Onychomycosis and the Role of Topical Antifungals

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Onychomycosis: An Infectious Disease

Warren Joseph, DPM, FIDSA

Onychomycosis is an infectious disease that should be treated with anti-infectives. Relatively rare 100 years ago, onychomycosis has become more common because of changes in lifestyle (in particular urbanization, communal bathing areas, use of occlusive footwear, and increasing incidence of diabetes and HIV infection). The correlation between diabetes, tinea pedis and onychomycosis is well known. Also, people are involved in occupations and activities today that carry an increased risk, such as miners, soldiers and runners.1

As an infection, onychomycosis has a genetic predisposition; an autosomal dominant trait with an inability to mount a cell mediated response to T. rubrum. Left untreated onychomycosis is a progressive disease, spreading within the toenail to the rest of the toenails, and to other parts of the body. It can also spread from one person to the other. As a result, patients will often ask, “Is this contagious?” It can cause an immunologic response, affect quality of life (QoL), and as with any infection lead to recurrence or re-infection. This relapse can be a major issue because whenever a new product comes out for onychomycosis, people will ask, “Why should I treat it? It is just going to come back.” We are not curing the disease. We are putting it into remission, and this leads to the important question about how we manage onychomycosis long-term.

Onychomycosis is progressive, recurring and requires treatment.2,3 There can be psychological issues if it impacts QoL, and it can be symptomatic causing pain on ambulation.4 There are risks for further complications especially in our diabetic patients, those with peripheral vascular disease (PVD) and the immunocompromised patient.5 Onychomycosis is a reservoir for infection, spreading to other nails and anatomical sites4 and other individuals.5 There can also be systemic or multi-system involvement. For example, it may be a trigger for asthma attacks in rare cases,6 and be a source of cellulitis.5

Onychomycosis is a common nail disease with over 35 million people having it in the United States. It causes 11.2 million office visits and the number of patients diagnosed with onychomycosis is about 6.3 million.7 There are a significant number of patients who have onychomycosis, but have never been to a physician to be diagnosed. There is an increase in incidence with age. In those patients who are diagnosed, 59% are aged 55 and over, and only 20.5% of the diagnosed population are between ages 30 and 45.7 In addition, podiatrists tend to see an older population than dermatologists.

Onychomycosis accounts for approximately 50% of all nail disease.8 In discussing the epidemiology of onychomycosis it is important to consider the host, the environment and the pathogen (Figure 1). There is little that can be done about the host (age, genetic make up, co-existing diseases), and the key pathogens, T. rubrum or Trichophyton mentagrophytes are ubiquitous organisms that you can find in most places.

Onychomycosis can be caused by dermatophytes, molds or yeast. While the most common are T. rubrum and T. mentagrophytes, variation exists worldwide.9 The role of molds as a pathogen is still not clear. Although they do not have the capability of digesting keratin, so it is unclear physiologically how they would cause infection. There appear to be 2-3 molds that can be pathogens and significant criteria do need to be met for diagnosis of a mold infection.

In diagnosing onychomycosis, most studies suggest that periodic acid-Schiff (PAS) staining of nail clippings is probably the most sensitive and predictive test,10,11 but it is not specific to the individual organism unlike mycological fungal culturing. Fungal culture is the only test that can confirm a specific pathogen, mode of infection and vitality of fungi.10,11 However, there are limitations. For example, it may take up to a month for cultures to grow, and the vitality of the cultures may be adversely affected by transport to a remote laboratory.12 There is a wide variability in KOH sensitivity and this test is prone to false positive/false negative results.10 Molecular means of diagnosis is probably the future (especially polymerase chain reaction [PCR] and molecular sequencing). What are the best ways to make a diagnosis in your everyday practice, and what will the payors accept to confirm a diagnosis of onychomycosis are two important practical questions we face every day.

As we have already discussed, onychomycosis can have a significant impact on QoL. A total of 258 patients with confirmed onychomycosis were surveyed by telephone at three centers using a validated questionnaire.13 Pain was found in 48% of patients, embarrassment 7%, nail pressure 40%, shoe discomfort 38% and physician visits averaged 3.8/year.13 This research is important for two reasons – the incidence of pain and the number of physician visits. Any condition in which pain exists in almost 50% of our patients cannot be considered a cosmetic condition, and four physician visits a year has significant economic consequences.

It is known that there is a genetic pre-disposition to T. rubrum in some families,14,15 with every affected child having at least one affected parent.15 In families...
Onychomycosis is the most common nail disease, accounting for approximately 50% of all nail problems. The most common primary *T. rubrum* infections present as tinea pedis with distal subungual onychomycosis (DSO) as a secondary infection. Patients predisposed to onychomycosis are also going to be predisposed to having fungal infections in other parts of their body, such as tinea corporis, tinea cruris and tinea pedis.

