Onychomycosis

by Boni E. Elewski, MD, University Hospitals of Cleveland

It has been estimated that only 50% of all dystrophic nails are caused by fungi[1]; of these, over 90% are caused by dermatophytes.[2] Because of these facts, no patient with dystrophic nails and suspected onychomycosis should be treated without first establishing a diagnosis—and, ideally, identifying the particular pathogen.

DEFINITION

Onychomycosis, or fungal nail infection, refers to fungal organisms invading the nail unit via the nail bed or nail plate. It affects about 20% of the U.S. population between 40 and 60 years of age[3]—an amazing incidence, in that onychomycosis is a relatively new disease, rarely seen in the United States prior to the Second World War. Dermatophytes are the most common pathogens (Table 1)—accounting for more than 90% of the infections in one large study (involving 2,662 cases).[2] The other infections in that study were caused by *Candida albicans* (5.5%), *Scopulariopsis brevicaulis* (1.6%), and miscellaneous organisms (1.7%).[2] As some antimycotics used for onychomycosis, such as griseofulvin, act only against dermatophytes, it is important to rule out a nondermatophytic yeast or mould that may be resistant to the selected antifungal.

Table 1. Major Causes of Onychomycosis

Dermatophyte Fungi
- *Epidermophyton floccosum*
- *Trichophyton mentagrophytes*
- *Trichophyton rubrum*

Nondermatophyte Fungi
- *Aspergillus* spp.
- *Acremonium* spp.
- *Fusarium* spp.
- *Scopulariopsis brevicaulis*
- *Scytalidium dimidiatum*
- *Scytalidium hyalinum*

Yeast
- *Candida albicans*

Onychomycosis occurs in distal subungual, proximal white subungual, white superficial, and *Candida* forms.[4] These four varieties differ by the pattern of fungal invasion into the nail unit, which directly affects the clinical appearance of the diseased nail. Also, each variety is caused by a different group of fungal organisms.

Distal subungual onychomycosis, the most common form, is generally caused by dermatophytes. The organism is usually established in the stratum corneum of the adjacent skin before it invades the nail unit. The fungus first invades the distal nail bed, causing hyperkeratosis of the nail bed, onycholysis, and thickening of the nail plate. Both fingernails and toenails can be infected, but toenail infection occurs four times more frequently,[5] probably because of the greater incidence of tinea pedis than of tinea manus.

In *proximal white subungual* onychomycosis, the organism invades under the cuticle and infects the proximal rather than distal nail bed. The nail plate remains intact and develops a white color proximally near the cuticle. Again, dermatophytes are the predominant pathogen. The clinician should be aware that proximal white subungual onychomycosis is common in immunocompromised patients, particularly in those infected with HIV.[6] The condition is rare in healthy, immunocompetent individuals and is seen in both fingernails and toenails.

In *white superficial* onychomycosis, fungal organisms invade the nail plate directly, producing a crumbled white surface. The dermatophyte *Trichophyton mentagrophytes* and a variety of moulds are causative pathogens, including species of *Acremonium*, *Fusarium*, and *Aspergillus*.[4] Toenail infection is significantly more common than fingernail infection.

Candida onychomycosis refers to a rare syndrome limited to patients afflicted with chronic mucocutaneous candidiasis; as the name suggests, it is caused only by *Candida*. However, *Candida* can cause chronic paronychia infection, and can also cause primary onycholysis, especially in those with peripheral vascular disease.[4]

DIAGNOSIS OF ONYCHOMYCOSIS

The diagnosis of onychomycosis is best established by a fungal culture. In addition, a potassium hydroxide preparation (KOH) may be helpful in ruling out nonfungal etiologies. Direct microscopy using 15% to 20% potassium hydroxide will reveal only the presence or absence of fungal elements, but not the fungal pathogen. A fungal culture will ascertain the causative organism, and therefore allow the clinician to determine an appropri-

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ate therapy.[7] Although over 90% of patients with onychomycosis are infected by dermatophytes, other potential pathogens—including *Candida* and nondermatophyte moulds—are important to identify, as in some instances no effective systemic or topical therapy exists.

Material for culture and KOH should be taken from the infected nail bed and nail plate. In distal subungual onychomycosis, the nail bed generally has the highest number of viable fungal particles. A 1-mm curet is the best device for removing infected nail particles and debris. When nail bed debris is either unavailable or insufficient, nail plate clippings can be used, but they must be pulverized prior to culturing or direct microscopy. Material can be sent to a reference laboratory in a sterile container such as a sterile urine cup, or in commercially available collection devices such as the Derma-Pak. To search adequately for all pathogens, the laboratory should use media with and without cycloheximide, such as Mycosel and Sabouraud's glucose agar.[2,7] Cycloheximide is an antifungal added to agar to isolate dermatophytes and other pathogenic fungi. Ideally, the culture should be performed when the patient has not been using topical or systemic antifungal drugs for 2 to 4 weeks.

