REVIEW

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Fungal nail infection: Assessing the new treatment options

ABSTRACT

Onychomycosis can be improved or eradicated with appropriate treatment. Newer oral antifungal drugs are highly effective and have few adverse effects, although care in prescribing is needed because of potential drug interactions and hepatobiliary dysfunction.

KEY POINTS

The prevalance of onychomycosis is increasing, due to the aging of the population and to an increasing number of immunocompromised patients. The popularity of public and private spas and swimming pools is also increasing the risk of exposure.

Oral antifungals are now the gold standard for treating and eradicating onychomycosis.

Physicians need to be aware of interactions between some oral antifungal agents and a variety of commonly prescribed drugs.

Toenail infections are several times more common than fingernail infections and are generally more difficult to treat because the toenails grow more slowly.

Hepatic enzymes should be monitored in patients who will be taking an oral antifungal agent for more than 1 month.

WE NOW HAVE NEW options to treat fungal nail infection, a condition with serious consequences in people who have diabetes or are immunocompromised.

Onychomycosis is neither untreatable nor trivial, as was once thought, but is certainly difficult to treat. A new generation of antifungal agents, however, are more effective and better tolerated than older agents and have revolutionized our approach to this problem.

ONYCHOMYCOSIS ON THE RISE

Onychomycosis accounts for approximately half of all nail disorders and one third of cutaneous fungal infections.[1] A US study suggested a prevalence of 18.5%,[2,3] with the number of persons affected apparently on the rise.[4]

Why is the prevalence increasing? The aging of the population may partly account for it. Onychomycosis affects 32% of people between ages 60 and 70, and some studies suggest that 48% of the population may be affected by age 70.[5,6]

Other reasons include greater use of immunosuppressive medications, the increased number of people infected with human immunodeficiency virus (HIV), increasing exposure to pathogens in spas and public swimming pools, the use of tight-fitting shoes for fashion, and athletic activities such as long-distance running. Onychomycosis has a particular affinity for the elderly, people infected with HIV, and people with diabetes.

In general, toenail infections are several times more common than fingernail infections and are more difficult to treat because the toenails grow more slowly.[5,6]

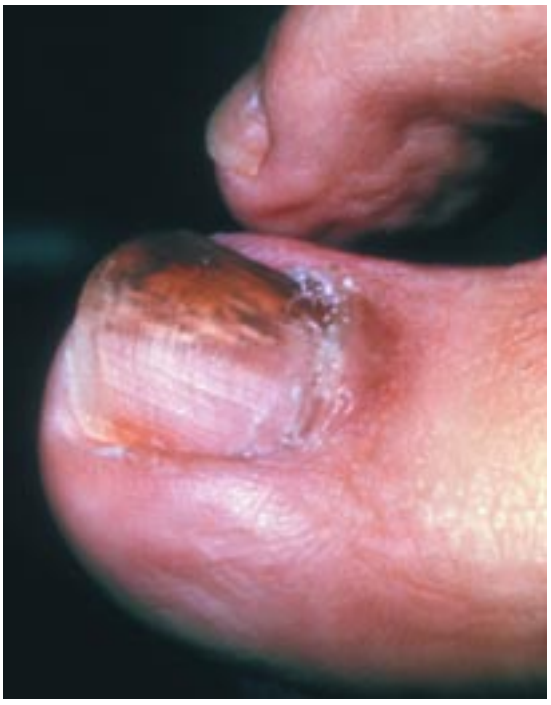

FIGURE 1. Distal lateral onychomycosis has three major clinical features: subungual hyperkeratosis, onycholysis, and paronychia. The most common causal organism is *Trichophyton rubrum*, and the most common route of entry is via the distal subungual space and the distal lateral groove.