Tinea pedis is inexorably linked to onychomycosis. Onychomycosis starts in almost every case as tinea pedis. The fungus infects the skin, minor trauma breaks the hyponychial seal and the fungus migrates beneath the nail. Maybe the patient doesn’t even recognize it is happening. Essentially, all patients with onychomycosis have or have had tinea pedis at one point, and you really need to treat both. If you treat patients with an oral antifungal for their onychomycosis it will treat their tinea pedis as well. But with a topical you have to treat the tinea pedis in addition, otherwise it will just act as a reservoir for re-infection of the tinea. Likewise if you only treat the tinea pedis the onychomycosis can re-infect the skin.

Onychomycosis is very common in patients with diabetes, where the prevalence is 2.8 times greater than in patients without diabetes. Thickened fungal nails can develop serious bacterial infections and foot ulcerations. Patients with diabetic neuropathy tend to wear shoes that are too small, because they can’t feel that the shoe doesn’t fit well, leading to ulceration. Foot ulceration has been reported in about 19% of diabetics, and in those with ulceration the prevalence of amputation ranges from 6%-43% depending on the severity of the ulceration. In patients who have had a unilateral amputation the 5-year mortality rate is between 39% and 68%. There is also a correlation between secondary gangrene infections in diabetics with onychomycosis.

**DISCUSSION POINTS: Prevalence**

**Jay Lifshen, DPM:** Onychomycosis is very prevalent in our practice; being in Texas with the Southern climate we see a lot more of these types of problems. From an economic perspective, our group has created our own lab to capture the technical component of the lab expense. In probably 15%-20% of all the patients we see, onychomycosis is their primary presenting complaint. Our practice has a lot of diabetic patients and many return for repeat foot care secondary to their diabetes; many are considered high-risk patients in light of PAD and/or neuropathy.

**Bryan Caldwell, DPM:** I have practiced in both Florida and Ohio, so I can concur about the prevalence of onychomycosis in Southern climates. In Ohio, we have 2 very different demographics, having a clinic in the suburbs and one in the city. The city clinic sees a predominantly African-American population. We see more onychomycosis patients here than in the suburbs. Indeed, almost every other patient we see has onychomycosis or at least a chronic tinea pedis leading to onychomycosis. I really believe that there is a genetic susceptibility for the development of chronic tinea pedis.
and onychomycosis, but also an increase in prevalence in the Southern states, so we have to consider environment and genetics. Does someone who is genetically predisposed to onychomycosis assume a greater risk if he or she moves to a Southern climate? Diabetes is increasing for a variety of reasons, so it is no surprise that onychomycosis rates are increasing as well, given that there is a 3:1 susceptibility issue.

Maureen Jennings, DPM: My podiatric practice is predominantly a medical practice in New Jersey, where patients are >55-years-old, have a high incidence of diabetes and I probably see 65%-70% of the practice having onychomycosis, either primary or secondary. For a lot of my patients, it is embarrassment—they don’t like the way it looks. Pain relief is a definite consideration with the hope of improving nail appearance.

Scott Ashton, DPM: As the presenting or at least secondary complaint, it is probably 30%-40% of the patients that I see. A lot choose not to have their onychomycosis treated; some don’t have the where-withal to treat it properly. But there are a lot of fastidious folks in North Dallas who want their toenails to be immaculate. It is a problem in populations that spend most of their time in sandals with their toenails visually exposed. I don’t see pain as the presenting complaint—dystrophy is the main issue, appearance and the fear of it spreading to other nails.

Alex Reyzelman, DPM: I agree we see a lot of onychomycosis in these communities. It may be an interesting area to explore. They are likely to have more diabetes and alcohol-induced neuropathies. I also think we have to look at the different age groups. Embarrassment is a key psychological issue. Onychomycosis is certainly more recognized following promotion to patients.

Richard Pollak, DPM: I used to think that onychomycosis was a “by the way disease” and not necessarily the primary reason patients were coming in to see us in the office. The Doyle data ties in with the public health issue and bears out our experience.21 The incidence of onychomycosis is clearly higher in the diabetic patient population, or the underserved patient population. I can’t think of one patient I didn’t amputate on (other than trauma) that didn’t have onychomycosis, or tinea pedis, meaning that these people have bad disease state. This is an underserved patient population, they are not being treated and they are just not taking care of themselves.

Tracey Vlahovic, DPM: I am seeing patients with the absence of tinea pedis, but with the presence of nail disease due to pedicures. We are typically seeing this because they have been inoculated with a dirty unsterilized instrument. I do a lot of education on appropriate pedicures and looking for places that autoclave. Another concern I get in my practice is nail discoloration. They might have already been treated by another physician and been given oral terbinafine, but what they have is not fungal. I see a lot of misdiagnosis. I am telling patients that it is more likely they don’t have fungal disease than they do. It is my job to determine if it is really onychomycosis or not.

