Onychomycosis is a relatively common dermatologic presentation (Table 1). The incidence of the disease varies regionally and with age. Although in most cases the condition poses no significant long-term health risk, treatment is indicated. Affected nails can be cosmetically unsightly and may become painful and cause functional impairment. In some cases, such as among diabetic patients, treatment of onychomycosis is imperative. These patients typically are concurrently using other medications, so treatment must be selected to minimize or anticipate any adverse drug interactions. Clinicians may encounter three clinical types of onychomycosis:

- **Distal lateral subungual onychomycosis** develops when the fungus enters via the lateral nail groove and distal subungual area.
- **Superficial white onychomycosis** is the result of infection via the dorsal surface of the nail plate.
- **Proximal white subungual onychomycosis** develops following infection of the undersurface of the proximal nail fold. Although rare in the general population, this presentation may be found in immunocompromised patients. The nail fold remains normal in this presentation. Inflammation may indicate chronic paronychia with secondary nail involvement.

More than 90 percent of cases of onychomycosis are caused by dermatophytes. Although dermatology care providers may highly suspect onychomycosis based on the presentation of dystrophic, yellowed nails, many experts now urge the use of diagnostic cultures to confirm the diagnosis and potentially direct treatment. A common mimicker of onychomycosis is psoriatic nail disease, discussed in the sidebar on p. 4.

ExamPrep

New Onset Symptoms of Testosterone Insufficiency

A male patient in his late 50s with a history of diabetes has been undergoing treatment over the past 10 months with fentanyl for the management of diabetic neuropathic pain. He recently has been experiencing fatigue, decreased libido, erectile dysfunction, night sweats, and insomnia. His blood glucose levels have been consistently well maintained with insulin detemir injection.

*Could his symptoms be linked to the pain medication?*  
Turn to p. 5
Physician assistants continue to grow their presence in healthcare. According to the AAPA, the number of PAs in the US increased by 100 percent over the past decade. Today 86,500 certified physician assistants practice medicine across the country.

As the healthcare field continues to evolve over the next several years—AAPA predicts a shortage of 62,900 doctors in the US in 2015—PAs will continue to help fill the gaps in care provision. In dermatology specifically, we know that there is the potential for a workforce shortage as the number of dermatology residency positions has remained unchanged even as the population has bloomed.

There are apprehensions about the future of healthcare, and challenges certainly loom. However, there are also opportunities for PAs to meaningfully impact patient care. As you strive to serve patients, hopefully DermPerspectives continues to support your efforts.

I hope that 2012 has been productive for you and that 2013 holds much professional success and satisfaction!

– Coyle S. Connolly, DO, Medical Editor
KOH slide evaluation, using 15-20% KOH in dimethyl sulfoxide, is the easiest method to confirm dermatophyte infection. Chlorazol E stain specific for fungus cell walls is sometimes supportive. If identification of specific causative organisms is desired, culture using one of the commercially available media is possible.\(^2,3\)

The quality of the sample evaluated will determine the utility of any analysis or culture. For distal subungual onychomycosis, a small 1ml curette can be used to obtain a specimen from the onychomycotic border, where the highest number of viable hyphae exist.\(^2,3\)

In the case of proximal white subungual onychomycosis, a No. 15 blade scalpel can be used to remove superficial layers of the nail, after which a curette can be used to remove samples from the infected area.\(^2,3\)

For superficial white onychomycosis a No. 15 blade scalpel can be used to scrape the nail to obtain sample materials.\(^2,3\)

**Oral Therapy for Onychomycosis**

Oral therapy is generally recognized as offering the highest likelihood of cure of onychomycosis, compared to current FDA-approved topical options. Systemic drugs are thought to remain in the nail following discontinuation of therapy, which may allow them to confer continuing antifungal effect. However, there are some practical limitations to oral antifungal therapy. Of greatest interest is the fact that theazole antifungal drugs may affect liver function.\(^4\) (Table 2) Although the risk may be relatively low for a given patient, it is actually well known in the public and may cause some patients to refuse oral therapy. There are also important drug interactions to consider when prescribing oral antifungals, as described below. Table 3 reviews oral therapy options.