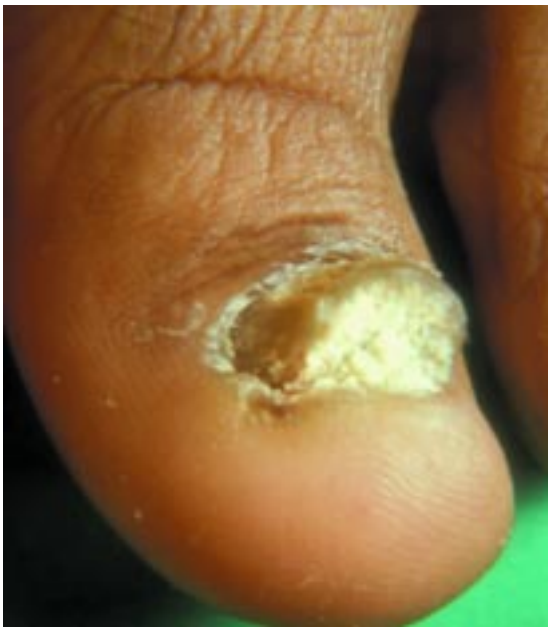

FIGURE 2. Total dystrophic nail can represent a subtotal infection that has progressed to total nail infection. It may also represent a primary condition such as chronic mucocutaneous candidiasis.

CLASSIFICATION OF ONYCHOMYCOSIS

Onychomycosis is classified into five types on the basis of the part of the nail involved. The organisms that cause each type and their response to treatment tend to differ, affecting the choice of treatment.

Distal and lateral subungual onychomycosis is by far the most common type (FIGURE 1). It has three major features: subungual hyperkeratosis (thickening of the nail bed), onycholysis (separation of the nail from the nail bed), and paronychia (inflammation of the skin along the edge of the nail).[7]

Trichophyton rubrum is the most common pathogen, and the most common route of entry is via the distal subungual space and the distal lateral groove.[8] Distal and lateral onychomycosis caused by *T rubrum* may be an autosomal-dominant condition.[7] Predisposed persons are likely to have recurrent episodes of athlete's foot (tinea pedis), which can eventually spread to the toenails. In fact, this happens in about one third of cases of athlete's foot.[8]

Use of spas, public swimming pools, and public showers raises risk

Superficial onychomycosis is the next most common presentation.[9,10] Although it is sometimes called "superficial white onychomycosis," it may also appear black.[8] The most common organism is *T mentagrophytes* var *interdigitale* and, less frequently, *T rubrum*.

Proximal subungual infection usually affects the fingernails. It is usually due to *Candida*, but in patients with HIV infection, in whom it is more common, it tends to be caused by a dermatophyte such as *Trichophyton*.

Total dystrophic onychomycosis (FIGURE 2) is a term used to describe either a nail infection that has spread to involve the entire nail, or a primary condition (eg, chronic mucocutaneous candidiasis) in which all the tissues of the nail apparatus may be involved simultaneously, including the nail folds.[7]

Endonyx is a relatively new classification for lamellar splitting caused by organisms that normally produce endothrix scalp infections, namely *T soudanense*.[7,9–11] *T violaceum* may also produce this pattern of invasion of the

superficial surface, as well as deeper penetration of the nail plate without involvement of the nail bed.[8]

DERMATOPHYTES VS NONDERMATOPHYTES

Dermatophytes account for about 90% of mycotic nail infections. *T rubrum* is most common, followed by *T mentagrophytes* and *Epidermophyton floccosum*.

Yeasts account for 5% to 17% of cases, most often *C albicans*.

Nondermatophyte molds account for 3% to 5% of cases, the most prevalent being *Scopulariopsis*, *Scytalidium*, *Acremonium*, and *Fusarium*.

It is important to recognize, identify, and confirm onychomycosis caused by nondermatophytes, as studies have shown that a clinical diagnosis often is inaccurate. In one study involving 2,750 cases of onychopathy, 70% were diagnosed clinically as fungal infections, but only 40% of these could be confirmed as fungal by direct examination and culture.[12] Different diagnoses may include psoriasis, lichen planus, or a traumatized dystrophic nail.

