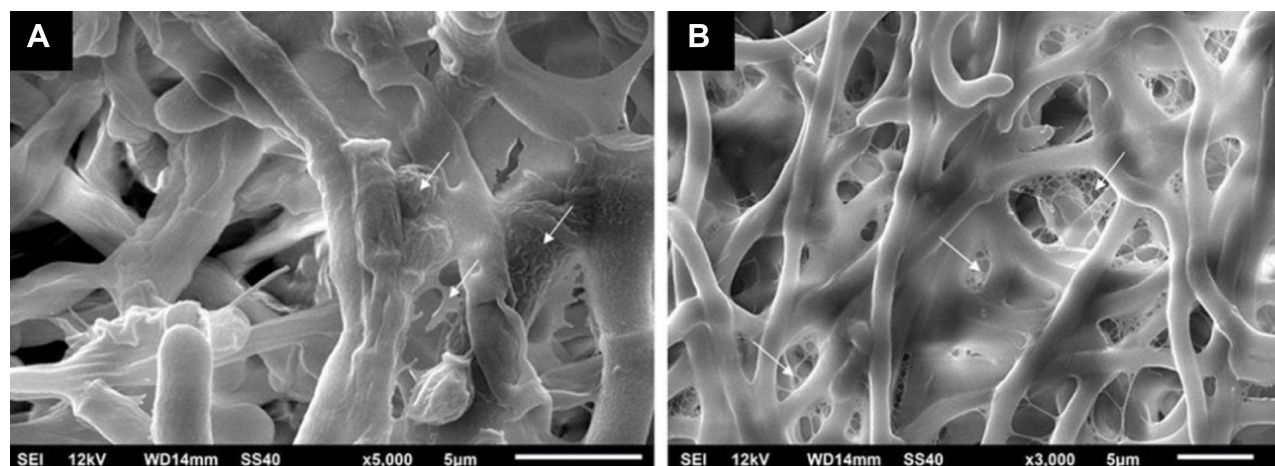
Onychomycosis is a fungal infection of the nail unit caused by dermatophytes, non-dermatophyte molds (NDM) and yeast.<sup>1,2</sup> It is the most common nail infection encountered in clinical practice,<sup>3</sup> with a worldwide prevalence of 5.5%, and an estimated prevalence of 2% to 14% in the United States (US),<sup>4</sup> and 0.5% to 24% in Europe.<sup>5-8</sup> Risk factors include prior dermatologic conditions, such as hyperhidrosis, tinea pedis, and psoriasis, as well as exogenous factors, including occlusive shoes, trauma, and poor nail grooming. Comorbidities, such as diabetes mellitus, immunosuppression, malignancy, venous insufficiency, peripheral arterial disease, obesity, and inflammatory bowel disease also increase risk.<sup>4</sup> Altered foot biomechanics due to biomechanical malalignments, congenital deformities, or neurological deficits can result in repetitive microtrauma during walking and increase the risk of infection and recurrence.<sup>9,10</sup> Genetics may predispose to developing infection<sup>11,12</sup> and transmission risk increases when members of the same household are infected.<sup>13</sup> Onychomycosis may occur at any age, however prevalence increases with age,<sup>14,15</sup> affecting roughly 50% of patients greater than 70 years old,<sup>16</sup> and is rather rare in the pediatric population, with increased risk seen in children with Down's syndrome or immunodeficiency.<sup>17</sup>

Onychomycosis, especially with secondary bacterial infections, can result in local pain and paresthesia, which pose significant psychosocial consequences. Limited dexterity and ambulation and difficulty finding comfortable fitting footwear can lead to social embarrassment and decreased self-esteem, which can be largely distressing, even when the infection is not

severe.<sup>1,4</sup> Patients also report stigmatization and dissatisfaction with the aesthetic appearance of their nails, and thus may avoid social interactions.<sup>18</sup> In a systematic review of 30 studies evaluating the effect of onychomycosis and treatment on quality of life (QoL),<sup>19</sup> women and patients with fingernail involvement had the poorest QoL scores. There were greater improvements in QoL with oral treatments versus topical therapies. Therefore, onychomycosis is more than just a cosmetic concern, and dermatologists and podiatrists should inquire about nail concerns during routine office visits in addition to evaluating all 20 nail units.<sup>1</sup> In an analysis of the top 51 search engine hits for onychomycosis,<sup>20</sup> overall readability was poor, with only one-third of websites meeting the acceptable seventh grade reading level for patients. Therefore, internet-based information about onychomycosis is lacking, highlighting the need for proper in-office patient education and counseling for this chronic and recurrent disease.

## Pathogenic Organisms

The majority of onychomycosis cases are due to dermatophytes (60–90%), most commonly *Trichophyton rubrum* and *T. mentagrophytes*. Less common dermatophytes include *T. verrucosum*, *T. violaceum*, *T. kraidenii*, *Epidermophyton floccosum*, and *Arthroderma* spp., with infection due to *Microsporum* spp. being very rare. Cases secondary to dermatophyte infections are specifically referred to as tinea unguium.<sup>1,4,13</sup> Infection with NDMs account for about 10% of cases worldwide, with the most common organisms being, *Aspergillus* spp., *Fusarium* spp., *Acremonium* spp., *Scopulariopsis brevicaulis*, *Alternaria alternata*, and *Neoscytalidium* spp.<sup>21–24</sup> Yeast infections account for up to 10–20% of cases, with the most common pathogen being *Candida* spp., including *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. glabrata* and *C. tropicalis*. Yeast infections are more frequent in the fingernails, especially if the hands are routinely submerged in water.<sup>4,25–27</sup> Onychomycosis due to the yeast *Kloeckera apiculata* is uncommon but has been isolated in select cases.<sup>28,29</sup> In children, infection with *T. tonsurans* may occur.<sup>13</sup> Infections with two or more organisms can occur, and mixed dermatophyte-NDM infections account for estimated 3–11% of onychomycosis cases, which may potentially be more difficult to treat and more prone to recurrences.<sup>1,4</sup> Importantly, prevalence and infecting pathogen can vary according to the population studied<sup>1</sup> due to differences in geographic location, climates, and daily activities, including professions and personal habits. Specifically, prevalence in North America ranges from 8.7% to 13.8%<sup>14,25</sup> and is predominately caused by dermatophytes due to immigration of dermatophytes from other parts of the world.<sup>30</sup> Prevalence in Europe is broader at about 0.5–24%.<sup>5–8</sup> In tropical and warmer climates, infection with NDM and yeasts are more common.<sup>31–33</sup> Additionally, instead of acting planktonically (in suspension, independent, and free-floating), pathogens may merge into groups and form biofilms.<sup>4,34</sup> Biofilms attach to surfaces, such as the nail plate, via an extracellular matrix,<sup>35</sup> which protect fungi from host immune responses and give them increased virulence<sup>36</sup> (Figure 1). Resultantly, biofilms may contribute to treatment resistance and difficulty controlling chronic infections.<sup>37,38</sup>



**Figure 1** Scanning electron microscopy demonstrating mature fungal biofilms that were formed in 24-well plates. White arrows depict extracellular matrix covering and connecting the hyphae. (A) *Trichophyton rubrum* ATCC 28189. (B) *Trichophyton mentagrophytes* ATCC 11481. Reprinted from *J Am Acad Dermatol*, 1:80(4), Lipner SR, Scher RK, Onychomycosis: Clinical overview and diagnosis, 835–851, Copyright (2019), with permission from Elsevier.<sup>4</sup>

## Clinical Presentation

### History

Patients may fail to disclose nail conditions to their dermatologists or podiatrists due to the apprehension of discussing something that may seem trivial. Therefore, dermatologists and podiatrists must routinely inquire about nail problems as part of a complete history.<sup>1</sup> Patients with onychomycosis typically complain of nail discoloration (most commonly yellow, white, or brown if the fungus is dense), nail separation, brittleness, and thickening.<sup>39</sup> Symptoms may worsen progressively until the nail crumbles away,<sup>1</sup> and in untreated cases, the skin may become sore and inflamed.<sup>40</sup> Patients may report local pain and paresthesia in affected nails, trouble fitting into shoes, difficulty with ambulation, and social embarrassment.<sup>1,41</sup> Medication use, including oral, topical, and over-the-counter therapies, should also be thoroughly reviewed with the patient, as diagnostic testing and treatment regimens can be impacted by current use of antifungals.<sup>4,42</sup>

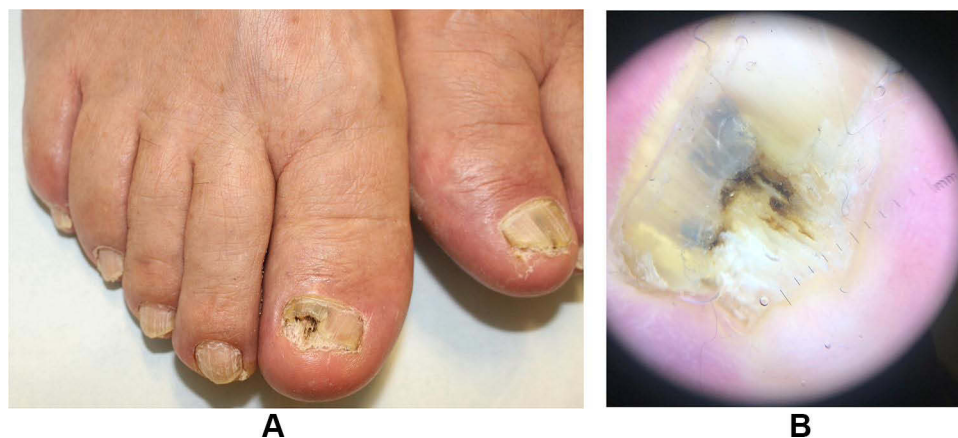
### Physical Examination

Onychomycosis may affect either fingernails or toenails or both,<sup>43</sup> however, toenail involvement is much more common than fingernail involvement. For toenails, the great or second toenail is most frequently affected.<sup>44</sup> Unless there has been antecedent trauma or the patient is immunosuppressed, it is unusual for a fingernail to be involved without concomitant toenail infection.<sup>1</sup> Regardless, all 20 nails should be examined in clinical practice.<sup>24</sup> Since it is common to have accompanying scale in the web spaces and/or plantar feet, dermatologists and podiatrists should perform a comprehensive physical examination including the hands and feet in addition to the nail units.<sup>4</sup>