Harry Goldsmith, DPM: Total annual Medicare reimbursement for routine foot care (eg, debridement and trimming of nails) is $350-375 million. Compared to overall Medicare expenditures, that’s a relatively small amount, but for podiatry, it is significant. CPT 11721 (debridement of nails 6 through 10) is the #1 billed code to Medicare by podiatrists in just about every state. CPT 11720 (debridement of nails 1-5) consistently is listed in the top 10 codes billed by podiatrists. Debridement of nail codes are the #1 audited codes for podiatrists. Prior to billing these codes, Medicare does not require laboratory proof that onychomycosis is present; it only needs the doctor to document clinical findings consistent with onychomycosis. Some Medicare contractor policies will also allow the billing of these debridement codes because the nails are thick, dystrophic or misshaped. One should keep in mind that the performance of nail debridement, while reducing the “fungal load” in the nails, in and of itself does not mean that the nail has been or is actively being treated, unless you consider debridement a primary treatment. Typical qualifying conditions for billing either CPT 11720 or CPT 11721 are either associated with “at risk” routine foot care or symptoms (ie, pain) associated with nails. Regardless, payers have been increasingly aware that in addition to the debridement of nails, the identification and treatment of the nail fungus is critical to the prevention of fungal spread to other nails and surrounding skin. The public as a result of years of direct marketing—pharmaceutical companies, laser manufacturers and podiatrists—are increasingly aware that a nail infected with fungus can be treated and that it wasn’t just an ugly nail anymore. Awareness is driven by market activity and market activity is driven by public awareness.

Dr. Joseph: Dermatologists say that 50% of nail dystrophies are not onychomycosis. In a podiatric practice more likely 75% of the nails we see are onychomycotic toenails.

DISCUSSION POINTS: Diagnosis

Dr. Pollak: I will often do a PAS stain to confirm the diagnosis of fungus. I occasionally will do a PAS stain to prove the negative. Often times, fungus may be misdiagnosed. Many patients would like treat-
ment for fungus when they clearly have dystrophic nails and the etiology is trauma and not fungus. In practice, sometimes I will do a KOH in the office to verify if there is tinea pedis when I am considering a topical medication for athlete’s foot. I rarely do a fungal culture in the office for onychomycosis. When I question the etiology, I prefer the PAS stain over the culture because of the high sensitivity of the PAS stain as well as it only takes a few days to receive the result from the laboratory.

**Dr. Vlahovic:** I have predominantly Medicaid patients, a lot of whom are formally capitated so I am forced to do KOH and culture (I have difficulty getting generic ciclopirox lacquer covered). I virtually never order a PAS because Medicaid won’t pay for it. Also, the patient may have seen several podiatrists before me so that is why I have started doing more of the PCR to see what kind of nondermatophyte mold I am dealing with. I use a dermatoscope that allows me to see pitting and other nail pathologies a little bit easier, which allows me to try to rule out melanoma.

**Dr. Lifshen:** Cost is not an issue because if I am going to treat someone with oral terbinafine, I am going to get a PAS. There are a lot of patients who come in that have failed various treatments before. You look at their nails and clinically they look like onychomycotic toenails, but they are not. Why would I subject them to another course of terbinafine or switch them to itraconazole, if I don’t get the laboratory confirmation of onychomycosis? We have a standard protocol in our lab that if the PAS is negative we will do a Gomori methenamine silver (GMS) stain. This stain can pick up some positives, even when the PAS is negative. If I am putting someone on a topical medication, I am not as strict. If patients say in advance that they are not interested in any oral medication, only topical, I would probably not do a PAS. Then if the topical doesn’t work, is it just that it was one of those 90% cases where it is not effective or is it because it was not a dermatophytic infection to begin with? You don’t know why it didn’t work and this can sometimes be a problem.

**Dr. Reyzelman:** I tend to lean on the clinical diagnosis a lot. If they have tinea pedis/multiple nails involved and fungal debris then I don’t necessarily get a PAS, only with high risk.

**Dr. Goldsmith:** In the past, some Medicare contractor policies required the doctor to perform lab work to confirm the presence of onychomycosis or other pathology prior to allowing palliative care of the fungus nails. Those carriers found out in pretty short order that the volume of nail debridement did not significantly diminish. Rather the expenses associated with these mandated laboratory tests were adding significant dollars to provide the debridement of mycotic nails benefit. Most of the Medicare carriers have dropped lab work requirements and leave it up to the doctor to clinically make and document the diagnosis. This is currently Medicare’s approach in cases of palliative care. In cases of definitive treatment of onychomycosis (eg, use of anti-fungal medications), the need for laboratory confirmation and identification of the organism(s) is predicated on the standard of care. I encourage doctors treating onychomycosis to have a specific office protocol that will be followed for that treatment.

