Update on Diagnosis, Treatment, and Management of Onychomycosis

A review of the importance of confirming diagnosis and a look at the efficacy of approved therapies.

BY ROBERT HIGHAM, PA-C, NICOLE GELLINGS LOWE, PHD, AND NEAL BHATIA, MD

Onychomycosis is a common fungal nail infection caused primarily by dermatophytes, yeast, and nondermatophytic molds.\(^1,2\) It affects people from all walks of life, and as a result, it is commonly seen in clinical practice. Prevalence of the infection increases with age, and it affects males more than females; however, women tend to seek treatment more frequently than men.\(^1,2\)

There are a variety of risk factors associated with onychomycosis, including family history of onychomycosis,\(^3\) nail trauma,\(^4\) older age,\(^1,2\) male sex,\(^5,15\) high-risk exposure (e.g., communal showers, gyms, and public pools),\(^6,7\) as well as hot and humid climates.\(^8\)

An increased risk of contracting onychomycosis is seen in patients with diabetes, peripheral arterial disease, and/or moccasin type tinea pedis.\(^1,9–13\) Factors contributing to the recurrence of onychomycosis are reviewed in Table 1.

**DIAGNOSTIC TESTS FOR ONYCHOMYCOSIS**

**Visual Diagnosis.** Onychomycosis appears clinically as white/yellow or orange/brown patches or streaks and may be accompanied by onycholysis, subungal hyperkeratosis, and/or nail-plate thickening. Although studies suggest there is about an 80 percent accuracy rate of visual diagnosis alone, there are a number of nail anomalies that can mimic these clinical features so laboratory confirmation of onychomycosis is necessary (Table 2).\(^14\)

**Potassium Hydroxide and Periodic Acid-Schiff Stain.** The quickest diagnostic tests (one to two days) are Potassium Hydroxide (KOH) and Periodic Acid-Schiff Stain (PAS).\(^15\) Direct microscopy examination of a KOH-prepared nail sample is simple, inexpensive, and can be performed in the office.\(^16\) PAS of formalin-fixed toenail debris/clippings can be sent to an off-site laboratory. KOH and PAS are sensitive for fungal pathogens at rates of up to 93 percent, but neither can identify the fungal

---

**TABLE 1: FACTORS CONTRIBUTING TO RECURRENCE OF ONYCHOMYCOSIS\(^1\)**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic susceptibility</td>
</tr>
<tr>
<td>Concomitant disease</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td>Trauma, faulty biomechanics</td>
</tr>
<tr>
<td>Moisture/exposure</td>
</tr>
<tr>
<td>Tinea pedis</td>
</tr>
<tr>
<td>Incorrect dosage/treatment time too short</td>
</tr>
<tr>
<td>Poor patient compliance/hygiene/choice of footwear</td>
</tr>
</tbody>
</table>

**TABLE 2: DIAGNOSTIC TESTS FOR ONYCHOMYCOSIS**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (percent)</th>
<th>Specificity (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>77</td>
<td>47</td>
</tr>
<tr>
<td>KOH</td>
<td>67-93</td>
<td>38-78</td>
</tr>
<tr>
<td>Culture</td>
<td>31-59</td>
<td>83-100</td>
</tr>
<tr>
<td>Periodic acid-Schiff stain</td>
<td>92</td>
<td>72</td>
</tr>
</tbody>
</table>
pathogen. These tests check for fungal debris, but do not detect whether the fungus is viable or not.16

**Fungal Culture.** Identifying the exact microorganism causing the infection may be necessary in situations where onychomycosis is not responding to treatment or an uncommon causative agent is suspected.17,18 Fungal culture of the subungal debris is the “gold standard” for specificity of a pathogen; however, it can take up to four weeks and false-negative results are common.16,19

**Polymerase Chain Reaction.** Polymerase Chain Reaction (PCR) for detection of fungal pathogens is not currently widely accessible or practical due to cost. PCR has the potential to generate false-positives because it amplifies fungal DNA, which is present regardless of fungal viability.20 As a result, other diagnostic options are more pragmatic.

**Proving Your Diagnosis.** Correct diagnosis is crucial when treating onychomycosis. Treatment is long and potentially costly, non-fungal causes are common,6,17,18 and misdiagnosis may compromise the patient’s perception of therapeutic benefit. Citing inappropriate risks for the side effects of antifungal therapy, the American Academy of Dermatology specifically recommends, ”Don’t prescribe oral antifungal therapy for suspected nail fungus without confirmation of fungal infection.”21 Finally, mixed infection may occur as a patient may have psoriasis and onychomycosis, or onychomycosis obscuring an underlying tumor, among other possible complications.1

**TREATMENT STRATEGIES**

Unlike dermatophytoses of other body sites, onychomycosis can be difficult to treat.22 Normal toenails will not appear until the fungus is eradicated and the damaged nail has grown out (i.e., 12-18 months).23 Even after successful treatment, the nail may be left abnormal from residual changes that may be unrelated to the infection (e.g., onychoschizia) or the results of damage to the nail unit from long-standing disease (e.g., onycholysis).24 Finally, 20-25 percent of patients are considered poor responders or non-responders to treatment.1

There are a variety of treatment options to consider. The only FDA-approved treatments are oral (terbinafine, itraconazole, griseofulvin) and topical (ciclopirox, efinaconazole, and tavaborole). All these treatments underwent Phase 3 clinical trials mandated by the FDA. Below we discuss itraconazole, terbinafine, tavaborole, and efinaconazole, which were all evaluated by at least two endpoints after 52 weeks: negative mycology (negative KOH and negative fungal culture) and complete cure (negative mycology plus a completely clear nail).

