CLINICAL REVIEW

# Onychomycosis

## *Recognition, Diagnosis, and Management*

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About 20% of the US population between the ages of 40 and 60 years have fungal nail disease, or onychomycosis. The incidence of this infection is increasing worldwide. Most cases of onychomycosis in the United States are caused by dermatophytes, but nondermatophyte fungi (molds or yeasts) may also be causative agents. To confirm the diagnosis of onychomycosis, a potassium hydroxide examination should be performed. A culture is necessary to determine the fungal pathogen and to aid in selecting appropriate therapy. Worldwide, fluconazole (not yet approved in the United States for onychomycosis), itraconazole, and oral terbinafine have superseded griseofulvin and ketoconazole as the agents of choice in treating onychomycosis. These newer systemic compounds have higher cure rates and cause fewer side effects than traditional agents. Intermittent dosing with itraconazole (3 or 4 one-week pulses of 200 or 400 mg daily) is the latest advance in the treatment of onychomycosis. This regimen has been found to be at least as safe and effective as short-term continuous therapy, yet more flexible, convenient, and economical.

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Onychomycosis, or fungal infection of the nails, is a common disease, especially in older persons. About 20% of the US population between the ages of 40 and 60 years have onychomycosis.[1] Only in the last 2 decades have safe, effective systemic treatments been available for this chronic superficial fungal disease. The recent introduction of oral terbinafine, the newer azoles, and especially pulse-dose therapy with itraconazole has greatly improved the treatment of this stubborn infection.

The worldwide incidence of onychomycosis is increasing, and a number of factors contribute to this rise. First, as the population ages, there are corresponding increases in chronic health problems, such as diabetes and poor peripheral circulation. Second, the number of persons who are immunocompromised because of infection with human immunodeficiency virus and the use of immunosuppressive therapies, cancer chemotherapy, or antibiotics continues to expand. Third, avid sports participation is increasing the use of health clubs, communal swimming pools, and occlusive footwear for exercise.[2(ppS25-S30)] In a small percentage of persons, onychomycosis may be caused by a genetic defect that causes alterations in immune function.[3]

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### PATTERNS OF INFECTION AND CAUSATIVE ORGANISMS

Perhaps 50% of all nail diseases are caused by fungi[4] that invade the nail unit through the nail bed or nail plate (**Figure 1**). Often, more than 1 type of organism is involved. Most cases of onychomycosis in the United States are caused by dermatophytes, but nondermatophyte fungi (molds or yeasts) may also serve as causative agents.[6(p5)]

Onychomycosis can be classified into 4 types according to the pattern of infection. *Distal subungual onychomycosis*, the most common type, affects the distal portion of the nail bed and the underside of the nail. In *proximal white subungual ony-*

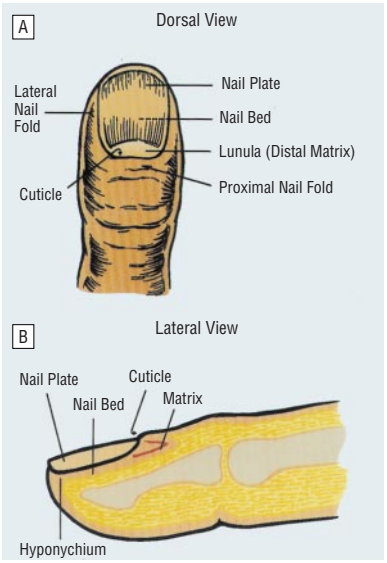


**Figure 1.** *The nail unit. A, Dorsal view; B, lateral view. Reprinted with permission from Scher et al.*[5]

*chomycosis*, the fungus enters through the cuticle to invade the proximal portion of the nail bed. The nail plate turns white proximally near the cuticle. This type is common in immunosuppressed patients, especially those with human immunodeficiency virus infection.[7,8] In both subungual types, *Trichophyton rubrum* is the most common causative organism. In *white superficial onychomycosis*, found mostly in the toenails of otherwise healthy individuals, direct fungal invasion of the nail plate surface, usually by *Trichophyton mentagrophytes*, produces a white, crumbly appearance.[6(p7)]