Common physical examination findings include yellow nail plate discoloration and thickening and subungual hyperkeratosis, which may cause nail plate onycholysis (Figure 2). In severe cases, there may be onychodystrophy with nail plate ridging, thickening, and crumbling, onychocryptosis, and nail loss. Trauma may result in red, black, or brown nail plate discoloration (hematoma).<sup>1,4</sup> Dermatophytomas are fungal abscesses that present as orange and brown or white and yellow longitudinal streaks or patches in the subungual space. NDM infections can also result in nail matrix involvement, causing periungual inflammation and tenderness.<sup>24</sup> A standardized composite score, such as The Scoring Clinical Index for Onychomycosis, can be used to assess overall disease severity and aid in the development of an individualized treatment plan.<sup>45</sup>

### Dermoscopy

Dermoscopy can aid in differentiating between other nail diseases, including onychomycosis (Figure 2), psoriasis, pseudomonas colonization, and traumatic onycholysis.<sup>1,46</sup> Typical dermoscopic findings of onychomycosis are a jagged proximal margin of onycholysis and longitudinal striae, with vertical streaks of differing colors in the onycholytic area that resemble an aurora borealis.<sup>4,47</sup> The subungual area may have a ruin-like appearance, representing hyperkeratosis



**Figure 2** Patient with laboratory confirmed onychomycosis. (A) Clinical appearance of toenails with onycholysis, nail plate thickening and subungual debris. (B) Dermoscopy showing ruin-like appearance and streaks of various colors.

and debris.<sup>48,49</sup> Linear bands, multicolored or yellow/white patterns or streaks, subungual keratosis, reverse triangular or nonlongitudinal homogenous patterns, nail plate scales,<sup>50</sup> and rarely, pseudo-Hutchinson sign or longitudinal patterns<sup>51</sup> may be seen in fungal melanonychia. Importantly, dermoscopy should be used only as an aid and not for definitive diagnosis. Confirmatory testing should be performed prior to initiating both oral and topical treatments and is especially important considering that different nail pathologies can have similar clinical presentations.

## Diagnostic Testing

History, clinical examination, and dermoscopy alone are not sufficient to make a definitive diagnosis of onychomycosis. Mycologic laboratory testing is necessary for diagnosis and is cost-effective.<sup>52</sup> Laboratory confirmation is quick, easy to perform, and prevents treatment failures, inaccurate diagnoses, avoidable adverse effects, and possible drug–drug interactions.<sup>53,54</sup> In 2013, the American Academy of Dermatology, as part of the ABIM Foundation's Choosing Wisely campaign, recommended that confirmatory testing of onychomycosis be performed before prescribing oral antifungal therapy.<sup>55</sup> In a retrospective analysis of 1774 patients with a diagnosis of onychomycosis, 2002–2018,<sup>56</sup> only 39.3% underwent diagnostic testing, with a steady decrease in testing from 2007 onwards, except for an isolated spike in 2014. Therefore, diagnostic testing for onychomycosis is underperformed, with a need for increased physician education regarding the importance of confirmatory testing. Prior to any diagnostic testing, a three-to-six-month washout period of antifungal therapies, including all oral, topical, and over-the-counter medications, should be performed. Antifungals may be retained in the subungual debris and nail plate, which may be transported to culture media and can impede fungal growth for culture as well as affecting other diagnostic tests.<sup>4,57</sup>

There are multiple techniques available for diagnosing onychomycosis (Table 1). The specific method should be chosen after careful consideration of patient characteristics, clinician expertise, and cost, sensitivity, specificity, and turnaround time for the result.<sup>4</sup> For potassium hydroxide (KOH) and microscopy, fungal culture, and polymerase chain reaction (PCR), the nail is cleaned with 70% isopropyl alcohol and soap and water to prevent contamination of the sample with the skin flora and/or environment. The affected nail plate is then clipped<sup>1,39</sup> (Figure 3), with the precise location of sample collection determined by the clinical presentation.<sup>4</sup> The subungual debris can be scraped onto a paper with a contrasting background to better visualize the quantity collected.<sup>58</sup> Histopathology does not require similar preparation of the sample. Sampling the nail is a specialized technique learned and perfected during residency training and physician experience is an integral component of this process. Patient performed clippings are not appropriate for diagnostic testing.<sup>59</sup>

## KOH and Microscopy

Fungal elements can be visualized with microscopic examination (positive direct microscopy) of nail scrapings treated with 5–40% KOH.<sup>40,53</sup> The addition of KOH aids in dissolving larger keratinocytes, making them flatter and limiting reflection of cell borders. Light microscopy is used to look for the presence or absence of fungal elements.<sup>39,60</sup> Although KOH is the most frequently used reagent, alternative reagents include sodium sulfide, sodium hydroxide, Parker blue black ink, or calcofluor white. Calcofluor white requires use of a fluorescent microscope for visualization.<sup>4,40</sup> Enhancement of KOH with chlorazol black E can increase sensitivity and cost-effectiveness.<sup>61</sup> Light microscopy with staining can be performed in the clinic in a matter of minutes; however, it lacks sensitivity, especially for detection of NDMs, cannot determine fungal viability or provide precise fungal identification, and is dependent on clinician expertise.<sup>4,62</sup>

## Fungal Culture

Fungal culture is the only technique that can identify both the organism and determine its viability. In the laboratory, sabouraud dextrose agar with cycloheximide (to encourage dermatophyte growth) or without cycloheximide (to culture NDMs) is used.<sup>63</sup> Chloramphenicol and gentamicin can be added to the agar to inhibit growth of bacterial contaminants.<sup>40</sup> The culture is grown at 25–30°C for up to a month. Alternatively, dermatophyte test medium is a simple and rapid method that can be utilized to culture dermatophytes. Alkaline metabolites are released upon growth of dermatophytes, with the increase in pH resulting in a color change from yellow to red approximately 10 to 14 days later.<sup>64</sup> There are high

**Table 1** Summary of the Diagnostic Testing Methods

Technique	Procedure	Advantages	Disadvantages	Sensitivity, % (Range) <sup>221,222</sup>	Specificity, % (Range) <sup>221,222</sup>	Turn Around Time	Fungal Viability	Fungal Identity
KOH and microscopy	<ul style="list-style-type: none"> <li>- Clean and clip the nail</li> <li>- Scrape the subungual debris onto a glass slide with a #11 curette</li> <li>- Add KOH to dissolve larger keratinocytes</li> <li>- Examine using light microscopy</li> </ul>	<ul style="list-style-type: none"> <li>- Performed quickly in the office</li> <li>- Inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>- Low sensitivity</li> <li>- Dependent on physician expertise</li> <li>- Fat droplets, air bubbles, and cotton fibers can interfere with the test</li> </ul>	61 (44–100)	95 (75–100)	Minutes to hours (depending on nail thickness)	No	No
Fungal culture	<ul style="list-style-type: none"> <li>- Clean and clip the nail</li> <li>- Scrape the subungual debris with a #11 curette onto a paper or cardboard with contrasting background</li> <li>- Grow in laboratory in sabouraud dextrose agar with or without cycloheximide</li> </ul>	High accuracy	<ul style="list-style-type: none"> <li>- High rate of false negatives</li> <li>- Delay in test results</li> <li>- Contaminants</li> </ul>	56 (29–82)	99 (83–100)	3–4 weeks	Yes	Yes
Histopathology	<ul style="list-style-type: none"> <li>- Nail is clipped and placed in 10% buffered formalin</li> <li>- Sample sent to laboratory for hematoxylin and eosin staining (to visualize fungal elements) and periodic acid-Schiff or Grocott methenamine-silver staining (to enhance visualization of the hyphae)</li> </ul>	<ul style="list-style-type: none"> <li>- Most sensitive technique</li> <li>- Can differentiate from other nail conditions</li> </ul>	Dependent on dermatopathologist expertise	84 (61–93)	89 (44–100)	Days	No	No
PCR	<ul style="list-style-type: none"> <li>- Clean and clip the nail</li> <li>- Scrape the subungual debris with a #11 curette onto a paper or cardboard with contrasting background</li> <li>- Send to specialized laboratory, where primers are used to amplify gene fragments</li> </ul>	<ul style="list-style-type: none"> <li>- Low rate of false negatives</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive</li> <li>- Contaminants</li> </ul>	85–100	94–100	Hours to days	No (Yes, for real-time PCR)	Yes

**Abbreviations:** KOH, potassium hydroxide; PCR, polymerase chain reaction.





**Figure 3** A nail clipper is used to clip the most proximal area of onycholysis.

rates of false-negatives (up to 40%) with fungal cultures, which can be even lower when there is residual antifungal medication and/or partial treatments.<sup>1,40</sup> Insufficient incubation time or temperature as well as the presence of more than one species in a sample may also contribute.<sup>64,65</sup> There is higher culture yield when there is adequate quantity of subungual debris for evaluation.<sup>66</sup>

## Histopathology

Histopathology is performed on nail plate clippings in 10% buffered formalin,<sup>4,53</sup> with turnaround time for results within days, and is more sensitive than both KOH and fungal culture.<sup>67</sup> It may also be more reliable in ascertaining whether the pathogen is permeating the nail plate or merely colonizing the nail.<sup>52</sup> Hematoxylin and eosin staining is used to visualize fungal elements. Periodic acid-Schiff (PAS) or Grocott methenamine-silver staining enhance visualization of the hyphae,<sup>1</sup> which are the preferred staining methods.<sup>68</sup> Immunofluorescence, Fontana-Masson, and Mayer mucicarmine stains can also be used.<sup>69</sup> Histopathology can identify yeast, spores, hyphae, and pseudohyphae,<sup>4</sup> but cannot identify or determine viability of the causative organism.<sup>1</sup> Histopathology can also differentiate between other nail conditions, such as nail psoriasis.