**Dr. Caldwell:** When a new patient presents with fungal appearing nails we give them all the options straight away—we discuss debridement (you either go the infectious disease route or the pain management route and in the latter that is where debridement comes in regardless of reimbursement), topicals, laser and orals. We review the advantages of each, including the success rates and financial ramifications and let them choose. If they choose debridement we do not usually confirm with PAS stain or culture. If the patient chooses an oral treatment, or even topical/laser we will then do a PAS stain and a fungal culture. However, we don’t routinely test prior to topical therapy, but as new products come out we may modify our protocols depending on cost to patient. Do I believe we are treating some non-onychomycosis with topicals as a result? Probably.

**Dr. Ashton:** I rarely do KOH on a non-trial patient, so I am looking at a PAS stain in just about every patient with what I think is onychomycosis. But if they refuse I will still give them oral therapy if I agree with it clinically, and document that they refused the tests on economic grounds. I rarely use ciclopirox and if I do, I wouldn’t do a PAS (although before it went generic we would to ensure coverage).

**Dr. Jennings:** I give my patients a complete list of all of the options. I am a firm believer in education. If the choice was an oral agent, I would definitely do a PAS to confirm diagnosis. If using a topical and 95% sure it was onychomycosis, I probably wouldn’t do diagnostic testing.
Onychomycosis: Treatment Considerations
Warren Joseph, DPM

There is a disconnect between how we approach onychomycosis, and what we know about the disease. There is a disconnect between how many patients have the disease, and how many are treated; what patients perceive of the disease, and the need to treated versus those who are actually treated; and between what podiatrists see as being efficacious, and what we use, and the fear of risks of oral therapy versus the facts (that the risk is minimal).

Overall, it is estimated that 35–36 million Americans have onychomycosis. Of these, only 6.3 million have been diagnosed by a physician, and only 2.5 million receive treatment each year. That leaves 33 million untreated patients!

Current therapies include prescription antifungals, soaking, debridement/avulsion and “over-the-counter” (OTC) medications. What is most striking is the 42% of patients who have tried OTC treatments, compared to 12% who are receiving a prescription antifungal. Of course, there are going to be patients who come in to our practice who just don’t care; they have lived with their onychomycosis for years and don’t want to do anything about it, but the OTC group represent people who are actively doing something for their onychomycosis, because they want to get rid of it.

Podiatric physicians’ treatment choices and their perceptions of treatment efficacy are quite different. For example, only 23% of podiatrists perceive that debridement is efficacious, and yet it is the #1 treatment recommended by podiatrists (in 75% of cases). Eighty percent of podiatrists perceive that oral antifungals are the most effective treatment, but they only recommend them in 30% of cases. Topicals are somewhere in the middle—perceived as effective by 7% of podiatrists yet fairly widely used (in 48% of cases).

Current approaches to treatment include mechanical/surgical (ie, debridement, P&A technique, nail avulsion), topical therapy, oral therapy and combination therapy with debridement. Of course with ciclopirox, combining with debridement is in the package insert, but with newer products, this may not be the case. By combining debridement would you increase efficacy?

Medical debridement has been the mainstay of the podiatric approach, and it does reduce thickness and length of the nail, causes decreased pain/pressure (one of the chief patient complaints) and may decrease the fungal load. It also makes the nail temporarily look a little bit better, but it does not address the fungus. Debridement is not a treatment for fungal infection.

The surgical approach (ie, removal of the nail) tends not to be used the same time as a topical, and tends to be used less currently as it can be painful and lead to secondary bacterial infection. If re-growth occurs, it is important to address the fungus.

So what’s new in the world of onychomycosis? As of March 2013, 63 clinical trials were listed at www.clinicaltrials.gov with only 5 currently recruiting. Lots of treatment approaches are being looked at, including patches, iontophoresis with terbinafine (not being pursued anymore), itraconazole 200 mg once daily (now FDA approved), various lasers, micro drilling to increase the penetration of the topical and various new topicals are being investigated including luliconazole, amorolfin, transfersome and antimicrobial plasma.

Ciclopirox nail lacquer is currently the only FDA-approved topical therapy for onychomycosis. Two products (efinaconazole and tavaborole) have recently completed their phase 3 trials and luliconazole is in phase 2/3.

Based on the pivotal trials and FDA strict criteria, the cure and success rates were 8.5% and 12%, respectively, after 48 weeks treatment with ciclopirox nail lacquer. A subsequent meta-analysis reported a clinical response rate of 52.4% ± 9.0%. These data and those from other studies that followed have brought up the whole debate of how we define treatment success in onychomycosis and what is an appropriate length of treatment (especially with the topical products).