The fourth type, *Candida* onychomycosis, is usually caused by *Candida albicans* and has 3 subtypes. *Candida* paronychia, the most common of the 3, is marked by swelling and erythema of the proximal and lateral nail folds. In *Candida* onycholysis, the nail plate separates from the nail bed. *Candida* granuloma is characterized by direct invasion and thickening of the nail plate and associated paronychia. This type of yeast infection occurs mostly in immunocompromised patients.[5(p7)]

Progression of any of the 4 types so that the entire nail unit becomes involved is known as *total dystrophic onychomycosis*. The photographs in **Figure 2** illustrate this condition and the 4 basic patterns of infection.

## WHY TREAT ONYCHOMYCOSIS?

Increasingly, onychomycosis is being viewed as more than a mere cosmetic problem. Persons with unsightly infected nails may suffer embarrassment and upset over the condition; they may fear intimate situations or avoid touching their social partners; and they may experience pain during physical activities. In addition, persons with thickened, diseased nails, especially the elderly, may have to depend on health care professionals to clip their nails regularly.[9]

Healthy, intact nails serve as a protective barrier between the internal and external environments and are essential to proper balance (toenails) and normal motor coordination, sensory perception, and manual dexterity (fingernails). Fungi from the nails may precipitate secondary bacterial infections, cellulitis, id reactions, and chronic urticaria. Infected toenails may act as reservoirs for fungi, facilitating their transmission to other areas of the body and perhaps even to other people.[10]

## DIAGNOSIS OF ONYCHOMYCOSIS

Clinical diagnosis of onychomycosis is based on the patient's history, a physical examination, microscopy, and culture of nail specimens. Several nail disorders may mimic fungal nail infections:

- Hallopeau acrodermatitis (usually accompanied by painful nail inflammation)
- Lichen planus
- Nail bed melanoma
- Nail bed psoriasis (may be concomitant with fungal infection)
- Onycholysis
- Paronychia
- Reiter syndrome
- Yellow nail syndrome

Clinicians must be able to differentiate these entities from one another to initiate the most appropriate therapy. The differential diagnosis includes other disorders that lead to nail dystrophies, such as lichen planus and psoriasis of the nails. One should look for cutaneous signs of psoriasis on the scalp, gluteal folds, elbows, and knees, and nails should be evaluated for other signs of psoriasis, especially for pitting and small salmon-colored droplets evident in the nail plate. A practitioner can differentiate lichen planus by looking for the violaceous purple papules indicative of lichen planus on the extremities or by other signs on the mucous membranes.[11,12]

A potassium hydroxide preparation may help rule out nonfungal causes of nail disease, such as psoriasis or bacteria. Using direct microscopy, the physician can determine whether fungal elements are present, but not the specific pathogen. A fungal culture is essential to determine the causative organism and, in turn, to aid in selecting appropriate therapy. Although the potassium hydroxide examination cannot differentiate between pathogens, a positive reading indicates a greater than 90% probability of a dermatophyte infection in the toenails, and therefore has some merit as a sole diagnostic test.[12]

### Specimen Collection

Proper specimen collection is essential to accurate diagnosis. First, the nail area is cleansed with alcohol. Then, for distal subungual onychomycosis, the abnormal nail is clipped proximally and the nail bed and underside of the nail plate are scraped with a 1-mm curette; the outermost debris should be discarded. For proximal subungual onychomycosis, the normal surface of the nail plate is pared down at the lunula and the white debris is collected from the deeper portion of the plate. For white superficial onychomycosis, the white spots on the nail are scraped and the outermost surface is discarded; the white debris directly underneath is then collected. For *Candida* infection, the material closest to the proximal and lateral nail edges should be obtained. If *Candida* onycholysis is suspected, the lifted nail bed and, if necessary, the undersurface of the nail plate are scraped. For total dystrophic onychomycosis, any abnormal area of the nail plate or bed can be used as a specimen.[6(pp13-24)]