## PCR

PCR is a newer technique that uses specific primers to amplify DNA segments in order to identify dermatophytes, NDMs and *Candida* spp.<sup>1,40,70</sup> Common targets include a gene fragment of the fungal small ribosomal subunit 18s rRNA, the chitin synthase I gene, the topoisomerase II gene, or the internal transcribed spacer region of ribosomal DNA.<sup>70,71</sup> Distinction between yeasts, dermatophytes, and molds is possible by using  $\geq 2$  restriction enzymes to digest amplicons.<sup>72</sup> Results are available within 24 to 48 hours<sup>40</sup> and PCR is three to four times less likely than fungal culture to yield false-negatives.<sup>73</sup> Potential false-positive results with PCR are due to the stability of fungal DNA and possible contaminants.<sup>40</sup> The test is expensive compared to culture or microscopy,<sup>1</sup> however it is becoming more widely available and is covered by many insurance plans.<sup>4</sup> A similar technique is real-time PCR, which quantitates relative transcript amounts<sup>40</sup> and provides indirect information on fungal viability.<sup>74</sup> A commercial PCR kit is another alternative, which is more accessible than regular PCR, is

cost-effective, has high sensitivity and specificity for diagnosing onychomycosis, can reduce delays in diagnoses, and may be more accurate than fungal culture, especially in cases of NDM infections.<sup>75–77</sup>

## Artificial Intelligence (AI)

A convolutional neural network is a type of deep-learning algorithm that resembles the organization of the visual cortex<sup>78</sup> and has been used to diagnose a variety of dermatologic conditions, including psoriasis, melanoma, non-melanoma skin cancer, rosacea, and atopic dermatitis.<sup>79–84</sup>

AI has also been applied for diagnosis of onychomycosis.<sup>78,85,86</sup> In a prospective study of 90 patients with onychodystrophy of the toenails,<sup>78</sup> clinical photographs of the nails were taken by nonphysicians and evaluated clinically by five board-certified dermatologists (mean 5.6 years of experience), as well as by two board-certified dermatologists using dermoscopy and compared to AI to diagnose onychomycosis. KOH microscopy or fungal culture was used to confirm the diagnosis in all cases. The area under the curve (AUC) value of the AI [0.751; 95% confidence interval (CI), 0.646–0.856] was comparable to dermoscopy (0.755; 95% CI, 0.654–0.855) (Delong's test;  $p = 0.952$ ). The Youden index score (sensitivity+specificity-100%) of the AI (0.429) was also comparable to the mean Youden index score of the five board-certified dermatologists ( $0.230 \pm 0.176$ ) (Wilcoxon rank-sum test;  $p = 0.667$ ). In a study evaluating 1155 dermoscopic images (603 onychomycosis, 227 normal nails, 221 nail psoriasis, 104 traumatic onychodystrophy),<sup>85</sup> the diagnostic performances between the AI and 54 dermatologists were compared. There was high specificity (>82%) of diagnosing onychomycosis for five dermoscopic nail plate patterns, including jagged edge, longitudinal striae, marble-like turbid areas, distal irregular termination, and cone-shaped keratosis. The Youden index of the AI (0.715) was significantly higher than mean Youden index of 54 dermatologists ( $0.427 \pm 0.188$ ,  $0.444 \pm 0.172$ ) ( $p < 0.05$ ). Not all diagnoses were confirmed by histology and the study included resident physicians. In a study comparing the diagnostic accuracy of AI to four dermatopathologists,<sup>87</sup> 199 PAS-stained nail tissue samples were evaluated, with 101 positive and 98 negative for onychomycosis, respectively. The AUC of the AI was 98.1% (CI 96.1–99.8%), with two senior dermatopathologists having higher AUC and specificity and two junior dermatopathologists having lower AUC and specificity than the AI. All dermatopathologists had higher sensitivity than the AI. Therefore, the use of AI on whole-slide images is statistically non-inferior regarding AUC and specificity compared with dermatopathologists using a conventional analogous setting with a microscope. Together, these studies show that AI may be an emerging tool that can be used to diagnose onychomycosis effectively and objectively. Prior to widespread adoption of new AI tools for onychomycosis diagnosis, more prospective studies incorporating AI into routine clinical workflow are necessary.

## Treatment

Treatment for onychomycosis should be aimed at eliminating the fungal pathogen and restoring the normal state of the nail. This process can be quite slow, given that toenails and fingernails grow approximately 1 to 2 mm and 2 to 3 mm per month, respectively.<sup>88</sup> It is important to educate patients that confirmation of the diagnosis is relatively quick compared to the amount of time that they had the condition, and that it is necessary to make sure of the diagnosis before starting treatment rather than treating empirically.<sup>53</sup> Onychomycosis can mimic other benign conditions, including trauma, nail psoriasis, nail lichen planus, subungual exostosis, verruca, onychomatricoma, and bacterial infections, as well as malignant conditions, including squamous cell carcinoma and amelanotic melanoma.<sup>39</sup> Empiric antifungal treatment in these cases increases the risk of unnecessary side effects, would not improve, and may even worsen, benign conditions, and may increase morbidity and mortality in cases of malignant conditions.<sup>53</sup>

There are several treatment options available for onychomycosis, including oral and topical antifungals, device-based therapies (ie, lasers), surgical nail avulsion, nail debridement, and combination therapies.<sup>40,88,89</sup> Oral antifungals are generally recommended for moderate to severe onychomycosis and topical antifungals for mild to moderate disease<sup>2</sup> (Tables 2 and 3). Nail debridement can decrease fungal load and can be used as an adjunct with topical therapies,<sup>40</sup> while nail avulsion has limited use, primarily for cases of a painful and/or nongrowing single nail.<sup>90</sup> Laser therapies are United States (US) Food and Drug Administration (FDA) approved for temporary increases in clear nail; however, cure rates are lower than for oral and topical antifungals with less rigorous endpoints required by the FDA for approval and definitive guidelines for use are currently lacking.<sup>1,2,88</sup> Regardless, treatment plans should be individualized, with consideration of disease severity, infecting

**Table 2** Summary of Commonly Used Oral Onychomycosis Medications

Medication	Dosing, Fingernails	Dosing, Toenails	Mycologic Cure Rate (%), Fingernails	Mycologic Cure Rate (%), Toenails	Complete Cure Rate (%), Fingernails	Complete Cure Rate (%), Toenails	US FDA Approval
Terbinafine	250 mg daily for 6 weeks	250 mg daily for 12 weeks	79	70	59	38	Yes
Itraconazole	200 mg twice daily for 1 week separated by 3 weeks of washout for 2 treatment pulses	200 mg daily for 12 weeks	61	54	47	14	Yes
Fluconazole	150 mg weekly for 6–9 months	150 mg weekly for 12–18 months	NR	47–62	NR	37–48	No

**Abbreviations:** FDA, Food and Drug Administration; NR, not reported; US, United States.

**Table 3** Summary of FDA-Approved Topical Onychomycosis Medications

Medication	Dosing	Mycologic Cure Rate (%), Toenails	Complete Cure Rate (%), Toenails	Penetrates Nail Polish	Degrades Nail Polish	Debridement Recommended With Use	US FDA Approval
Ciclopirox lacquer	8% once daily for 48 weeks	29–36	5.5–8.5	NR	NR	Yes	Yes
Efinacazole solution	10% once daily for 48 weeks	53.4–55.2	15.2–17.8	Yes	Yes	No	Yes
Tavaborole solution	5% once daily for 48 weeks	31.1–35.9	6.5–9.1	Yes	No	No	Yes

**Abbreviations:** FDA, Food and Drug Administration; NR, not reported; US, United States.

pathogen, medication cost, and patient comorbidities, medication history, and likelihood of compliance.<sup>88,89</sup> Combination therapy should not be considered first-line treatment and should be reserved for patients with poor prognostic factors (ie, older age, immunosuppression, mixed infections) or for those who have failed monotherapy for onychomycosis.<sup>91</sup> In a systematic review of race reporting in onychomycosis clinical trials, less than a fifth (17.5%; 32/182) of trials reported on race and/or ethnicity, with only one trial comparing treatment efficacy in different subgroups.<sup>92</sup> Therefore, treatment recommendations garnered from these trials should be interpreted with caution in patients of color.