Itraconazole has the broadest spectrum of effect (active against dermatophytes, *Candida*, and some nondermatophyte molds). Recommended dosage is usually 200mg BID without food for one week a month. Treatment of toenail onychomycosis requires a six-week course at that dose.\(^2,3\) Fingernail infections require a six-week course at that dose.\(^2,3\) Complete response, non-response, and relapse are all possible with oral antifungal therapy for onychomycosis. Patients should be educated that it will take time for the affected portion of the nail to grow out. As with most diseases and therapies, incom-plete response, non-response, and relapse are all possible with oral antifungal therapy for onychomycosis.

### Table 1. Rates of Dermatophyte Infections\(^14\)

- Dermatophytose prompt 4+ million physician visits per year in the US
- Onychomycosis is most common (23.2 percent of all dermatophytose)
- Incidence of other presentations:
  - Tinea corporis (20.4 percent)
  - Tinea pedis (18.8 percent)
  - Tinea capitis (15 percent)
  - Tinea cruris (8.4 percent)

### Table 2. Liver Injury Incidence\(^4\)

The rates of acute liver injury per 100,000 person-months were:

- Ketoconazole: 134.1 (95% CI: 36.8, 488.0)
- Itraconazole: 10.4 (95% CI: 2.9, 38.1)
- Terbinafine: 2.5 (95% CI: 0.4, 13.9)

Relative risk versus non-users was:

- Ketoconazole: 228.0 (95% CI: 33.9, 933.0)
- Itraconazole: 17.7 (95% CI: 2.6, 72.6)
- Terbinafine: 4.2 (95% CI: 0.2, 24.9)

Psoriatic Nail Disease

In an investigation of nail changes in a cohort of 312 psoriasis patients, 21.5 percent of subjects were found to have experienced nail changes. Of these, only 23 were related to onychomycosis.\(^12\) Nail abnormalities may be due to:

- Nail psoriasis.
- Fungal infection.
- Systemic treatment. (Etretinate may cause paronychia. Methotrexate slows down nail growth and may alter the immune status and can aggravate onychomycosis.)
- A combination of the first three factors.\(^13\)

The potential of terbinafine for drug interaction is generally considered low, especially relative to the azoles. Terbinafine is metabolized extensively in the liver, via the action of various P-450 enzymes and requiring less than five percent of the total liver CYP450 capacity. Clinically significant drug interactions are limited to cimetidine and rifampicin; cimetidine decreases the rate of terbinafine plasma clearance and rifampicin increases it.\(^5\)

Though not commonly used for onychomycosis therapy currently, griseofulvin is an option. Practical limitations of griseofulvin have led to its lower rate of use relative to newer oral antifungal options. Griseofulvin has poor absorption, unless micronized, coated with polyethylene glycol, or given with fatty meals. The drug is also known to interact with phenobarbital and anticoagulants (especially warfarin-type) and may cause contraceptive failure especially of low dose pills.\(^6\)

For any of these agents, it is important to note that the nail will not appear normal upon completion of the treatment course, even if mycologic cure is obtained. Patients should be educated that it will take time for the affected portion of the nail to grow out. As with most diseases and therapies, incomplete response, non-response, and relapse are all possible with oral antifungal therapy for onychomycosis.

**Topical Interventions**

Although conventional topical antifungal therapy does not permit diffusion of the active agent into the nail plate, ciclopirox 8% lacquer nail lacquers demonstrates sufficient penetration. Ciclopirox 8% lacquer produces a polymer film reservoir on the nail. As the solvent within the lacquer evaporates, the concentration of the active antifungal within the film increases. The antifungal diffuses through the nail plate to the nail bed over time. While the lacquer may be used as monotherapy, it may also be used in conjunction with oral agents.\(^13\)
Several novel topical investigational treatments are in various stages of clinical development. The one that is closest to approval is efinaconazole topical solution. Results of a multicenter, randomized, double-blind, vehicle controlled Phase 2 study of efinaconazole solution in mild to moderate toenail distal lateral subungual onychomycosis were recently presented. The multi-arm study investigated efinaconazole 10% semi-occlusion, efinaconazole 10%, efinaconazole 5%, and vehicle. At Week 40, complete cure (16-26 percent) was numerically higher in all efinaconazole solution treated groups compared to vehicle (nine percent). Mycologic cure rates with efinaconazole 10% semi-occlusion, efinaconazole 10%, efinaconazole 5%, and vehicle were 83 percent, 87 percent, 87 percent, and 73 percent, respectively.