**Figure 2.** *Four patterns of onychomycosis. A, Distal subungual onychomycosis. B, Proximal subungual onychomycosis. C, White superficial onychomycosis. D, Chronic mucocutaneous candidiasis.*

### Microscopy, Culture, and Histological Analysis

Using some of the scrapings, the physician prepares a wet mount or smear with a solution of 20% to 25% potassium hydroxide mixed with 5% glycerol. Direct microscopy will indicate whether fungi are present or absent. For culture, 1 of the 2 media should contain cycloheximide, which inhibits the growth of many nondermatophytes. Growth on both media suggests a dermatophyte; growth on only the medium without cycloheximide may suggest a nondermatophyte. Treatment may be initiated on the results of direct microscopy but may need to be adjusted once the laboratory results are available. If neither microscopy nor culture yields a diagnosis, histological analysis of pulverized nail plate clippings will determine whether the pathogen is a fungus. This procedure is helpful when the patient has a dystrophic nail that has repeatedly failed to show a positive response with potassium hydroxide or culture.[6(pp13-24)]

## TREATMENT OF ONYCHOMYCOSIS

In choosing therapy, the physician needs to consider the patient's age and health, the infecting organism, potential side effects and drug interactions of the various agents, the cost of treatment, the dosage schedule, and patient compliance.[13] Oral griseofulvin and ketoconazole, once the agents of choice for the treatment of onychomycosis, have been superseded by newer systemic compounds that have higher cure and lower relapse rates, cause fewer side effects, and are suitable for short-term dosing.[14]

## NEWER ORAL COMPOUNDS FOR ONYCHOMYCOSIS

In the past few years, the Food and Drug Administration has approved 2 new antifungal agents for the systemic treatment of onychomycosis: the triazole itraconazole and the allylamine terbinafine. A second triazole, fluconazole, has shown efficacy, although it is not approved by the Food and Drug Administration for the treatment of onychomycosis.[15]

### Fluconazole

Fluconazole, a triazole developed in the 1990s, is active against dermatophytes, *Candida* species, and cer-

tain other fungi.[16] There is no clear dosage regimen that has been published with the use of fluconazole in onychomycosis; however, because fluconazole does not accumulate in the plasma or skin, it must be given daily or on an intermittent basis until the nail grows out, which would be 6 to 9 months for fingernails and longer for toenails.[17]

The most common side effects reported with fluconazole have been gastrointestinal tract upset, headaches, and rashes. Fluconazole-associated thrombocytopenia has also been reported, as well as rare cases of hepatotoxic reactions.[17]

### Terbinafine

Terbinafine, the first orally active allylamine to be extensively studied, is active against dermatophytes but not against yeasts, such as *C albicans*.[13] In a study of patients with dermatophyte infections of the nails receiving 250 mg/d for 3 months, terbinafine produced a mycological cure in 82% of cases at 1 year.[18] Terbinafine significantly reduces treatment time over the older systemic agents. At least 3 weeks, and sometimes up to 8 weeks, must pass before the drug can be detected in the distal nail plate for the first time.[19] When treatment is completed, the patient's nails are not normal; because of its pharmacokinetics, terbinafine stays in the nail for 3 months after it is discontinued. Terbinafine also remains in the blood for 6 weeks after it is discontinued.

The most common side effects of this compound have been mild to moderate dyspepsia and rashes, including rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis.[17,20] There have also been reports of taste disturbance, neutropenia, pancytopenia, and hepatic reactions.[21]

### Itraconazole

Itraconazole, one of the newer members of the azole family, has the broadest spectrum of action of any oral antimycotic agent used in dermatology.[16] It is highly effective in the treatment of dermatophyte, yeast, and some nondermatophyte mold infections of the nails.[16,19] Clinical cure rates as high as 90% may be achieved during a period of several months.[22] Itraconazole's penetration of the exact area of organism infection—the nail bed—and its persistence in the nails explain the high cure rates achieved with this compound.[23] Although infected nails do not appear normal until several months after the completion of treatment, they grow out free of fungus.