## Oral Therapies

Systemic medications are widely used for the treatment of onychomycosis due to their accessibility, high efficacy, and comparatively low cost.<sup>1,88</sup> Oral medications reach the nail bed systemically and must penetrate the ventral nail plate.<sup>1,93</sup> The amount of drug that can reach the infected site is therefore limited by low blood circulation to the nail bed.<sup>94</sup> Oral medications may have poor penetration of biofilms<sup>95</sup> and there is increased risk of serious side effects and drug–drug interactions.<sup>96</sup>

Currently, terbinafine, itraconazole, and griseofulvin are US FDA approved for onychomycosis treatment.<sup>88</sup> Griseofulvin is rarely used because it requires longer treatment durations, with lower efficacy and higher risk of adverse events and recurrence compared to other oral antifungals.<sup>90</sup> It is dosed at 375 up to 750 mg once daily for at least six months for toenails.<sup>2,97</sup> Fluconazole is not US FDA approved of onychomycosis treatment but is frequently used off-label.<sup>40</sup>

## Terbinafine

Terbinafine is an allylamine that inhibits squalene epoxidase, with broad-spectrum activity against dermatophytes and some activity against NDMs and *Candida* spp.<sup>98</sup> It is dosed at 250 mg daily for 6 and 12 weeks for fingernails and toenail infections, respectively.<sup>88</sup> The complete cure rates are 59% and 38% and the mycologic cure rates are 79% and 70% for fingernails and toenails, respectively.<sup>1</sup> Potential side effects are mild and include headaches, rashes, and gastrointestinal symptoms. Rarely, hepatotoxicity and taste disturbances can occur.<sup>88,99</sup> Although terbinafine-related hepatotoxicity is rare, patients are often hesitant to start terbinafine in fear of developing liver injury.<sup>100</sup> In an analysis of 35 websites with information on terbinafine,<sup>100</sup> only 51.4% provided accurate information on terbinafine-related hepatotoxicity and less



than a quarter (20.0%) stated that hepatotoxicity was rare. Few websites (11.4%) were authored by board-certified dermatologists. Therefore, accurate information regarding terbinafine-associated hepatotoxicity must be disseminated online in order to ease terbinafine fears and increase the likelihood of non-dermatologist providers and patients prescribing and accepting efficacious onychomycosis therapy, respectively.

According to the package insert, laboratory evaluation of liver function is recommended for all patients prior to initiating terbinafine therapy.<sup>101</sup> Periodic laboratory monitoring during terbinafine treatment for adults is controversial.<sup>102</sup> In a retrospective analysis of 944 adult patients taking a 12-week course of oral terbinafine for onychomycosis,<sup>103</sup> only 2.4% and 2.8% of patients had abnormal monitoring liver function tests (LFT) and complete blood count (CBC) results, respectively, and were threefold more likely to be  $\geq 65$  years old versus the overall study population. In a retrospective analysis of 4309 adults and children taking terbinafine for dermatophyte infections, 2006–2016,<sup>104</sup> grade 2 or higher monitoring ALT and AST elevations were found in only 0.2% and 0.07% of patients, respectively. Six patients (0.14%) discontinued treatment due to grade 1 to 3 terbinafine associated LFT abnormalities. In a retrospective review of the Taiwanese Longitudinal Health Insurance Database,<sup>105</sup> 12,376 patients took oral terbinafine with only two cases (0.016%) of drug-induced liver injury. Therefore, interval monitoring is unnecessary in healthy adults without preexisting hematologic and hepatic abnormalities but may be considered in older patients with comorbidities. There are fewer risk factors for terbinafine-induced hepatotoxicity in children, with no consensus regarding laboratory surveillance during treatment. In a retrospective analysis of 134 children prescribed terbinafine (average treatment course 8.2 weeks) for superficial fungal infections,<sup>106</sup> 0% and 1.7% had baseline and monitoring LFT elevations, respectively, and 3.9% and 4.4% had baseline and monitoring CBC elevations, respectively. All abnormal laboratory results were mild and resolved with treatment discontinuation or completion. In a retrospective review of 269 children prescribed terbinafine for onychomycosis,<sup>107</sup> 53.5% had laboratory monitoring of LFTs and/or CBC, with 23.6% before treatment and 70.8% before treatment and at 6 weeks. Most patients (87.5%) had normal laboratory results. Grade 1 abnormalities were noted in 8.3% and 4.2% of patients before or during therapy, respectively, with three patients discontinuing treatment. Therefore, monitoring tests in healthy children are also unnecessary. Baseline tests should be performed in both adults and pediatric patients to rule out pre-existing liver or hematologic diseases prior to initiating terbinafine treatment.

Terbinafine can be administered as pulse therapy as an off-label treatment option for onychomycosis and may be cost-effective and improve patient compliance.<sup>42,108</sup> These pulse-dosed regimens have been studied in clinical trials but are not US FDA approved.<sup>88</sup> In a meta-analysis evaluating different terbinafine treatment regimens for onychomycosis,<sup>109</sup> a pulsed regimen of two cycles of 250 mg/day for four weeks on and four weeks off had similar mycologic cure rates to continuous terbinafine [risk ratio (RR) for intention to treat: 0.94 (95% CI: 0.74–1.19,  $p = 0.6$ ,  $n = 2$ ); RR for evaluable patients: 1.01 (95% CI: 0.84–1.22,  $p = 0.92$ ,  $n = 2$ )]. Complete cure was also comparable to that of 12 weeks of continuous therapy (250 mg/day). In a systematic review of 30 studies comparing continuous and pulsed terbinafine regimens for treatment of onychomycosis,<sup>110</sup> there were no significant differences in mycologic cure or likelihood of experiencing adverse events for terbinafine administered continuously (250 mg for 12 weeks) or pulsed (500 mg daily for one week per month, pulsed 3 times). Therefore, for patients that are hesitant to accept treatment with terbinafine, pulse treatment regimens can be considered since safety and efficacy are comparable to continuous treatments.

## Itraconazole

Itraconazole is a triazole that inhibits lanosterol 14 $\alpha$ -demethylase and is efficacious against dermatophytes, *Candida* spp. and NDMs.<sup>111,112</sup> The dosing for toenails is 200 mg daily for 12 weeks and for fingernails is 200 mg twice daily for 1 week separated by 3 weeks of washout for 2 treatment pulses.<sup>88</sup> The complete cure rates are 47% and 14% and the mycologic cure rates are 61% and 54% for fingernails and toenails, respectively. Potential side effects include headaches, upper respiratory tract infections, gastrointestinal symptoms, hypertriglyceridemia, elevated transaminases, and rarely, peripheral neuropathy and hepatitis.<sup>1,88</sup> Drug–drug interactions are common and a thorough medication history should be performed prior to treatment initiation. Ventricular dysfunction, including congestive heart failure, is a contraindication to use.<sup>113</sup>

## Booster Therapy

Additional doses of terbinafine or itraconazole can be used as booster or supplemental therapy after completion of the original full antifungal course.<sup>1,88</sup> It may improve cure rates in onychomycosis patients with specific nail plate characteristics (lateral involvement, >2mm in thickness, >75% surface area involvement), slow growing nails, immuno-suppression, and matrix involvement.<sup>114,115</sup> The suggested dose is an additional four weeks of terbinafine or itraconazole six to nine months after the original initiation of antifungal treatment.<sup>116,117</sup> However, booster therapy has not been studied in clinical trials, but given the low risk of additional oral therapy, it may be warranted in challenging cases.

## Fluconazole

Fluconazole is a triazole that inhibits lanosterol 14 $\alpha$ -demethylase. It is approved for onychomycosis treatment in Europe and China and is used off-label in the US, with efficacy against dermatophytes, *Candida* spp., and some NDMs.<sup>1,88</sup> Due to a short residual concentration in the nails, longer treatment courses are necessary. Dosing for fingernails and toenails are 150 mg weekly for 6–9 months and 12–18 months, respectively.<sup>118,119</sup> It may be challenging to remember to take fluconazole on a weekly rather than daily basis; therefore, patients can implement a reminder text or alarm notification system on their mobile devices to increase medication compliance.<sup>120</sup> In a double blind, randomized study in 362 patients receiving fluconazole 150, 300, or 450 mg once weekly, complete cure rates were 37%, 46%, and 48%, respectively, for toenails at 12 months, with a low (4%) recurrence rate 6 months after treatment.<sup>121</sup> The most common side effects include nausea, rash, headache, abdominal pain, and elevated LFTs. Rarely, liver injury or failure can occur, but is more common in immunosuppressed patients.<sup>122</sup> Drug–drug interactions are also common, especially with warfarin and hypoglycemic agents.<sup>99</sup> Fluconazole has advantages over itraconazole, including absorption that is non-dependent on gastric pH or food, once-weekly dosing, and ability to use in patients with comorbidities, including cardiac dysfunction.<sup>123</sup> Prescribing patterns amongst dermatologists for fluconazole have trended upwards in recent years.<sup>124</sup>

In a 2017 Cochrane Review of 48 studies (10,200 participants) examining oral antifungal therapies for the treatment of toenail onychomycosis,<sup>125</sup> terbinafine and the azoles were more effective in achieving clinical cure (RR 6.00, 95% CI 3.96–9.08; RR 22.18, 95% CI 12.63–38.95, respectively) and mycologic cure (RR 4.53, 95% CI 2.47–8.33; RR 5.86, 95% CI 3.23–10.62, respectively) compared to placebo. There was moderate quality evidence that terbinafine was likely more effective than the azoles for achieving clinical cure (RR 0.82, 95% CI 0.72–0.95) and mycologic cure (RR 0.77, 95% CI 0.68–0.88). There were no differences in recurrence rates (RR 1.11, 95% CI 0.68–1.79) or the risk of adverse events (RR 1.00, 95% CI 0.86–1.1) between terbinafine and the azoles, with the most common adverse events being headache, nausea, and viral infection in both groups.