Phase 3 trial results show that efinaconazole 10% solution was significantly more effective than placebo in providing mycologic and complete cure rates for distal lateral subungual toenail onychomycosis. Data come from two identical, multicenter, randomized, double-blind, vehicle-controlled studies in patients with toenail distal lateral subungual onychomycosis (20-50 percent clinical involvement [study 1: N = 870, study 2: N = 785]). Patients were randomized (3:1) to efinaconazole or vehicle, once daily for 48 weeks, with four-week post-treatment follow-up. The primary end point was complete cure rate (0 percent clinical involvement).

### Table 3. Common Oral Treatments for Onychomycosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Drug Interactions</th>
<th>Potential Adverse Effects</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Enzyme-inducing drugs, rifampin, isoniazid, phenobarbital, phenytoin, oral hypoglycemic agents, warfarin, digoxin, terfenadine, astemizole, cyclosporine, histamine type 2 (H2) receptor antagonists</td>
<td>Embryotoxicity, GI disturbance, rash, pruritus, hypokalemia, reversible oligonucleic acid, very rare hepatotoxicity</td>
<td>Fingertip: 200mg BID for 1 week/month x 2 pulses OR 200mg QD x 6 weeks. Toenail: 200mg BID for one week/month x 2 pulses OR 200mg QD x 3 months.</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Rifampin, histamine type 2 (H2) receptor antagonists</td>
<td>GI disturbance, taste disturbance, rare hepatobiliary dysfunction</td>
<td>Fingertip: 250mg QD for 6 weeks. Toenail: 250mg QD for 3 months.</td>
</tr>
<tr>
<td>Fluconazole (unapproved indication)</td>
<td>Warfarin, hypoglycemics, thiadiazides, phenytoin, rifampin, cyclosporin, theophylline</td>
<td>GI disturbances, rare hepatotoxicity</td>
<td>Fingertip: 150-300mg once per week x 6 months or until clear. Toenail: 150-300mg once per week x 9 to 12 months or until clear.</td>
</tr>
</tbody>
</table>

### ExamPrep: Resolution

**Hypogonadism Related to Long-term Opioid Therapy**

Hypogonadism is a well-known endocrine side effect of short- and long-term opioid use, with a reported prevalence ranging from 21 to 86 percent. Symptoms and signs of hypogonadism include fatigue, decreased libido, erectile dysfunction, depression, night sweats, decreased muscle mass, infertility, anemia, insomnia, and osteoporosis. Despite these symptoms being fairly specific for hypogonadism, these symptoms are often observed in patients with chronic pain, owing to a possible missed diagnosis.

The hypothalamic-pituitary-gonadal (HPG) axis controls production of the primary sex steroids: testosterone (androgen) and estradiol (estrogen). It begins with the secretion by the hypothalamus of gonadotropin releasing hormone (GnRH), which stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH). These hormones are released into the systemic circulation and stimulate the gonads—the testes and ovaries—to secrete testosterone or estradiol, respectively.

These sex hormones then exert a negative feedback on the hypothalamus and pituitary to control the secretion of GnRH, LH, and FSH.

The function of the HPG axis is under the influence of multiple factors including both endogenous and exogenous opioids; opioid receptors are present in the hypothalamus, pituitary, and on testicular tissue.

Suspected hypogonadism can be confirmed with laboratory work-up, including both free and total testosterone, as well as a serum prolactin level; these are the most common etiologies for hypogonadism. Total testosterone values, however, must be interpreted carefully in the aging male because sex hormone-binding globulin (SHBG) levels might be elevated. If the total testosterone level is normal in the aging male presenting signs of hypogonadism, the clinician can rely on free testosterone or measure SHBG and calculate bioavailable testosterone.