The most common side effects reported with itraconazole have been headache and minor gastrointestinal tract upset. Also, a low incidence of elevated liver function test results has been reported, but these levels return to normal on cessation of therapy.[24] Both itraconazole and terbinafine have excellent safety profiles, but itraconazole has been used by a much larger number of patients than terbinafine.[22]

### Pulse Therapy

Several small studies indicate that intermittent (pulse) dosing with fluconazole, combined with pretreatment with urea, may be useful in treating onychomycosis.[25-27] However, the pharmacokinetics of fluconazole necessitate the continuation of therapy until the diseased nail has grown out.

The itraconazole dosing strategy for onychomycosis has progressed from long-term therapy to 3-month therapy to short-term pulse therapy. The recommended dosage in the United States for fungal toenail disease is 200 mg/d for 12 consecutive weeks. Pulse dosing has been approved by the Food and Drug Administration for fingernail infection with the use of 200 mg twice daily for 1 week per month for 2 months, while pulse dosing of both fingernails and toenails is being used successfully in Europe. Research indicates that an effective pulse regimen is 200 mg twice daily for 1 week per month for 3 or 4 consecutive months for toenails.[28,29] When this regimen was used in a recent study of 28 patients with toenail onychomycosis (dermatophytes or some nondermatophyte molds), 26 patients (93%) experienced a clinical cure by their final visit (month 12, on average, after the start of treatment).[28] The only adverse reaction reported was a mild headache in 1 patient. In an earlier pulse-dosing pilot study in which 50 patients were enrolled, similar results were achieved.[28]

The efficacy of pulse dosing in the studies completed to date can be explained by the pharmacokinetic properties of itraconazole. As a recent study[29] demonstrated, the compound penetrates the nail via the nail bed within 7 to 14 days and persists at therapeutic levels for 6 to 9 months after treatment, even though plasma levels fall rapidly once therapy has ended. That study compared the uptake and elimination of oral itraconazole in the nails of volunteers who received either 200 mg or 400 mg daily for 7 days with the pharmacokinetics of itraconazole in the nails of volunteers who received either 3 or 4 monthly 1-week cycles of 400 mg daily. In the fingernails, drug penetration was found to occur in 2 waves; the first wave began at day 7 of treatment, and the second wave at month 4. In the toenails, no biphasic penetration could be detected, perhaps because the toenails grow more slowly. However, the study confirmed that higher drug dosages produce much higher drug concentrations in the nails and that, in turn, these higher concentrations produce higher cure rates.

Pulse therapy with itraconazole has obvious advantages over continuous therapy. First, the pulse-dosing schedule can be readily adapted to the individual patient and the clinical situation. For example, the dosage size and number of pulses can be tailored to the severity of the infection. Second, clinical experience with pulse-therapy regimens of 200 mg twice daily has shown this treatment to be highly effective and to be associated with a low incidence of side effects and high patient compliance.[19,28] All 28 patients in the study by De Doncker and colleagues[28] expressed a preference for pulse therapy over continuous therapy. Finally, pulse therapy is cost-effective, because it reduces the total amount of drug administered. In 1 study,[2(ppS103-S106)] the cost of 3 pulses of itraconazole therapy (200 mg twice daily) was less than half the cost of 3 months of continuous itraconazole therapy (200 mg/d) and less than one fourth the cost of

**Guidelines for Laboratory Monitoring***

| Treatment | Complete Blood Cell Count | Liver Function Tests |
|---|---|---|
| Terbinafine, continuous therapy >4 wk | Baseline, repeat after 4 wk | Baseline, repeat after 4 wk |
| Itraconazole, continuous therapy >4 wk | No | Baseline, repeat after 4 wk |
| Itraconazole, pulse therapy | No | One pulse: not indicated; 2 or 3 pulses: no specific recommendations |
| Fluconazole, pulse therapy | No | No specific recommendations |

**Data from Del Rosso and Gupta.[32]*

9 months of continuous fluconazole therapy (100 mg/d).