## Novel Oral Therapies

Recent attention has been given to novel oral therapies for use in onychomycosis treatment. Posaconazole is an extended-spectrum triazole that is approved in the US and Europe for oropharyngeal candidiasis and for prophylaxis of invasive fungal infections.<sup>126</sup> In a phase IIb, randomized, multicenter study,<sup>126</sup> 218 adult patients with toenail onychomycosis received posaconazole (oral suspension) 100, 200, or 400 mg once daily for 24 weeks, posaconazole 400 mg once daily for 12 weeks, oral terbinafine 250 mg once daily for 12 weeks, or placebo for 24 weeks. All posaconazole groups had significantly greater proportions of patients achieving complete cure vs placebo at 48 weeks ( $p \leq 0.012$ ). Patients receiving posaconazole 200 or 400 mg for 24 weeks had higher complete cure rates (54.1%, 45.5%, respectively) vs terbinafine (37%), while complete cure was lower for patients taking posaconazole 400 mg for 12 weeks (20%) ( $p > 0.05$ , all). Mycologic cure at week 48 for patients taking posaconazole 200 mg and 400 mg for 24 weeks (70.3%, 78.8%, respectively) was similar to terbinafine (71.4%), while mycologic cure was lower for patients taking posaconazole 100 or 400 mg for 24 weeks (37.1%, 42.9% respectively). Posaconazole was well tolerated, with only 3.8% (7/182) of patients withdrawing from the study due to asymptomatic elevations in transaminases.

Fosravuconazole L-lysine ethanolate (F-RVCZ) is an azole prodrug of ravuconazole with improved bioavailability and hydrophilicity that is approved in Japan (100 mg/day for 3 months) for onychomycosis treatment.<sup>127</sup> In a phase-III, multicenter, randomized, double-blind study,<sup>128</sup> 153 Japanese patients with toenail onychomycosis received either 100 mg F-RVCZ or

placebo once daily for 12 weeks. At 48 weeks, the complete and mycologic cure rates were significantly higher in the F-RVCZ group (59.4%, 82.0%, respectively) vs placebo (5.8%, 20.0%, respectively) ( $p < 0.001$ , both). Adverse drug reactions were mild and reported in 23.8% of patients taking F-RVCZ.

Oteseconazole is a tetrazole that inhibits the lanosterol demethylase (CYP51) enzyme, which is required to produce the membrane lipid ergosterol necessary for fungal survival. It is not yet US FDA approved for onychomycosis treatment, but has been studied in recent clinical trials.<sup>129</sup> In a phase II, multicenter, randomized, placebo-controlled, double-blind study,<sup>130</sup> 259 patients with toenail onychomycosis received either oteseconazole 300 mg or 600 mg once daily for 14 days, followed by a once-weekly dose for 10 or 22 weeks. At week 60, complete and mycologic cure rates were higher in the oteseconazole groups (41–45%, 65–75%, respectively) vs placebo (0%, 13%, respectively) ( $p < 0.001$ , all). All of these novel agents show promise as well-tolerated and efficacious onychomycosis treatment options but must be validated in phase III studies before widespread treatment recommendations can be made.

## Topical Therapies

Topical medications for onychomycosis treatment are becoming increasingly popular because they may penetrate biofilms, have lower risks of drug–drug interactions given there is little to no systemic absorption of the medication, and do not require laboratory monitoring.<sup>88,96,131,132</sup> Topical therapies must penetrate the nail plate to reach the transungual space where the fungus resides and applied concentrations must therefore be adequate to retain the minimal inhibitory concentration.<sup>1,93</sup> There are barriers to penetration, including slow growth and thickness of the nail, a hard nail plate that functions as a concentrated hydrogel, an impermeable dense network of keratin fibers, and nails in diseased states (ie, thickened nail or nail plates that are detached from the nail bed). Nail keratin can also adversely affect antifungal activity.<sup>93,133–136</sup> The newer topicals are costly and compliance may pose an issue due to lengthy treatment requirements (ie, 48 weeks for the toenails) and for patients with limited mobility and/or dexterity.<sup>1,88</sup> Clear instructions outlining medication usage should be disseminated to patients in addition to counseling about common adverse effects.<sup>137</sup> In a retrospective review of adverse events reported to the United States Food and Drug Administration Adverse Event Reporting database,<sup>137</sup> the most common adverse reactions reported with ciclopirox 8% nail lacquer, efinaconazole 10% solution, and tavaborole 5% solution were drug ineffectiveness, with nail discoloration and application site erythema reported with all three drugs. Currently, ciclopirox 8% nail lacquer is US FDA approved for the treatment of fingernail and toenail onychomycosis and efinaconazole 10% solution and tavaborole 5% solution are approved for toenail onychomycosis.<sup>40</sup> Amorolfine 5% nail lacquer is approved in Europe for onychomycosis treatment but is not available in the US.<sup>138</sup>

## Ciclopirox

Ciclopirox 8% nail lacquer is a hydroxypyridone that chelates trivalent cations, resulting in inhibition of metal-dependent enzymes.<sup>139</sup> It is effective against dermatophytes, *Candida* spp., and some NDMs and gram-positive and gram-negative bacteria.<sup>140</sup> In two double-blind, placebo-controlled studies of 460 patients with onychomycosis of the great toenails without lunula involvement treated with ciclopirox 8% nail lacquer for 48 weeks, complete cure rates were between 5.5–8.5% and mycologic cure rates were between 29%–36%.<sup>141</sup> A 2020 Cochrane Review found that ciclopirox 8% lacquer may be more effective than vehicle in achieving complete cure (RR 9.29, 95% CI 1.72–50.14) and mycologic cure (RR 3.15, 95% CI 1.93–5.12) based on two studies. There were little to no differences in adverse events observed (RR 1.61, 95% CI 0.89–2.9).<sup>142</sup> Efficacy is increased with weekly nail clippings and monthly office debridement.<sup>143</sup> Patients should be instructed to remove the lacquer with alcohol on a weekly basis.<sup>144</sup> Side effects are localized and include periungual erythema, burning, and application site reactions.<sup>88</sup>

## Efinaconazole

Efinaconazole 10% solution is a triazole that inhibits lanosterol 14a-demethylase, thereby disrupting ergosterol synthesis in the fungal cell membrane. It has activity against dermatophytes, *Candida* spp., and NDMs<sup>1</sup> and is the preferred treatment in cases of dermatophytoma.<sup>2,145</sup> In two multicenter, double-blind, randomized, vehicle-controlled phase III trials in 1665 patients (study 1:  $n = 870$ ; study 2:  $n = 785$ ) with DLSO of the toenail with 20–50% nail involvement,<sup>146</sup>

patients received efinaconazole or vehicle once daily for 48 weeks without debridement. Mycologic and complete cure rates were greater in efinaconazole (53.4–55.2%, 15.2–17.8%, respectively) vs vehicle (16.8–16.9%, 3.3–5.5%, respectively) groups (both  $p < 0.001$ ). Adverse events were application site reactions and ingrown toenails, which were similar to vehicle treated patients. A 2020 Cochrane Review found that efinaconazole was more effective vs vehicle in achieving clinical cure (RR 3.07, 95% CI 2.08–4.53, 2 studies), complete cure (RR 3.54, 95% CI 2.24–5.60, 3 studies) and likely mycologic cure (RR 2.31, 95% CI 1.08–4.94, 3 studies). There was a slightly higher risk of adverse events with efinaconazole compared to placebo (RR 1.10, 95% CI 1.01–1.20, 3 studies).<sup>142</sup>

Efinaconazole should be applied to the affected toenails once daily for 48 weeks, including the skin around the nails (nail folds, hyponychium, and ventral surface of the nail plate) to increase medication delivery.<sup>147</sup> In a study on human cadaver thumbnails painted with two coats of nail polish (three different brands),<sup>148</sup> permeation of efinaconazole was 0.56% of the applied dose on day seven, with cumulative concentrations of efinaconazole in the receptor using Franz diffusion cells ranging from 13.6–16.1  $\mu\text{g}/\text{cm}^2$  for polished nails versus 17.6  $\mu\text{g}/\text{cm}^2$  for unpolished nails. There were no significant differences in efinaconazole levels between polished and unpolished nails at all time points. Therefore, removal of nail polish prior to application is unnecessary since it can penetrate nails coated with polish.<sup>148</sup> However, the current formulation degrades nail polish.<sup>149,150</sup> In a study on 13 female patients with distal lateral subungual onychomycosis (DLSO) of at least 1 great toenail (thickness  $\leq 3$  mm) treated with daily topical efinaconazole 10% solution for 52 weeks,<sup>151</sup> average OSI scores in patients with concurrent nail polish use did not differ significantly from patients without nail polish use. Daily treatment with concurrent nail polish use was associated with diminished nail polish quality on average 60% of the time.