Most nail infections are due to dermatophytes

The diagnosis of onychomycosis is best confirmed through laboratory testing. Tissue samples should be taken by curettage of the undersurface of the nail plate and nail bed after debridement of the distal nail edge. A potassium hydroxide (KOH) preparation can then be evaluated under a microscope. The definitive diagnosis is made by culturing the organism or through periodic acid-Schiff staining.

CONSEQUENCES OF ONYCHOMYCOSIS

Onychomycosis rarely remits spontaneously, typically spreads to involve the entire nail anatomy, often spreads to other digits, and sometimes spreads to other sites (groin, skin, and scalp) and even to family members.

Secondary bacterial infections

Mycotic infections can provide a portal of entry for secondary bacterial infections.[13] Fissures on the soles, heels, toe web spaces, and in the hyponychium of mycotic nails may allow bacteria such as streptococci to enter, resulting in inflammatory disorders such as cellulitis or erysipelas. In fact, in several reported cases, patients with relapsing cellulitis had no visible source of reinfection other than onychomycosis.[13,14] A possible mechanism: *T rubrum* infection may suppress cell-mediated immunity.[14–17]

Patients with onychomycosis harbor a large fungal load and, from an epidemiologic viewpoint, may be a source of infection for other people, as well as for reinfection on the hands (tinea manuum) and feet (tinea pedis).

Risk in diabetes and immunodeficient states

Patients who have diabetes or are immunocompromised are at higher risk of complications from onychomycosis. In a diabetic patient, particularly one with peripheral neuropathy, fungal nail infections may contribute to the morbidity of the diabetic foot. Impaired sensation may cause paronychia secondary to a mycotic nail to go unnoticed, just as tinea pedis in combination with dry fissuring plantar skin can create a portal for secondary bacterial infection.

Fungal infection not only discolors the nail but also makes it thicker and deformed, often with a sharp, prominent nail edge that can abrade or ulcerate adjacent skin. The potential for serious sequelae is increased in diabetic patients with peripheral neuropathy or peripheral vascular disease. Just as tight shoes may cause pressure necrosis of the skin, so too can thickened, mycotic nails cause pressure necrosis of the nail bed, leading to ulceration, and infection, perhaps requiring amputation.

Effects on quality of life

Onychomycosis impairs quality of life. In several studies,[18] patients with onychomycosis reported significantly poorer general health, mental health, social functioning, and body pain than did people without this nail infection. Psychosocial limitations included fear of social situations that exposed an infected fingernail or toenail.

TREATMENT

Treatments for onychomycosis range from palliative to curative and include nail debride-

TABLE 1

Selected treatments for onychomycosis

TREATMENT	WHEN TO USE	CONTRAINDICATIONS
Oral drugs		
Terbinafine (Lamisil)	Painful nails Dermatophyte pathogen confirmed Total dystrophic or significant nail involvement Diabetes or immunodeficiency If other treatments have failed	Liver disease* Concomitant use of†: Beta-blockers Caffeine Cimetidine Cyclosporine Monoamine oxidase inhibitors Rifampin Selective serotonin reuptake inhibitors Terfenadine Theophylline Tricyclic antidepressants
Itraconazole (Sporanox)	Painful nails Dermatophyte or nondermatophyte Diabetes or immunodeficiency Total dystrophic or significant nail involvement If other treatments have failed	Liver disease* Congestive heart failure Pregnancy Concomitant use of‡: Astemizole, terfenadine Cisapride Dofetilide Lovastatin, simvastatin Midazolam, triazolam Pimozide Quinidine
Topical drugs	When oral antifungals are contraindicated When onychomycosis is mild, distal When the patient prefers it To soften the nail and facilitate debridement As an adjunct to other treatments	
Debridement	As an adjunct to topical or oral treatment Painful toenails When oral antifungals are contraindicated	

*Measure alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at baseline and repeat if therapy exceeds 1 month
†These drugs can increase or decrease the clearance of terbinafine
‡Itraconazole can increase the plasma concentrations of these drugs

ment, topical therapy, oral antifungals, and combinations of these treatments.