Itraconazole pulse therapy appears to modify the structure of the nail plate, either as a result of or in association with an increased rate of nail growth. A small study[30] compared the nail surfaces of patients who received either continuous or pulse therapy with itraconazole. Analysis of their nail surfaces by optical profilometry showed that the patients who received pulse doses had both greater nail growth and substantially more nail beading (ie, ridges and roughness) than those who received continuous dosing. Onychomycosis slows nail growth, so the investigators concluded that a higher dosage of itraconazole showing a better antifungal effect might be able to restore normal nail growth more rapidly.[30]

### Laboratory Monitoring During Treatment

Regardless of which continuous oral antifungal agent the physician prescribes for the patient with onychomycosis, a baseline liver profile and a blood chemistry study are recommended; however, liver function tests and complete blood cell counts are not indicated for itraconazole pulse therapy. Only patients with no preexisting liver dysfunction should be given antimycotic agents for onychomycosis.[24] All oral antifungal agents pose a small risk of hepatic injury,[31] so any patient who is receiving long-term antifungal therapy for onychomycosis should undergo laboratory monitoring approximately every 4 to 6 weeks.[17] Patients should be instructed to let the physician know immediately if any signs or symptoms of potential hepatic reaction develop—namely, jaundice, upper abdominal tenderness, malaise, dark urine, pale stools, fatigue, nausea, or vomiting during therapy. Along with the liver function tests, a complete blood cell count with platelet count should be recommended for patients taking fluconazole and terbinafine[17,32] (**Table**).

### Adjunctive Therapies

Topical antifungal agents are of limited efficacy when used alone or with older oral antifungal agents to treat onychomycosis, but they may result in a more rapid cure when used in conjunction with the newer systemic compounds. Studies are needed to test this hypothesis. Topical agents may also help prevent the recurrence of tinea pedis (athlete's foot), which often accompanies fungal toenail infection.[3]

Surgical nail removal is not often used because of the discomfort, cost, and possible cosmetic disfigurement. Another optional adjunctive therapy for patients with only 1 or 2 infected nails is the application of 40% urea ointment[27] under occlusion. This procedure removes only the infected portions of the nail, leaving healthy nail intact.

There are 6 key steps in the management of onychomycosis:

1. Perform clinical diagnosis; request laboratory diagnosis.
2. Débride nail while collecting specimen.
3. Begin patient counseling.
4. Begin oral therapy; perform baseline laboratory tests.
5. Reinforce hygienic measures; make sure expected results of therapy are being achieved.
6. Perform follow-up examinations and laboratory tests.

## PREVENTING RECURRENCES AND RELAPSE

The physician should urge patients who are receiving treatment for toenail onychomycosis to use hygienic measures that will help prevent relapses or recurrences. The following are some suggested measures.[3,6(pp13-24)]

- Avoid going barefoot in public places, especially health clubs, public showers, locker rooms, and hotel rooms. Instead, use appropriate footwear (such as thong sandals in public showers).
- Keep feet cool and dry. Wear absorbent cotton or wool socks.
- Apply topical antifungal medication regularly to the feet and toenails.
- Discard old shoes and "rest" shoes periodically to reduce their exposure to fungi.
- Apply an antifungal powder or spray to the inside of shoes once a week or more.

## CONCLUSION

Pulse therapy with itraconazole is the latest step in optimizing the treatment of onychomycosis. Studies completed to date indicate that this short-term regimen offers the advantages of greater flexibility, convenience, and economy than previous regimens, together with equal or superior efficacy, low incidence of side effects, high rates of compliance, and faster nail growth.

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