There are only two terms consistently applied in clinical trials—mycologic cure and complete cure. Mycologic cure is the lowest barrier, easiest to achieve and as a result reports the highest numbers. Complete cure is the highest barrier—how often is the nail 100% normal in appearance? Almost never, which is why the level of complete cure tends to be low. As a result a lot of intermediate endpoints (ie, clinical success, almost clear) have been reported in clinical trials, and different methodologies have been adopted to determine the extent of nail involvement. There is certainly confusion amongst podiatrists and comparing efficacy from different studies is difficult. Even the range of severity (percent nail involvement) varies amongst onychomycosis studies, however the mean values may be similar.

So what is the role of topicals in the treatment of onychomycosis? They are generally used for mild to moderate DSO (although even here the severity terms are not well defined). They certainly represent an alternative therapy for patients who cannot or will not take an oral therapy (and a lot of patients do come in and
say oral products are dangerous given what they have read about them on the Internet, or there is physician confusion about drug interactions). Topicals are potential adjunctive therapy along with the orals (inside out and outside in) in moderate to severe disease; and a big area that has not been seriously looked at is their use in prevention of recurrence/maintenance therapy.

Three oral agents are FDA approved: itraconazole, terbinafine and griseofulvin. Terbinafine is considered the gold standard in terms of cure rates (>70% success rate reported in a meta-analysis of the clinical studies).28 There is almost no research into new oral agents, probably because of the efficacy and the cost of generic terbinafine. In a large randomized, open label multicenter study with oral terbinafine and aggressive debridement (IRON-CLAD), no clinically significant changes in liver transaminase levels were observed 6 weeks after treatment or after 12 weeks in those tested.29 So oral drugs are not so dangerous, but there is still a perception out there that they are.

Relapse (recurrence or reinfection) is a significant problem in the treatment of onychomycosis. As we discussed earlier, because there is genetic predisposition to onychomycosis, we should be talking about remission rather than cure. Relapse of onychomycosis may be due to reinfection or incomplete eradication of the original fungus with treatment.2 It has been shown with orals that 22% of patients experience a relapse when followed up to 3 years after initial treatment.2 More recently, it was similarly shown that 4 years after an initial 12-week treatment course, only 33%-35% of patients still exhibited evidence of a clinical cure and 28%-35% of patients remained completely cured.30

In reality, the recurrence rate is 100% unless we manage the disease appropriately, and there are a number of preventative strategies we can adopt to minimize recurrence. These include using maintenance treatment regimens as well as practical steps the patient can follow at home (Table 1).

As mentioned earlier, comparing efficacy across studies is complex given the different degrees of nail involvement, patient age and demographic differences. Nevertheless, we can provide some guidance based on the pivotal studies and the common criteria of mycologic and complete cure rates. As can be seen in Table 2, reported mycologic cure rates range from 31% to 70% and complete cure rates range from 5.5% to 38%.

Use of lasers to treat onychomycosis has become more commonplace. However, there is very little data as to whether lasers work or not. There are only two published trials, and yet a number of lasers carry FDA clearance. The wording of the clearance is for temporary improvement in the appearance of the nail. None are labelled for the actual treatment of onychomycosis. Another area of significant promotion is the wide variety of OTC products claiming to be “effective 80% of the time” without defining what this means.

**DISCUSSION POINTS: Treatment Options**

**Dr. Lifshen:** I do not treat all cases of onychomycosis. Elderly patients who come in many times do not need to be treated. Usually, I just make sure they are comfortable and that they can get their shoes on, and that’s it. We also have to keep in mind the physical limitations of that age group. We have a lot of patients who are unable to bend over and cut their nails or apply medication to their toenails. Add to that the fact that nails are generally more involved than we would see in the 40-50-year-old population. They actually may be more suited to an oral medication, but many patients don’t want to take another medication orally regardless. It is a dilemma. It is going to be very difficult for

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<thead>
<tr>
<th>Table 1: Preventive Strategies to Control Recurrence of Onychomycosis</th>
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<tr>
<td><strong>Suggestions to patients</strong></td>
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<tr>
<td>Use maintenance regimens of antifungal agent</td>
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<tr>
<td>Discard old shoes</td>
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<tr>
<td>Alternate wearing different pairs of shoes</td>
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<tr>
<td>Periodically disinfect shoes</td>
</tr>
<tr>
<td>Wash feet regularly</td>
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<tr>
<td>Alert physician at first sign of infection</td>
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Onychomycosis and the Role of Topical Antifungals

Dr. Joseph: People did not want orals, and this is still true today. It doesn’t matter how much you educate them; they are not willing to do it. They have their family doctors telling them they are dangerous, the information is on the Internet and a lot of podiatrists don’t want to bother/risk it.