If both culture and KOH fail to yield a diagnosis, nail plate clippings can be sent in a formalin container for histologic analysis of fungal elements.[8] Again, as with the KOH, only the presence or absence of fungal elements—rather than the fungal pathogen—will be determined. This is a helpful technique, however, with a dystrophic nail that repeatedly has been culture-negative and KOH-negative. A nail biopsy is a last resort.

THERAPY

After onychomycosis has been established by KOH, fungal culture, or histologic analysis, the clinician can choose from a wide variety of therapeutic options. Factors to consider in choosing therapy include: causative pathogen, potential adverse effects and drug interactions, cost of treatment, dosage schedule, and patient compliance (Table 2).[9] When being treated with a systemic agent, the patient should see the physician every 1 to 2 months to monitor improvement in nail growth. Keep in mind that fingernails grow 2 to 3 mm per month and toenails about 1 mm per month, which also is the amount of new nail that should grow out monthly if the therapeutic regimen is effective. If this amount of new nail is not seen, the therapy is probably ineffective, and should be reevaluated. Factors to consider are incorrect dosage of antifungal agent, patient compliance, drug interaction, and wrong diagnosis.

Table 2. Factors to Consider in Selecting Therapy

- Age and health of patient
- Causative pathogen
- Dosage schedule
- Patient compliance
- Cost
- Potential drug interactions
- Potential side effects

SYSTEMIC ANTIFUNGALS

Griseofulvin

Introduced in 1958, griseofulvin was the first oral antimycotic used to treat onychomycosis. Although initially heralded as a promising therapy, griseofulvin has numerous limitations that restrict its use in onychomycosis.[4,9] It is effective only against dermatophytes and has no effect on *Candida* or other nondermatophyte fungi. *Candida* may be responsible for one out of twenty cases, mostly in fingernails. Because of its fungistatic activity, griseofulvin must be administered daily until the infected nail plate grows out, which is generally 6 to 9 months for fingernails and 12 to 18 months for toenails.

Griseofulvin appears to be delivered to the nail plate via the matrix, but the pharmacokinetics of the drug have not been well studied. It is clear, however, that the drug does not persist in the nail plate more than 1 or 2 weeks, another factor explaining the long course of therapy needed. The ultramicrosize form is best suited for onychomycosis, and most patients require 750 mg to 1000 mg daily of the ultramicrosize form to eradicate infection. This translates to Gris-Peg 250 mg three to four times a day or Fulvicin P.G. 330 mg two to three times a day, dosed daily until normal nail has grown out and replaced the dystrophic nail. It is important to stress that underdosing will not yield favorable results, and may account for many therapeutic failures.

Before griseofulvin is administered, a baseline complete blood count, liver profile, and urinalysis should be ordered, followed by monitoring of these parameters every 2 months. Griseofulvin is contraindicated in pregnancy, lupus, and acute intermittent porphyria. In addition, the drug appears to interfere with oral contraceptives, and, given its potential for producing fetal abnormalities,

caution should be exercised in women of child-bearing potential.[4] With long-term regimens, patients frequently experience minor annoyances, including headaches and gastrointestinal disturbances. The requirement for daily dosing, combined with numerous potential adverse effects (Table 3), restricts griseofulvin's use as an agent for onychomycosis. Further, cure rates are disappointing. Only about 25% of patients with toenail disease and approximately 70% of those with fingernail infection are cured, despite long-term dosing at appropriate levels.[4] Table 4 presents an analysis of comparative cost.

Table 3. Potential Adverse Effects of Griseofulvin

- Anemia
- Headache
- Hepatotoxicity
- Interference with oral contraceptives
- Leukopenia
- Nausea, gastrointestinal disturbance
- Photosensitivity
- Precipitation of subacute cutaneous lupus erythematosus
- Proteinuria
- Thrombocytopenia

Ketoconazole

Ketoconazole was the first broad-spectrum oral antifungal and the first oral azole. Ketoconazole acts against dermatophytes as well as *Candida*, and, like griseofulvin, must be dosed daily in onychomycosis.[4,9-11] It is fungistatic and has no persistent binding to the nail plate. Daily dosages of 200 mg are generally sufficient. Cure rates in onychomycosis are higher with ketoconazole than with griseofulvin. About 30% to 50% of patients with toenail disease and over 70% with fingernail infection are reported cured in clinical trials.[4]

Because of its broad spectrum, ketoconazole was initially touted as the ideal agent for onychomycosis, but the potential risk of hepatotoxicity has severely restricted its use. The published risk of 1 in 10,000 to 15,000 patients may be low, as a result of underreporting, and hepatotoxicity is more common in patients with onychomycosis.[4,12] Caution must be exercised in patients on long-term therapy. Ketoconazole is appropriate for patients who are allergic or intolerant to griseofulvin, and for those with *Candida* onychomycosis. Because an acidic environment enhances absorption, ketoconazole should be taken 2 hours before antacids or H-2 blockers. Preliminary data suggest, however, that the newer triazoles and members of the azole family, itraconazole and fluconazole, are safer than ketoconazole, and therefore more suited to onychomycosis therapy.