A survey of more than 900 patients with onychomycosis found that most said the main reason they sought treatment was that the condition would not go away on its own.[19]

Patients are most satisfied with oral treatment. In one survey[20] only 7% of patients with mycotic nail infections were satisfied after topical treatment, compared with 23% of patients who underwent nail debridement and 80% of patients treated with an oral antifungal drug.

Yet only 35% to 65% of physicians suggest or recommend oral medications to patients presenting for treatment of nail fungus.[21]

These statistics suggest that most patients with onychomycosis are undertreated. In view

of the consequences of onychomycosis and the effectiveness of the new oral drugs, we ought to treat onychomycosis more aggressively and try to cure it.

The ideal antifungal treatment

An ideal antifungal agent would be:

- Broad-spectrum
- Taken up and incorporated into the nail matrix, diffusing through the epithelium of the nail bed to reach the nail bed hyperkeratosis, and penetrating into the ventral surface of the nail plate
- Effective, with high rates of clinical cure and mycological cure (ascertained by laboratory testing, fungal culture) and a low rate of relapse
- Effective when used short-term (ie, the duration of new nail regrowth), with few adverse effects and few drug interactions
- Cost-effective.[22,23]

No treatment (TABLE 1) yet meets all these criteria, but the newer treatments are substantially better than the older ones (see below).

Griseofulvin and ketoconazole

Ciclopirox is most effective in mild distal and lateral nail infection

The older oral agents griseofulvin and ketoconazole fall far short of the ideal. They tend to result in neither mycological nor clinical cure, have severe adverse effects, and have to be taken for as long as 6 to 18 months.

Griseofulvin, approved in 1958, covers neither *Candida* nor nondermatophyte molds. It must be given at least twice as long as the newer agents, it has many side effects, and relapse is common.

Ketoconazole, approved in 1980, was the first imidazole and is effective against *Candida*, but it too is limited by side effects (specifically hepatitis), requires a long treatment duration, and has significant relapse rates.

Itraconazole

In October 1995, itraconazole (Sporanox) became the first triazole to be approved in the United States for the treatment of dermatophyte onychomycosis. Its broad spectrum of activity includes dermatophytes, nondermatophyte molds, and yeasts.

Dosage. There are two dosage regimens for itraconazole:

- Continuous therapy: 100 mg a day for 12 weeks
- Pulsed (intermittent) therapy: 200 mg twice a day for 7 days each month for 2 months (for fingernail infections) or 3 months (for toenail infections). Pulsed therapy is at least as effective as continuous therapy and causes fewer side effects. The rationale for pulsed therapy is that the drug reaches the nail within 7 days of initial dosing and remains there for 6 to 9 months, although it is no longer detectable in the serum 1 week after ingestion.[5]

Safety. The principal safety concern with itraconazole is the potential for drug interactions. Itraconazole and its major metabolite are potent inhibitors of the cytochrome P450 3A4 enzyme system. Concomitant use with drugs metabolized by this enzyme system may result in increased plasma concentrations of these drugs, leading to potentially serious, life-threatening events.[5] Terfenadine, astemizole, simvastatin, lovastatin, midazolam, triazolam, and cisapride are absolute contraindications to itraconazole. Its use in patients taking digoxin, cyclosporine, or phenytoin requires close monitoring.

Itraconazole should not be used in patients with ventricular dysfunction, such as congestive heart failure, or in patients taking dofetilide, a class III antiarrhythmic medication.

Itraconazole should be avoided during pregnancy.

Adverse effects. Overall, itraconazole is well tolerated, with adverse effects reported in approximately 3% of patients.[5] The more common adverse effects are:

- Headache
- Gastrointestinal symptoms such as diarrhea, dyspepsia, abdominal pain, constipation, nausea, and flatulence
- Dermatologic symptoms such as rash, pruritus, and urticaria
- Liver enzyme elevations, reported in 0.3% to 0.5% of patients receiving itraconazole therapy. In the US package insert, hepatic enzyme monitoring is recommended if the drug is used for longer than 1 month. Symptomatic hepatitis, possibly due to itraconazole, occurs in an estimated 1 in 500,000 patients.[24,25]

Effectiveness. Mycological cure rates with 3-month treatment average 54%; clinical cure rates average 75%.