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cal involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at week 52.

Mycologic cure rates were 55.2 percent and 53.4 percent for efinaconazole—significantly greater than for placebo (16.8 percent and 16.9 percent). Complete cure rates for efinaconazole were 17.8 percent and 15.2 percent, compared to 3.3 percent and 5.5 percent for vehicle. Treatment success as a measure of percent improvement in target toenail ranged from 17.9-44.6 percent for active treatment, compared to 5.6 percent to 16.8 percent for vehicle. Adverse events associated with efinaconazole (local site reactions) occurred in two percent of patients and were clinically similar to vehicle.

Another topical antifungal solution is currently in Phase 3 trials for toenail onychomycosis. Interim Phase 2 data (six of 12 months) have been reported for tavaborole (Anacor), which was compared to placebo for the treatment of toe- nail onychomycosis.9 After six months of therapy, 50 per- cent of subjects applying tavaborole 7.5% solution once daily had 2mm clear nail growth and negative fungal cultures. Roughly half of these subjects had 5mm clear nail growth. The trial also investigated the efficacy of tavaborole 5% solution; 45 percent of subjects had 2mm clear nail growth and negative fungal cultures.

Finally, an investigational compound was shown non-inferior to topical 5% amorolfine nail lacquer, which is used in Europe but not approved in the US. In the study, 1,029 patients with mild to moderate nail fungus were given either topical 10% terbinafine hydrogen chloride (MycoVa, Apricus) or 5% amorolfine nail lacquer. There was no significant difference in either the primary (complete cure) or secondary endpoints (mycologic cure and cosmetic improvement) between the treatments.

Elewski reports that a post-hoc analysis of two Phase 3, randomized, double-blind studies of efinaconazole were 17.8 percent and 15.2 percent, compared to 16.8 percent and 16.9 percent. Complete cure rates for efinaconazole—significantly greater than for placebo.10

Conventional topical antifungal creams and ointments may play a role in onychomycosis therapy when and if there is coexistent tinea pedis or tinea manuum. Skin involvement serves as a reservoir for fungi, which enhances the probability of treatment failure for onychomycosis or relapse. Long-term, intermittent use of topical antifungal agents on the plantar surface of the hands and feet and of the toe webs may help prevent tinea pedis or tinea manuum and subsequently limit the likelihood of reinfection of the nail. Patients can also employ strategies to minimize recontami- nation with dermatophytes by allowing footwear to dry thoroughly, treating footwear with antifungal powders, or if necessary, purchasing new footwear. Proper hot-water laundering11 of towels, socks, or other items can eliminate dermatophyte contamination of these items.


TreatmentTips

Sunscreen Labels Changing...Finally

This month is supposed to mark implementation of the final rule for sunscreen label revisions—at least for all products with annual sales over $25,000; those with lower sales have another full year to comply. Among key changes to look for:

- Manufacturers must make an explicit note of the duration of protection, or else they must include instructions for reaplication. “Sunscreens also cannot claim to provide sun protection for more than two hours without reaplication or to provide protection immediately after application without submitting data to support these claims and obtaining FDA approval,” the new rule states.

- Water resistance claims on the front label must now indicate whether the sunscreen remains effective for 40 minutes or 80 minutes while swimming or sweating, based on standard testing. In addition, sunscreens that are not water resistant must include a direction instructing consumers to use a water resistant sunscreen if swimming or sweating.

- One of the most significant markers of the final rule is the update on the “Broad Spectrum” term and the inclusion of a defined standard with which manufacturers must comply in order to use the term. According to the FDA, “Sunscreens that pass FDA’s Broad Spectrum test procedure, which measures a product’s ultraviolet A (UVA) protection relative to its ultraviolet B (UVB) protection, may be labeled as ‘Broad Spectrum SPF [value]’ on the front label.”

The rule contains more specific directives as to the placement and location of drug facts and various other items, but these categories above constitute the areas of greatest emphasis and shift from previous rulings.

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