Before ketoconazole is administered, a baseline liver profile should be ordered, followed by monitoring of hepatic parameters in 2 weeks, then at monthly intervals. Patients at highest risk for hepatotoxicity are women, persons more than 40 years of age, and

Table 4. Comparative Treatment Costs

Antifungal agent*	Unit (mg) (ultra-microsize)	Cost per unit ($)**	Dose range (mg)	Cost per dose	Doses per month	Duration (months)	Cost per course of treatment ($)
Griseofulvin	250	1.38	750-1000	4.14-5.52	30	12	1490.40-1987.20
	330	0.96	660-990	1.92-2.88	30	12	691.20-1036.80
Ketoconazole	200	2.35	200	2.35	30	12	846.00
Itraconazole	100	4.58	200	9.16	30	3	824.40
			400	18.32	7	4	512.96
			400	18.32	7	3	384.72
Fluconazole	100	5.82	150	8.73	4	9	314.28
	200	9.45	300	14.18	4	9	510.30

* This table does not include oral terbinafine, which is not yet available in the United States.

** Cost to patient in retail chain pharmacy, Cleveland, Ohio, July 15, 1994.

Note: This table does not take into consideration cost of blood work, physician office visits, or time missed from work.

those with a history of drug allergies or hepatotoxicity.

Ketoconazole is also contraindicated in patients taking terfenadine or astemizole.

INVESTIGATIONAL AGENTS

The newer triazoles, fluconazole and itraconazole, are currently investigational agents in the United States for onychomycosis, as is ketoconazole. However, they are approved by the FDA for other indications. Fluconazole is indicated for cryptococcosis and candidiasis and has been used extensively worldwide in the AIDS epidemic. Fluconazole is under investigation for use in onychomycosis in the United States and is currently used for this indication in other countries. Itraconazole is a newer agent and is indicated in the United States for histoplasmosis, blastomycosis, and, more recently, aspergillosis. Itraconazole is currently being used for onychomycosis in many other countries.

The oral allylamine, terbinafine, is being used for onychomycosis in many countries. It is under investigation in the United States for onychomycosis as well as other indications.

Fluconazole

Fluconazole is a member of the azole family and has activity against dermatophytes, *Candida*, and other fungi.[13] This agent has received much acclaim in the HIV-infected patient, for whom it is a useful prophylactic agent against *Candida* and disseminated *Cryptococcus*.

Fluconazole has only recently been studied as a therapy for onychomycosis.[14] As with griseofulvin and ketoconazole, long-term dosing is generally required. The pharmacokinetics in the nail have not been well studied, but the drug reaches the nail plate via the nail bed. Dosing at 50 mg or 100 mg either daily or on alternate days until normal nail has grown out is generally effective. A new "pulse," or intermittent, regimen also reported to be effective is 150 mg administered once a week for 9 months.[15] In those patients not responding, this pulse dose can be increased. Patients taking multiple medications may enjoy the freedom of only 1 day per week dosage.

Fluconazole has an advantage over griseofulvin in being effective against dermatophytes and *Candida,* and, unlike griseofulvin, it leads to a minimum of gastrointestinal disturbances. Preliminary data suggest that it is much safer than ketoconazole. To date, fluconazole has an excellent safety profile, fulfilling this requirement of an ideal antifungal for onychomycosis. Fluconazole can be administered with or without food, and without regard to gastric acidity. Despite its worldwide use in HIV-infected patients, adverse events are minimal.[16] In particular, hepatotoxicity is extremely rare. However, until more data are available, a periodic liver profile, complete blood count, and platelet count should be monitored in patients on long-term therapy.

Itraconazole

Itraconazole is the newest member of the azole family and is currently used as first-line therapy for onychomycosis in many countries. Effective against dermatophytes, *Candida*, and some nondermatophyte moulds, itraconazole has the broadest spectrum of all oral antifungal drugs.[17-19] In addition, the pharmacokinetics in the nail have been well studied.[20,21] Itraconazole is detected in the nail plate within 7 days of administration. It penetrates the nail plate from the nail bed and persists in the nail plate for up to 9 months after therapy is discontinued. This is probably related to its lipophilic property, causing the drug to adhere to the lipophilic cytoplasm of the keratinocytes in the nail plate (Table 5).[9,20,21]

Table 5. Pharmacokinetics and Potential Adverse Effects of Itraconazole

Pharmacokinetics

- Lipophilic
- Delivered to nail plate within 7 days
- Delivered to nail plate from nail bed
- The level in the nail plate rises 10-fold when the dose is increased from 100 mg four times a day to 200 mg four times a day
- Serum levels drop to 0 within 7 days of discontinuation
- Persists in nail plate for 6 to 9 months after therapy is discontinued

Potential Adverse Effects

- Nausea, gastrointestinal disturbance
- Rash
- Pruritus
- Hypokalemia
- Reversible telogen effluvium
- Hepatotoxicity

Based on the nail pharmacokinetics, there are two published dosage regimens in onychomycosis. The first, or "fixed," dose is 200 mg daily for 12 weeks in toenail disease and for 6 weeks in fingernail disease.[9,21] Cure rates are about 80%. It is important to emphasize to the patient that when therapy is discontinued, the nail appearance is not

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