Dr. Reyzelman: I treat those who want to be treated, unless they have significant comorbidities. I educate my patients about the options that are available, pros and cons and financial issues and help them decide the best solution for their problem. When thinking about severity, there is no specific classification. To me, severe would be total nail plate involvement; chronicity and duration are also important considerations. How much of the nail is infected is an important guide, as well as the number of toes involved. I think efinaconazole is going to be used a lot and patients are going to drive the market.

Dr. Pollak: I ask people if they want to be treated. I don’t treat everyone unless it is bothersome in terms of appearance, or in rare cases it is painful. I use terbinafine in almost every case. I rarely offer my patients topicals because I have not been impressed with results I saw with ciclopirox. If it is a one-fungus toenail, and really dystrophic, I will suggest permanent removal. I am not convinced about lasers. I believe it is important to take notice of the clinical evidence.

Dr. Ashton: Patients are asking for laser treatment, but the real impetus behind the laser I feel at times is the additional investigations (ie, they also do PAS stains, etc.), and that generates a lot of traffic in the office. As far as treating all comers with fungus, I have inquiries all the time. Patients come in with their yellow/brittle toenails, and yes it is likely to be fungal but there are multiple medications, both oral and topical available. If there were a topical that was more effective, I would be more inclined to use it except for a couple of things: all the clinical trials I have been involved in have selected patients who don’t have total nail involvement, and a lot of these elderly people do have total involvement. I don’t know how well a product priced similar to ciclopirox when it came out is going to go with these elderly Medicare patients. These people have a limited income, and if they are going to come in because they can’t manage the condition themselves and spend money, they will want to see results. I think the whole debate about OTCs comes down to one thing, and that is a big switch to misrepresentation. The FDA does not allow them to say they are treating onychomycosis specifically; it may be treating fungus all over the toe, but not within the nail. OTC products may have a role as maintenance therapy to take steps to see that you don’t get your onychomycosis back, especially something that treats tinea pedis. Sequential prescription topical might be the way to go?

Dr. Vlahovic: I am a big fan of oral terbinafine, and discuss with my patients the level of onychomycosis present, and if there are dermatophytomas, because they are much more difficult to treat. I am a firm believer in a company introducing a new topical antifungal with practices that have already established a protocol of dispensing within their practice. I think podiatrists who are dispensers and use combination therapy with oral terbinafine and a topical will continue to use an office based OTC product as their combination drug. If you are using efinaconazole by itself as the only form of treatment, and it does have significant efficacy results, that is where you will see growth.

Table 2: Efficacy of Topical and Oral Antifungals in Pivotal Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mycologic Cure</th>
<th>Complete Cure</th>
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<tbody>
<tr>
<td>Ciclopirox lacquer1</td>
<td>29% &amp; 36%</td>
<td>5.5% &amp; 8.5%</td>
</tr>
<tr>
<td>Tavaborole2</td>
<td>31.1% &amp; 35.9%</td>
<td>6.5% &amp; 9.1%</td>
</tr>
<tr>
<td>Itraconazole (oral)3</td>
<td>54%</td>
<td>14%</td>
</tr>
<tr>
<td>Efinaconazole4</td>
<td>53% &amp; 55%</td>
<td>15% &amp; 18%</td>
</tr>
<tr>
<td>Terbinafine (oral)5</td>
<td>70%</td>
<td>38%</td>
</tr>
</tbody>
</table>

in matching the patient to the treatment. If they have no cuticle involvement I might recommend a topical, it really depends on the patient. Can they reach their toenails? Maybe they don’t want to take an oral? I use cosmetic nail resin applied on top of the nail and it mimics the look of the nail. The patient doesn’t have to think about it. In theory, you are sealing the nail and not allowing any more environmental dermatophytes to get in, so I will do that for the patients who can’t reach down to their toes and don’t want to take an oral. I have been waiting for a new effective topical agent such as efinaconazole to come out because I have a patient population who would benefit from its broad spectrum and obviously from the efficacy. As far as payment goes, something that is affordable is great but I can tell you with certainty that my patients are so desperate to have clear nails they will find a way to pay. I have been impressed by the depth people will go to to solve their nail problem.

**Dr. Caldwell:** It is no shock to anyone that terbinafine is the gold standard in treating onychomycosis, given the information (ie, success rates, the ease of taking a pill). Many patients, even after you counsel them regarding the fact that there are very few cases of compromised liver function with oral terbinafine, will tell you, “I don’t care. I am not taking anything by mouth. I want the best thing I can apply to my toe.” Patients want a prescription topical solution that is covered by their insurance, which will beat any other OTC if the cost differential is there. If there is a large co-pay there could be a problem.