## Tavaborole

Tavaborole 5% solution is a benzoxaborole that inhibits fungal aminoacyl transfer RNA synthetase and therefore protein synthesis,<sup>152</sup> with broad-spectrum activity against dermatophytes, yeasts, and NDMs.<sup>1,88</sup> In two multicenter, randomized, double-blind, vehicle-controlled trials, 1194 patients with onychomycosis affecting 20–60% of the toenail without dermatophytoma or lunula involvement were treated with tavaborole or vehicle once daily for 48 weeks, with mycologic and complete cure rates between 31.1–35.9% and 6.5–9.1%, respectively.<sup>153</sup> A 2020 Cochrane review found that tavaborole is more effective than vehicle in achieving mycologic cure (RR 3.40, 95% CI 2.34–4.93) and likely complete cure (RR 7.40, 95% CI 2.71–20.24), but has a likely higher risk of adverse events (RR 3.82, 95% CI 1.65–8.85) based on two studies.<sup>142</sup>

Nail penetration of tavaborole is good due to its small size and hydrophilicity.<sup>154</sup> In a prospective study,<sup>155</sup> nails from cadaver donors were treated with 1, 2, or 4 coats of over-the-counter (OTC) or salon nail polish followed by tavaborole 5% topical solution applied to each nail once daily for 14 or 20 consecutive days. Tavaborole penetration through the nail was quantified using qualified liquid chromatography-tandem mass spectrometry and was compared to unpolished control nails. Mean cumulative tavaborole penetration on day 21 was higher for nails treated with 1 coat of OTC nail polish and tavaborole for 20 days ( $3526 \pm 1433 \mu\text{g}/\text{cm}^2$ ) vs unpolished nails ( $2661 \pm 1319 \mu\text{g}/\text{cm}^2$ ) ( $p > 0.05$ ). Mean cumulative tavaborole penetration on day 15 for nails treated with tavaborole and 1 or 4 coats of salon nail polish ( $1227 \pm 974 \mu\text{g}/\text{cm}^2$ ,  $1179 \pm 554 \mu\text{g}/\text{cm}^2$ , respectively) or 1 or 2 coats of OTC nail polish ( $1428 \pm 841 \mu\text{g}/\text{cm}^2$ ,  $1493 \pm 1322 \mu\text{g}/\text{cm}^2$ , respectively) for 14 days was higher vs control nails ( $566 \pm 318 \mu\text{g}/\text{cm}^2$ ), although significance was not assessed. Therefore, penetration is not significantly influenced by the application of cosmetic nail polish. Patients should be instructed to apply tavaborole daily for 48 weeks for toenail infections.<sup>40</sup> Side effects are local and include erythema, dermatitis, and exfoliation.<sup>156</sup>

## Amorolfine

Amorolfine 5% nail lacquer is a morpholine derivative that inhibits fungal enzymes 14- $\alpha$  reductase and 7,8 isomerase, thereby disrupting fungal sterol synthesis.<sup>157</sup> It has activity against dermatophytes, molds, and some yeasts.<sup>158</sup> In an open, randomized study of 456 patients with onychomycosis of the fingernails and/or toenails treated with amorolfine once or twice weekly for up to 6 months,<sup>159</sup> complete cure was 46.0% and 54.2%, respectively, and mycologic cure was 70.6% and 76.1%, respectively, after three months of treatment. Mild local irritation occurred in 0.9% of patients. In a randomized, double-blind study of 80 patients with toenail onychomycosis applying daily 5% amorolfine,<sup>160</sup> mycologic and complete cure rates were 60% and 38%, respectively. One patient reported mild burning sensation under the toenails. Amorolfine should be applied once or twice weekly to a cleaned nail plate and left for 3–5 minutes until dry. Organic

solvents should be avoided when removing the lacquer.<sup>161</sup> Since it penetrates the nail bed through the nail plate, concentrations remain for at least 14 days after application.<sup>162</sup>

## Novel Topical Therapies

Novel topical formulations for onychomycosis as alternatives to traditional topical treatments have been of recent interest. In a phase III, multicenter, randomized, double-blind study,<sup>163</sup> 365 patients (ages 12–74) with 20–60% distal and lateral subungual onychomycosis of at least one toenail received a once daily application of topical terbinafine (MOB-015 formulation) or matching vehicle for 48 weeks. At week 52, mycologic and complete cure were higher in the MOB-015 (69.9%, 4.5%, respectively) vs vehicle (27.7%, 0%, respectively) groups ( $p < 0.001$ ,  $p = 0.0195$ , respectively). Adverse events were mild to moderate and led to treatment discontinuation in 2.8% of patients in the MOB-015 group and 4.2% in the vehicle group. The formulation of the MOB-015 vehicle (urea, propylene glycol, lactic acid) may increase the opaqueness of the nail plate. These aesthetic color changes may interfere with analysis of complete cure and result in rates that were lower than expected.

Several other topical terbinafine formulations are still under investigation.<sup>1</sup> Ciclopirox hydrolacquer (P-3051) is another novel topical therapy that is not approved for onychomycosis treatment in the US, but is approved and marketed in more than 40 countries and is commonly used in Europe. It is made with hydroxypropyl chitosan, which forms an invisible film on the nail surface, prohibits fungal invasion, and facilitates nail penetration.<sup>164</sup> In a randomized, controlled, evaluator-blinded study,<sup>165</sup> 120 patients (ages 18–75) with toenail onychomycosis received a 48-week treatment course of once daily P-3051 or twice weekly amorolfine 5% nail lacquer. Complete and mycologic cure were higher in the P-3051 (35%, 100%, respectively) vs amorolfine (11.7%, 81.7%, respectively) groups ( $p < 0.001$ , both). No adverse events were serious or led to discontinuation in either group. Patient compliance is improved because P-3051 does not require nail filing before application and can easily be removed with water.<sup>165</sup> A 2020 Cochrane review found moderate-quality evidence from two studies (490 participants) that P-3051 is probably more effective than amorolfine 5% or ciclopirox 8% lacquer in achieving complete cure (RR 2.43, 95% CI 1.32–4.48) but not mycologic cure (RR 1.08, 95% CI 0.85–1.37). There was no differences in the risk of adverse events (RR 0.60, 95% CI 0.19–1.92), with the most common being rash, burning, and erythema.<sup>142</sup>

## Over-The-Counter Treatments

Recent attention has been given to natural remedies and OTC treatments for onychomycosis.<sup>166</sup> Tea tree oil (TTO) is a volatile oil that is used in Australia, Europe, and North America for treatment of tinea pedis.<sup>167</sup> In *C. albicans*, TTO has been shown to decrease glucose-induced acidification of media surrounding fungi and alter respiration and permeability of plasma membranes.<sup>168–170</sup> In a randomized, multicenter, double-blind trial of 117 patients with DLSO of the toenails who applied either TTO 100% or clotrimazole solution 1% twice daily for 6 months,<sup>171</sup> culture cure did not significantly differ between groups (18% vs 11%, respectively). Irritation and erythema occurred in 7.8% (5/64) of the TTO group. In a double-blind, placebo controlled study of 60 patients with DLSO who applied either cream containing TTO 5% and butenafine hydrochloride 2% ( $n = 40$ ) or a control cream containing only TTO ( $n = 20$ ) three times daily for eight weeks,<sup>172</sup> complete cure was 80% in the active group vs 0% in the placebo group ( $p < 0.0001$ ). Mild skin inflammation occurred in 10% of the active group patients.

Topical cough suppressants have also been used as home remedies for onychomycosis. The active ingredients are eucalyptus oil 1.2%, camphor 4.8%, and menthol 2.6%, and the inactive ingredients are nutmeg oil, cedarleaf oil, thymol, petrolatum, and turpentine oil.<sup>166</sup> In a pilot study of 18 adult patients with toenail onychomycosis who applied topical cough suppressants (Vicks VapoRub; The Proctor & Gamble Company, Cincinnati, OH) once daily,<sup>173</sup> 27.8% (5/18) had mycologic cure, 22.2% (4/18) had complete clinical cure, 55.6% (10/18) had partial clinical cure, and 16.7% (3/18) had no clinical improvement. The average ratio of affected to total nail area decreased from 63% to 41% ( $p < 0.001$ ) and there were no adverse events reported with treatment. Complete clinical cure was achieved in 83.3% (5/6) participants positive for either *C. parapsilosis* ( $n = 3$ ) or *T. mentagrophytes* ( $n = 3$ ), versus in none of the 12 participants with other organisms cultured (6 *T. rubrum*, 2 fungal elements, 1 *Cryptococcus lomentii*, 1 *C. albicans*, 1 *Penicillium* spp., 1 *Fusarium* spp.) ( $p < 0.001$ ). In a single-site, prospective pilot study of 20 HIV-positive patients with onychomycosis who



applied topical Vicks VapoRub (The Proctor & Gamble Company, Cincinnati, OH) daily,<sup>174</sup> 83% (15/18) had improvements in affected nails (median clearance 25%; range 6.3–87.5%) at week 24, with total resolution of infection in two participants. At 48 weeks, 53% (8/15) had stable or improved clearance of affected nails. No fungal organisms were identified in this study. There were no reported side effects.

Natural coniferous resin, derived from the Norway spruce tree (*Picea abies*) and mixed with boiled butter or animal fat, has been used for centuries to treat wounds and infections.<sup>166</sup> In a prospective, randomized, controlled, investigator-blinded study,<sup>175</sup> 73 patients with toenail onychomycosis received either natural coniferous resin 30% once daily for 9 months, amorolfine lacquer 5% once weekly for 9 months, or 250 mg oral terbinafine once daily for 3 months. At 10 months, mycologic cure rates were 13% (95% CI, 0–28%), 8% (95% CI, 0–19%) and 56% (95% CI, 35–77), respectively ( $p \leq 0.002$ ). Patient compliance was 100% in the resin group, with no treatment related adverse events.

*Ageratina pichinchensis* (AP) extract has been used historically in Mexico for fungal infections<sup>176</sup> and has shown efficacy in treating tinea pedis.<sup>177</sup> In a double-blind, randomized, controlled trial,<sup>178</sup> 110 patients with toenail onychomycosis received six months of either AP lacquer ( $n = 55$ ) or ciclopirox 8% lacquer ( $n = 55$ ). Clinical effectiveness (completely normal nails) was 71.1% and 80.9%, respectively ( $p = 0.596$ ), and mycologic cure was 59.1% and 63.8%, respectively ( $p = 0.328$ ). There were no serious adverse events in either group.

Ozonized sunflower oil is a petroleum jelly-like material created by the reaction of ozone with sunflower plant (*Helianthus annuus*) oil<sup>179</sup> and has clinical implications in Cuba for the treatment of impetigo and tinea pedis.<sup>180</sup> In a single-blind, controlled, phase III study,<sup>180</sup> 400 patients with onychomycosis received either ozonized sunflower oil solution or ketoconazole cream 2% twice daily for three months. Improvement in nail condition and cure were seen in 9.5% and 90.5% of the sunflower oil group, respectively, and in 27.5% and 13.5% of the control group ( $p < 0.0001$ ).