Over-the-counter treatments do not have documented clinical evidence supporting their efficacy.24 Additionally, while laser treatments for onychomycosis are common, their FDA-approved indication is for use in the temporary increase of clear nail in patients with onychomycosis. The evidence pertaining to their effectiveness in eradication of the fungus is limited and of poor methodological quality.25-26

**Oral Treatments**

The most common oral treatments for onychomycosis are terbinafine and itraconazole. Both medications have relatively short treatment courses (i.e, 12 weeks). Compared to other treatment options, terbinafine and itraconazole yielded high negative mycology rates (54 percent and 70 percent, respectively) and complete cure rates (14 percent and 38 percent, respectively) in toenail onychomycosis when evaluated in Phase 3 studies.27–29 The disadvantages associated with terbinafine and itraconazole come from their significant adverse events profiles. In particular, terbinafine is associated with the risk of drug interactions and hepatotoxicity.29 Itraconazole carries a black box warning for congestive heart failure, cardiac effects, and drug interactions.28

**Topical Treatments: Tavaborole and Efinaconazole**

Tavaborole, 5%, and efinaconazole, 10%, are solutions applied to the nail plate, nail folds, and the hyponicium. Both treatments should be applied once daily. Treatments continued for 48 weeks in Phase 3 trials, but based on your clinical judgement, longer treatment periods may be necessary. Tavaborole comes in 4ml and 10ml sizes with a dropper applicator. Efinaconazole is available in 4ml and 8ml sizes with a flow-through applicator with integrated brush.

Tavaborole has a novel mechanism of action for an antifungal: it kills fungus by interrupting protein synthesis.32 Efinaconazole combats fungal growth by interrupting the ergosterol synthesis pathway, similar to other antifungals.33 There is also a distinct difference in molecular weight of the treatments (i.e, tavaborole 151.3 Da and efinaconazole 348.3 Da).30,31 Though the specific impact of the molecular weights of tavaborole and efinaconazole on nail penetration has not been directly compared, smaller molecular weights correlate directly to increase permeability through the nail plate to the site of the infection.34–36

Tavaborole and efinaconazole are well tolerated. Because they are topically applied, they have low systemic absorption, and no systemic side effects have been observed. In Phase 3 trials, tavaborole and efinaconazole both had adverse events that were mild, transient, and localized to the application site.30,31

After 48 weeks of treatment and a four-week drug-free follow up, tavaborole demonstrated 31.1-35.9 percent
mycological cure and 6.5-9.1 percent complete cure. Efinaconazole had 53.4-55.2 percent negative mycology and 15.2-17.5 percent complete cure. It is tempting to compare these numbers; however, there were major differences between the trials precluding comparison. See Table 3.

Tavaborole investigated efficacy in patients up to 88 years old, while efinaconazole trials excluded patients over 70 years of age. Of note, there is a decrease in nail growth rate with age. Baseline infected toenail areas also varied between trials (tavaborole: 20-60 percent, efinaconazole: 20-50 percent). Greater than 50 percent nail involvement is a characteristic of a non-responder for treatment. In addition, the greater the involvement of the nail, the slower the rate of growth. Tavaborole trials restricted nail trimming to within 1mm of the free edge whereas there were no nail trimming restrictions in the efinaconazole trials. Additional diseased nail on the free edge may have influenced the study outcomes. Finally, approximately 29 percent of subjects in Study 1 of the efinaconazole studies were Asian because there were study centers in Japan. The patients in these Japanese centers had higher complete cure rates than the US and Canadian centers. The clinical relevance of these differences in study subjects is unknown.

OTHER TREATMENT CONSIDERATIONS

Consider the source of the infection before initiating treatment. It is very common for tinea pedis to be the source of the fungal infection, and appropriate treatment is necessary to achieve a cure. If toenails are particularly thick, chemical debridement may be helpful and is usually accomplished with urea under occlusion. Once you have diagnosed a patient and initiated them on a treatment regime for onychomycosis, it is a good idea to see them back every three months to monitor their progress unless additional therapy is necessary. At the initial visit and at subsequent visits, photographs and measurements to document progress may motivate patient to be compliant.

Use of topical treatments in combination with nail polish. Considering the lengthy treatment regimens and
PRACTICAL PEARLS

- Understand your patient’s risk factors and likelihood of recurrence
- Establish an accurate diagnosis before proceeding with treatment
- Oral treatments are effective but limited by their adverse events
- Topical treatments offer a low-risk, efficacious option for a wide patient demographic
- Use caution in comparing topical treatments based on Phase 3 study data given the differences in the study design
- Topical onychomycosis treatments may be compatible with nail polish use, and initial data suggests that tavaborole has a more favorable profile

slow nail growth, patients being treated for onychomycosis may want to use nail polish to mask the appearance of dystrophic nails.39–41

In vitro penetration and appearance studies have evaluated tavaborole and efinaconazole use in combination with nail polish on cadaveric nails. Nail polish does not appear to inhibit the penetration of tavaborole through nail plate.40 Efinaconazole penetrated into but not through the nail plate.39 The appearance of nail polish is aesthetically compatible with tavaborole but not efinaconazole treatment.41 (Table 4) No studies have evaluated the clinical efficacy of tavaborole or efinaconazole with nail polish. ■

Robert Higham, PA-C is with the American Skin Institute, Sherman Oaks, CA.
Nicole Gelings Lowe, PhD is with Sandoz Pharmaceuticals, Princeton, NJ.
Neal Bhatia, MD (pictured) is Clinical Dermatology Therapeutics Clinical Research, San Diego, CA

Disclosures: The authors were fully responsible for the content, editorial decisions, and opinions expressed in the current article. No author received an honorarium related to the development of this manuscript. N. Gelings Lowe is an employee of Sandoz, a Novartis Division.