**Dr. Jennings:** In our patient population, there is a certain sophistication. They come into my office with an armamentarium of things they have used in the past or are interested in using and want my opinion. I think the role of OTC products in podiatry is huge. Safety and efficacy are important in the patient’s decision-making process. The public is becoming more involved in the treatment of their own disease state.

**Dr. Goldsmith:** Ciclopirox had the same issues when it was launched as efinaconazole will face: ROI—return on investment for patients. Is there a reasonable chance that using the medication will eliminate the fungus and make the nail “appear” more normal? Will the medication prevent the spread of the fungus to other nails? If the medication is a topical, how practical is the application—the ability to reach down and apply—process? How much will the treatment cost overall? Will the fungus come back when I stop the treatment or can I continue treatment under a “maintenance” protocol? Historically, with patient awareness through continuous marketing (television ads, radio and print media) and information patients received from their doctors, issues related to pricing took a back seat to their desire to eliminate this infection in their nails. Consumer demand for a treatment took off although acceptance of topical treatments always exceeded oral medication use. There is a good market for an effective topical as you don’t have to go through a lot of thinking or effort to use it.

**Dr. Markinson:** There is a disconnect where the podiatrist is the driving force to OTC and topical, so I believe for instance if you ask a typical patient, he or she will tell you that the oral drug is dangerous when there is no data to support it. We have not been responsive to try to dispel the myth. I don’t think we have said as a profession, with any enthusiasm, that this is a chronic disease, and it should be managed as such. Sometimes a recurrence creates a bad impression of the efficacy of a product but this can be wrong. You are obligated to tell the patient that nothing comes close to terbinafine in curing the disease, but we don’t do that. The only thing that drove the success of ciclopirox was “you don’t have to worry about the liver.” That is what is driving the demand for OTC products as well. We hear all the time from our patients what they have used. I tell them there is only one FDA approved topical medication. Then I tell them the success rate and they are flabbergasted. I don’t think in-office dispensing is an obstacle. The single driver of all this is the emphasis of podiatry that it is safe and that safety outweighs efficacy all the time.
Efinaconazole 10% solution is the first topical triazole for onychomycosis and it has a broad spectrum of activity.

We all recognize the excellent in vitro potency of terbinafine against dermatophytes, but efinaconazole is more effective. Against Candida, itraconazole is known to be effective, but again efinaconazole is more effective than itraconazole. We have always been taught itraconazole is better than terbinafine against molds. Against Aspergillus, Fusarium and Scopulariopsis (considered to be a pathogen as well as some of the Aspergillus species), efinaconazole is more effective, itraconazole shows no activity. The fungicidal activity is superior to ciclopirox (again an agent that we are taught is a fungicidal agent).

Keratin binding is important as it is thought that a drug that is bound to keratin cannot get through the nail to get to the nail bed and the site of the infection, so strong keratin binding is considered a negative, with less free drug available to penetrate the nail. Efinaconazole shows weaker binding to keratin than ciclopirox and nail penetration is better as a result. Efinaconazole meets the pharmacological and pharmacodynamics parameters that should make the drug efficacious in onychomycosis.

It is a solution that is unlike a lacquer. Most of us have used ciclopirox and we talked about the problem with opening the bottle. We also know with ciclopirox we get “black hairy toenail” syndrome where people would put on their socks after applying the drug and sock fibres would stick to the toe. Ciclopirox stays tacky for a long period of time. Efinaconazole 10% solution also exhibits low surface tension, its concentration maintained after evaporation, and it does not require debridement (not a prerequisite in the study), but it is theoretically possible that debridement by thinning the nail might allow better penetration and also decrease fungal load.

Two phase 3 multicenter, randomized, double-blind studies were conducted in 1,655 patients with mild to moderate toenail onychomycosis (defined as 20%-50% target nail involvement, although the mean affected toenail was 37%). Efinaconazole 10% solution or vehicle (randomized 3:1) was administered once-daily at bedtime for 48 weeks.

### Table 3: Efficacy Outcomes with Efinaconazole 10% Solution and Vehicle at Week 52 (LOCF)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Efinaconazole 10%</th>
<th>Vehicle</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Cure&lt;sup&gt;1&lt;/sup&gt;</td>
<td>205/1236 (16.6%)</td>
<td>18/415 (4.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mycological Cure&lt;sup&gt;2&lt;/sup&gt;</td>
<td>672/1236 (54.4%)</td>
<td>70/415 (16.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete or Almost Complete Cure&lt;sup&gt;3&lt;/sup&gt;</td>
<td>309/1236 (25.0%)</td>
<td>30/385 (7.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clear Nail&lt;sup&gt;4&lt;/sup&gt;</td>
<td>244/1236 (19.7%)</td>
<td>26/415 (6.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Almost Clear Nail&lt;sup&gt;5&lt;/sup&gt;</td>
<td>398/1236 (32.2%)</td>
<td>45/415 (10.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical Efficacy&lt;sup&gt;6&lt;/sup&gt;</td>
<td>527/1236 (42.6%)</td>
<td>67/415 (16.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>1</sup>Area ≤5% of the clinical involvement of the target toenail in addition to a negative KOH examination and fungal culture.
<sup>2</sup>Area ≤5% of the affected toenail.
<sup>3</sup>Area ≤10% of the affected toenail.
Figure 2: Primary Efficacy Endpoint Complete Cure Weeks 12-52 (LOCF) ITT Subjects Individual Studies (Study 1 and Study 2).