Limitations to these studies on natural or OTC therapies include their small number of participants and differences in trial design that prohibit comparison of results across studies or with other treatments.<sup>166</sup> Many studies did not identify fungal organisms, calling into question whether these patients did indeed have onychomycosis. Although they appear to exhibit good tolerability and safety, more research is needed to demonstrate efficacy in larger randomized controlled trials. Physicians should inquire if patients are using or have tried any OTC or natural remedies for self-treatment of onychomycosis, as these compounds may have important pharmacological interactions with prescribed antifungals.

## Devices

### Laser Therapies

Lasers were approved by the US FDA in 2012 for temporary increases in clear nail. Short-pulsed and Q-switched 1064 nm Nd:YAG lasers have been approved, although others, including carbon dioxide and the diode 870, 930 nm laser, are in development.<sup>1</sup> A 2020 Cochrane review found low-quality evidence from two studies (85 participants) that there are little or no differences in mycologic cure at 52 weeks between 1064-nm Nd:YAG laser and no/sham treatment (RR 1.04, 95% CI 0.59–1.85). It was uncertain whether there were differences in adverse events.<sup>142</sup> In a review comparing improvement rates to laser therapies ( $n = 2$  studies) versus those of FDA-approved oral and topical onychomycosis therapies ( $n = 21$  studies),<sup>181</sup> laser treatment was associated with lower mycologic cure rates (11%) vs oral and topical therapies (29–61%).<sup>181</sup> In a retrospective review of 23 patients with onychomycosis treated with Nd:YAG 1064-nm laser and debridement,<sup>182</sup> 78% of patients had temporary improvement in target nail appearance, 46% had  $\geq 50\%$  decrease in nail involvement from baseline, 17% had  $< 10\%$  surface area involvement at last clinical assessment, and only 9% achieved clinical cure. Therefore, laser treatments may be beneficial for achieving temporary improvements in nail appearance but there is limited evidence that they can maintain clinical improvements or eradicate pathogenic fungi. Importantly, inclusion criteria, endpoints, and definitions of efficacy outcomes vastly differ between clinical trials for lasers and oral and topical therapies for onychomycosis, making comparisons across studies difficult and unreliable.<sup>88,183</sup> Lasers are attractive in that there is minimal potential for systemic adverse events, given that they target the infecting fungi on the nail plate, and require a lower degree of patient compliance since they are administered by the physician.<sup>40</sup> The laser should be delivered at a wavelength of 750–1300 nm in order to penetrate the nail and the pulse duration period should be shorter than the thermal relaxation time of the pathogen.<sup>40</sup> There are important disadvantages to laser

treatment, including the requirement for multiple treatment sessions (up to 19 months),<sup>181</sup> the high expense of therapy, costing on average \$400-\$1200 per treatment session and usually not covered by insurance,<sup>184</sup> and the significant transient pain and discomfort patients may experience during the procedure.<sup>185</sup>

## Photodynamic Therapy

Photodynamic therapy (PDT) is another non-invasive device-based treatment that is US FDA approved for treatment of actinic keratoses and is used off-label for onychomycosis. It combines light-based modalities with photosensitizers, such as 5-aminolevulinic acid, methyl aminolevulinate or methylene blue.<sup>1,186,187</sup> This results in the production of reactive oxygen species and free radicals, which exhibit antimicrobial properties in addition to being cytotoxic and inducing apoptosis in fungal cells.<sup>188,189</sup> There have been few studies evaluating PDT for the treatment of onychomycosis. In a prospective, open, single center study of 30 patients with DLSO caused by *T. rubrum* treated with three PDT sessions,<sup>187</sup> clinical cure rate at 18 months was 36.6%. In an open label, controlled study of 22 patients with mild/moderate (n = 11) or severe (n = 11) toenail onychomycosis treated with two sessions of PDT,<sup>186</sup> mycologic cure rate was 100% in both groups and complete cure rates were 100% and 63.6%, respectively. PDT has limited utility for onychomycosis treatments because it requires numerous treatment sessions, pretreatment with urea or nail avulsion, and causes pain.<sup>88</sup> More extensive randomized controlled trials in larger patient populations are required before PDT can be recommended for routine off-label use for onychomycosis treatment.

## Plasma Therapy

Non-thermal plasma (NTP), or low-temperature plasma, is an emerging tool that has been studied for treatment of onychomycosis. NTP is created from short pulses (approximately 10 ns) of strong (approximately 20 kV/mm peak) electric fields, which results in generation of active chemical species, including ions, electrons, nitric oxide, ozone, and hydroxyl radicals. Given its small current and duration, there is limited tissue heating.<sup>190–192</sup> In a study evaluating the efficacy of NTP in treating onychomycosis caused by *C. albicans* and *T. mentagrophytes* in an in-vitro toe/nail-plate model,<sup>190</sup> 12 minutes of NTP resulted in complete killing at doses of 39 and 15 kPulses, respectively. In a pilot study on 19 patients with DLSO affecting 25–50% of at least one great toenail treated with three weekly NPT sessions,<sup>191</sup> overall clinical cure and mycologic cure were 53.8% and 15.4%, respectively. Singeing of the nail due to a faulty electrode was the only treatment-related adverse effect in one patient, with no long-term sequelae. In 40 patients with toenail onychomycosis treated with nail plate abrasion and refreshment (NPAR) alone (n = 12), NPT combined with NPAR (n = 17), or NPT combined with antimycotics (n = 11),<sup>193</sup> mycologic cure was achieved in 85.7% of patients treated with NPAR and NPT combination therapy. Moderate clinical improvement was observed in 50% and 36.4% of patients treated with NPAR monotherapy and NPT/antimycotic combination therapy, respectively. Therefore, NPT is a non-invasive therapeutic tool that may synergistically improve onychomycosis treatment but requires validation in larger randomized controlled trials.

## Microdrilling

Nail drilling regimens have been investigated to improve penetration of medications through the nail plate. In an open comparative study of 98 patients (106 infected nails) with toenail DLSO treated with nail drilling and combination (oral and topical terbinafine) therapy (group 1), nail drilling and topical terbinafine (group 2), and topical terbinafine only (group 3),<sup>194</sup> group 1 and group 2 had significant improvement in percent clear nail (80.39%, 73.73%, respectively) compared to group 3 (48.52%) at 28 weeks (p < 0.001). Mycologic cure rate was higher in group 1 (47.1%) compared to group 2 (34.2%) and group 3 (8.0%). Overall, treatment was well tolerated; however, pain was higher in patients treated with nail drilling vs topical treatment only (p = 0.040). Therefore, antifungal treatments in combination with nail drilling may improve treatment efficacy.

## Combination Treatments

Combination therapy for treatment of onychomycosis is attractive in that it has potential for drug synergy and prevention of antifungal resistance.<sup>195</sup> However, it is not well studied and standardized treatment regimens have not been established. In a systematic review of 30 onychomycosis clinical or randomized controlled trials [15 medication only

studies, 15 medication and procedural (laser, debridement, PDT) studies],<sup>91</sup> significant clinical benefit of medication combination therapy vs monotherapy was observed in more than half (60%) of studies. However, trials were not robustly designed and lacked sufficient follow-up compared to pivotal monotherapy trials. Almost all (93.3%) procedural and medication combination therapy studies showed benefit over monotherapy studies; however, long-term follow-up was insufficient and efficacy was not upheld in severe cases of onychomycosis. Given the cost of combination treatment, potential for drug–drug interactions, and lack of robustly designed randomized controlled trials with long-term follow-up, combination therapy should be reserved as a second-line treatment option in patients with poor prognostic factors or resistant cases of onychomycosis.

## Treatment in Children

There are no US FDA approved systemic therapies to treat onychomycosis in children, although terbinafine, itraconazole, and fluconazole are used-off label.<sup>196</sup> In a retrospective review of 26 studies (18 case reports, 5 clinical trials, 3 retrospective analyses) evaluating systemic treatment of onychomycosis (terbinafine, itraconazole, griseofulvin, and fluconazole) in children, 1976–2011,<sup>197</sup> the complete cure rate was 70.8%, with a safety profile similar to the adult population. Topical tavaborole 5% and efinaconazole 10% solution are US FDA approved for treating onychomycosis in children ages  $\geq 6$  years old. Topical ciclopirox 8% nail lacquer is US FDA approved for children  $\geq 12$  years old.<sup>198</sup> There is no data on the efficacy of medical devices for treating pediatric onychomycosis.<sup>40</sup>

### Oral Terbinafine

In 17 children receiving continuous oral terbinafine (dosage based on body weight) for 12 weeks,<sup>199</sup> 88.2% (15/17) achieved mycologic cure within one to five months after treatment discontinuation. In 14 children treated with terbinafine for two to five months,<sup>200</sup> mycologic and complete cure were observed in 77% and 62% of patients, respectively. There were no serious or adverse side effects reported in either study.

### Oral Itraconazole

In 18 children receiving itraconazole 200 mg once daily for 12 weeks,<sup>199</sup> 94.7% (18/19) achieved mycologic cure. In 27 children treated with itraconazole (16 continuously, 11 pulsed) for 2–4 months,<sup>200</sup> mycologic and complete cure were observed in 84% and 76% of patients, respectively. One patient had mild elevations in transaminases, and one patient discontinued treatment due to ataxia. In one child with onychomycosis due to *T. rubrum* treated with continuous itraconazole therapy (5 mg/kg/day) for 12 weeks,<sup>201</sup> mycologic cure and clinical cure were observed at 12 months follow-up. The capsule formulation of itraconazole may be difficult for children to swallow; it can be broken and the granules mixed with food, such as apple sauce or mashed potatoes. The oral suspension (10 mg/mL) should be administered under fasting conditions for better bioavailability.<sup>202,203</sup>

### Oral Fluconazole

In two children with toenail onychomycosis treated with fluconazole 200 mg or 300 mg once weekly for 20 weeks,<sup>204</sup> both achieved clinical cure.