Cost. A 3-month course of itraconazole costs about $800.

Terbinafine

Terbinafine (Lamisil), approved in 1996 for the treatment of onychomycosis, is an allylamine with fungicidal activity capable of eradicating onychomycosis. It is indicated for dermatophyte infections. It has relatively poor efficacy against *Candida* and nondermatophyte molds.

In studies comparing terbinafine with itraconazole for *T rubrum* infections, terbinafine consistently proved more effective at attaining clinical and mycological cure.[23]

Dosage is 250 mg daily for 12 weeks for toenail infections. The drug can be detected in the plasma 8 to 12 weeks after completion of a 12-week continuous course.[26,27]

Safety. Liver enzyme testing is recommended when the drug is to be taken longer than 6 weeks. The incidence of clinically significant hepatobiliary dysfunction, for which no other cause was apparent and in which terbinafine was considered the possible causative agent, is estimated at 1 in 45,000 to 120,000 patients.[25,26]

A number of drugs can either increase or decrease the clearance rate of terbinafine.[26] Patients taking terbinafine should therefore avoid caffeine, cimetidine, cyclosporine, terfenadine, theophylline, and rifampin. Drug interactions have also been reported with tricyclic antidepressants, beta-blockers, selective serotonin reuptake inhibitors, and type B monoamine oxidase inhibitors.

Adverse events are infrequent but may include headache, taste disturbance, gastrointestinal symptoms, rash, pruritus, and urticaria.

Effectiveness. Mycological cure rates average 70%, and clinical cure rates approach 76%.

Cost. A 3-month course typically costs about $800.

Relapse rates

Relapse rates range from 3% to 20% for terbinafine, depending on follow-up, and from 21% to 27% for itraconazole.[23] Since 9 to 18 months may be necessary for an entire nail to grow out, any reappearance of onychomycosis before 18 months after initiating treatment may be mistakenly viewed as an unsuccessful cure rather than as a recurrence. Relapse has been attributed to chronic or recurrent tinea pedis, genetic predisposition, and *T rubrum* infections.[23]

Fluconazole

Fluconazole (Diflucan) is an oral treatment option, particularly when *Candida* is the suspected pathogen.

Although not approved for the treatment of onychomycosis, this medication has been used once weekly (100 to 200 mg) for infections caused by *Candida*.

Topical agents

Topical antifungal agents, while commonly used, have not (until recently) been approved by the US Food and Drug Administration for the treatment of onychomycosis. In 2000, ciclopirox nail lacquer 8% (Loprox, Penlac) became available in the United States for the treatment of mild to moderate onychomycosis.[28]

In double-blind, placebo-controlled clinical trials, once-a-day application of ciclopirox lacquer for 48 consecutive weeks was associated with mycological cure rates between 29% and 36% and complete (clinical and mycological) cure rates of 5.5% to 8.5%. The lacquer has a wide spectrum of activity against fungi, yeasts, and bacteria, along with the ability to penetrate the nail plate, all of which may account for its success.

Like other topical therapies, however, ciclopirox is most effective when used to treat mild distal and lateral onychomycosis. The necessarily long treatment course may hinder its effectiveness because of poor patient compliance.

Cost. A 6.6-mL bottle costs approximately $120.

Preventing athlete's foot and hyperhidrosis can help avoid toenail infection

PATIENT EDUCATION FOR PREVENTION

The foot is a perfect incubator for fungal infection, and it is important to educate patients about how to prevent athlete's foot and hyperhidrosis. To minimize the risk of fungal nail infection, we need to educate our patients about nail care and hygiene, factors that increase the risk of infection, and the proper daily use of topical antifungals and powders.

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Itraconazole inhibits cytochrome P450 3A4