Adapted from the Journal of the American Academy of Dermatology, Copyright 2013, with permission from Elsevier.

- **Study 1**
  - Efinaconazole (N=656): 18% at Week 52
  - Vehicle (N=214): 15% at Week 52

- **Study 2**
  - Efinaconazole (N=580): 15% at Week 52
  - Vehicle (N=201): 13% at Week 52

*P<0.001
Both agents were applied to the clean, dry nail plate surface, lateral and proximal nail folds, hyponychium and the undersurface of the nail plate. The mean affected toenail involvement is important; this has been similar (no significant differences) across all onychomycosis studies even when the inclusion range may have been different. The average number of non-target toenails (<3) is typical and has been
consistently shown that the average patient with onychomycosis has fewer than four toenails involved. It is also important to remember that these are vehicle controlled studies and not placebo.

The key efficacy outcomes of complete cure and mycologic cure were 16.6% and 54.4% compared to 4.3% and 16.9% with vehicle, respectively (Table 3). Complete cure rates continue to rise throughout the studies and one can only speculate as to the likely success with longer treatment or follow-up (Figure 2). Comparing efinaconazole 10% solution to results reported for ciclopirox 8% nail lacquer, efinaconazole 10% solution appears to be more effective (Figures 3 and 4).

Safety issues are rare with topical antifungals and efinaconazole 10% solution is no exception. Adverse events were few and mainly related to application site reactions.

**DISCUSSION POINTS: Efinaconazole 10% solution**

**Dr. Jennings:** I like the pharmacokinetics/penetration data, as these are vitally important issues when it comes to a topical product. I think efinaconazole 10% solution is going to replace ciclopirox because of the solution formulation versus lacquer. Studies show the solution penetrates better, therefore getting further down into the matrix where the fungus resides. I believe that debridement helps with better penetration. Efinaconazole 10% solution has better efficacy than what is currently available and offers a better topical option for treatment.

**Dr. Ashton:** There is no doubt that efinaconazole 10% solution is a ciclopirox killer. The product is working very well, and I am looking forward to using it. The biggest issue we have, and always have, is use with nail polish. In fact for some even though they don’t want to take pills to damage the liver they would rather take the pills than not use their nail polish. Cost could also be an issue.

**Dr. Goldsmith:** As long as the cost is perceived as reasonable, I wouldn’t worry. Cost of treatment has always been a consideration with onychomycosis and, from the time of the “fungal wars” to today, companies providing fungus treatments have had the same problems and done well with patient acceptance. The problem for those patients with insurance coverage is whether the specific medication is included in their benefit formulary. Generic medications are favored while brand name medications are either not included in the formulary or “not favored” with higher copayments. What is interesting is that if the patients are truly motivated to eliminate their onychomycosis, they will be willing to pay out of pocket to achieve that goal. In the early days of the “fungal wars” in the 90s, I had a patient who came to the office with a ripped page from Time magazine with an ad for an oral antifungal who was ready and willing to pay $1,400 for terbinafine before it was covered on the patient’s insurance formulary. My practice advice is to give patients every reasonable choices of treatment possible—and their costs—and let them make the decision on how or if they want to proceed in treatment.

**Dr. Reyzelman:** Efinaconazole 10% solution should be more successful than ciclopirox—it is more efficacious, easier to apply and there are still a significant number of patients who are not going to take an oral. Based on the clinical data, I think the product is great—it is the best topical we have had so far. Patients are going to use it; even the women with nail polish will find a way to use it. I think it is important to show the almost clear data as most of our patients would be delighted to see that much success, and who knows if you treat them longer?

**Dr. Vlahovic:** I have my female patients who want to use nail polish to treat around the nail, proximal nail fold and cuticle to the hypernicium. At least it is a way for me to get something to the infection.

**Dr. Lifshen:** It is not going to replace ciclopirox exclusively given it is more effective than itraconazole. But will run into issues in the pharmacy with generic products.

**Dr. Caldwell:** Plain and simple, you overcome any insurance barriers and efinaconazole 10% solution replaces other topicals.
References