### Topical Ciclopirox

In a prospective, randomized, double-blind, vehicle-controlled study,<sup>205</sup> 37 children with toenail onychomycosis received either ciclopirox lacquer or vehicle lacquer daily for 32 weeks, with weekly removal of the lacquer and mechanical trimming. Children receiving vehicle treatment with poor responses (Investigator Global Assessment score  $>3$  or positive fungal culture at week 8) were crossed over to the ciclopirox group at week 12. At 12 and 32 weeks, mycologic cure was higher in the ciclopirox group (70%, 77.1%, respectively) vs the vehicle group (20%, 22.0%, respectively) ( $p = 0.03$ ). Nail plate discoloration was the only adverse event and was reversed after weekly use of acetone-free nail polish remover. No patients discontinued treatment.

## Topical Efinaconazole

In a Phase 4, open-label, multicenter study in 62 children with mild-to-severe toenail DLSO treated with efinaconazole once daily for 48 weeks,<sup>206</sup> mycologic and complete cure were 65% and 40%, respectively. Clinical efficacy, defined as affected target great toenail area <10%, was achieved in 50% of participants. Systemic exposure was low, with average area under the concentration-time curve of 11.4 ng\*h/mL and maximum plasma concentration of 0.549 ng/mL. All treatment-emergent adverse events (TEAEs) were mild or moderate, with the most common being nasopharyngitis in 18 participants. No TEAEs resulted in study discontinuation.

## Topical Tavaborole

In an open-label, single arm study of 55 children with toenail DLSO who applied tavaborole once daily (2 drops/great toenail, 1 drop/other toenails) for 48 weeks,<sup>207</sup> mycologic and complete cure were achieved in 36.2% and 8.5% of patients, respectively, at 52 weeks. After 28 days of daily dosing, tavaborole was detected in plasma and was at steady state. TEAEs were reported in 55.6% of patients, with the most common being nasopharyngitis, contusion, sinusitis, and vomiting. No deaths or permanent discontinuations occurred due to TEAEs. Appendicitis was the only serious adverse event but was deemed unrelated to treatment.

## Elderly Adults

In a single blind, randomized, prospective study evaluating the efficacy of continuous terbinafine (250 mg/day for 12 weeks) and pulse itraconazole (200 mg twice a day for 1 week x 3 pulses) in treating toenail onychomycosis in 101 elderly ( $\geq 60$  years old) patients,<sup>116</sup> mycologic cure and clinical efficacy at 18 months were 64.0% and 62.0%, respectively, for terbinafine, and 62.7% and 60.8%, respectively, for itraconazole, with no significant differences between the two groups. At six months, 26% (13/50) of terbinafine patients were given an extra 4 weeks of terbinafine therapy and 45% (23/51) of itraconazole patients were given an extra pulse since they had <50% reduction in affected nail plate area or <3mm outgrowth of unaffected nail plate. All adverse events were mild and transient. In a sub analysis of an open label, randomized, multicenter study of patients  $\geq 65$  years old with toenail onychomycosis treated with terbinafine (250 mg/day for 12 weeks) with or without toenail debridement,<sup>208</sup> mycologic and complete cure at 48 weeks were 64% and 28%, respectively, in patients treated with terbinafine alone ( $n = 34$ ) and 63.4% and 39%, respectively, in patients treated with terbinafine + debridement ( $n = 41$ ). Nausea (4%), sinusitis (4%), arthralgia (2.7%), and hyperlipidemia (2.7%), were the most common adverse events. In a subgroup analysis of a multicenter (36 sites), open-label, single-arm study of 219 Japanese patients with severe (>50% clinical involvement) toenail onychomycosis receiving daily efinaconazole 10% solution for up to 72 weeks,<sup>209</sup> treatment success rate (<10% clinical involvement of the target toenail) was 54.2% in the elderly (aged  $\geq 65$  years) and 59.4% in the non-elderly (aged <65 years). Overall, 6.4% of patients reported local site reactions, with all resolved or recovered during treatment or after discontinuation of the medication.

Elderly patients have specific risk factors that predispose to poor responses to antifungal therapy, including slow nail growth, recurrent nail dystrophy, and increased prevalence of diabetes mellitus and peripheral vascular disease.<sup>210</sup> A large proportion of the elderly population is on multiple drug therapy secondary to numerous comorbidities. Therefore, topical therapy alone is the preferred method of treatment in this select group.<sup>2</sup> If systemic treatment is required, oral terbinafine should be first line due to decreased risk of drug–drug interactions compared to the azoles.<sup>196</sup>

## Pregnant and Lactating Women

Pregnant and lactating women are often excluded from onychomycosis clinical trials, precluding the ability to make treatment recommendations in this population. Oral itraconazole is pregnancy class C and oral fluconazole is pregnancy class D when >1 dose is consumed. Neither should be used during pregnancy.<sup>88,196</sup> Oral itraconazole should be avoided for 2 months before planning pregnancy and oral fluconazole is secreted into breast milk and therefore should not be started until breastfeeding is complete.<sup>88</sup> Oral terbinafine is pregnancy class B and is excreted into breast milk, with a ratio of terbinafine in milk to plasma of 7:1. Since there is limited data and therapy for onychomycosis is non-emergent, initiation of oral terbinafine should be avoided during pregnancy or while nursing.<sup>101</sup> Topical ciclopirox is pregnancy

category B but it is unclear whether it is excreted into breast milk and should therefore be deferred in people who are pregnant or lactating.<sup>141</sup> Topical efinaconazole is pregnancy class C due to embryotoxicity in rats and therefore should not be used during pregnancy. It was found in milk of nursing rats receiving repeated subcutaneous doses, and although there is no data in human milk, efinaconazole should not be used during breastfeeding.<sup>88,146,211</sup> Topical tavaborole is pregnancy category C, with no data in pregnant women or during lactation and should therefore be avoided in these patients.<sup>153</sup>

## Prevention of Recurrence

After initial onychomycosis treatment, recurrences are reported at a rate of 20–25%, including relapse (same infection after incomplete cure) or reinfection (same infection after complete cure).<sup>10,212,213</sup> Patients with genetic predispositions, positive family histories of onychomycosis, and those with immunosuppression are more susceptible to recurrences.<sup>214,215</sup> Biofilms may also contribute by shielding fungal organisms.<sup>38</sup> Patient education and pharmacological intervention are paramount to preventing recurrence.<sup>1</sup> In a retrospective chart review (2010–2015) on 320 patients with complete cure treated with oral terbinafine or itraconazole for toenail onychomycosis who then used a topical antifungal for prophylaxis,<sup>216</sup> the recurrence rate was significantly lower in patients with topical antifungal prophylaxis vs no prophylactic treatment following oral terbinafine ( $p < 0.001$ ) but not itraconazole ( $p = 0.185$ ). Overall, regardless of initial oral treatment, the use of topical antifungals as prophylaxis significantly decreased the likelihood of recurrence ( $p < 0.001$ ). After steady-state levels of the antifungal agent have been achieved in the nail plate, twice weekly application of a topical antifungal can be used for prophylaxis,<sup>217</sup> however, the ideal duration for prophylaxis is uncertain and may be a life-long requirement.<sup>88</sup> Patients should also be counseled on lifestyle modifications to prevent recurrence, including keeping the feet cool and dry, avoiding occlusive footwear, discarding or treating infected footwear with topical antifungals, ultraviolet light, or ozone, discarding or treating infected socks by washing with hot water, trimming the nails short to avoid trauma, using flipflops in wet and public spaces, and promptly treating affected family members.<sup>215,216,218–220</sup>

## Conclusion

Onychomycosis is the most common nail disease encountered in clinical practice and can significantly impair QoL, with patients experiencing pain, difficulty with ambulation, and social stigmata. Following history and physical examination, dermoscopy can be used to differentiate onychomycosis from other nail diseases, with definitive diagnosis made with KOH and microscopy, fungal culture, histopathology, PCR, or a combination of techniques. AI is a newly emerging tool for diagnosis that requires further validation before it can be used in clinical practice. Onychomycosis is highly treatable and a variety of therapies can be utilized, including oral and topical medications as well as device-based treatments. Systemic treatments have higher cure rates, while topical treatments have more favorable safety profiles. Device-based therapies require investigation with similar endpoints to those used in oral and topical medication clinical trials to make accurate comparisons. Patients should be counseled about recurrences and be started on a topical antifungal prophylaxis to minimize recurrence risk. Future research should focus on establishing robustly designed clinical trials in diverse patient populations to further investigate novel therapies and determine optimal and standardized guidelines for combination treatment.

## Abbreviations

NDM, non-dermatophytes molds; US, United States; QoL, quality of life; KOH, potassium hydroxide; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; AI, artificial intelligence; AUC, area under the curve; US, United States; FDA, Food and Drug Administration; LFT, liver function test; CBC, complete blood count; RR, risk ratio; F-RVCZ, Fosravuconazole L-lysine ethanolate; DLSO, distal lateral subungual onychomycosis; OTC, over the counter; TTO, tea tree oil; AP, *Ageratina pichinchensis*; PDT, photodynamic therapy; NTP, non-thermal plasma; TEAEs, treatment-emergent adverse events.

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