Onychomycosis is an increasingly common fungal infection of the nail unit. Although the exact incidence of onychomycosis is unknown, studies estimate that between 2% and 18% of the population worldwide is affected [1]. The results of a recent survey of persons with nail dermatophytosis in the United Kingdom suggested a prevalence of 2.7% in the general population [2]. In the previous century, onychomycosis was rare and generally occurred in the fingernails of persons with tinea capitis and in their care givers. Both onychomycosis and tinea pedis are now common and have been estimated to occur in 15%–20% of persons aged 40–60 years [3].

The rise in the incidence in onychomycosis is caused by a variety of factors including the aging of the population, an increase in the use of immunosuppressive therapies, an increase in exposure to organisms through communal bathing and health spas, and the use of tight-fitting occlusive footgear for many athletic activities [4]. The increasing incidence of infection due to HIV also contributes to the rise in the incidence of onychomycosis [5] because nails are commonly infected and are one of the important dermatologic signs of the progression of HIV disease. Toenail infections are four times more common than fingernail infections [6].

An accurate diagnosis of onychomycosis depends on proper collection of the specimen, suitable transport of the specimen to the laboratory, correct microscopic examination, use of appropriate culture media, and correct identification of the causative organism. Treatment of the infection includes a combination of topical therapy, surgical or chemical nail avulsion, and systemic therapy. The new generation of systemic agents (itraconazole, fluconazole, and terbinafine) is associated with a higher cure rate and shorter courses of treatment than are the older systemic antifungal drugs (i.e., griseofulvin and ketoconazole); these characteristics have sparked new interest in onychomycosis. Of these newer antifungals, itraconazole and terbinafine are the only agents currently approved by the U.S. Food and Drug Administration for the treatment of onychomycosis.

The Etiology of Onychomycosis

Onychomycosis is caused by dermatophytes, yeasts, and nondermatophytic molds. The dermatophytes Trichophyton rubrum and Trichophyton mentagrophytes cause ≥80% of all cases of onychomycosis in temperate zones [7]. Approximately 5%–17% of fungal nail infections are caused by yeasts, and Candida albicans is isolated in >70% of these cases [6]. C. albicans is more frequently cultured from fingernails than from toenails. Nondermatophytic molds such as Scopulariopsis, Scytalidium, Acremonium, and Fusarium cause approximately 3%–5% of cases of fungal nail disease, which may develop secondary to dermatophytic infection, trauma, or direct invasion into the nail [8]. The relative percentages of cases due to these etiologic agents vary according to geographic location (table 1) [7, 9–12]. For example, scytalidium infections have been reported as a major cause of nail disease in tropical and subtropical countries and may account for 50% of cases of onychomycosis in Southeast Asia [13]. It is important to identify fungal nail infections due to nondermatophytic
molds because the nondermatophytes are not effectively eradicated by most of the available antifungal agents.

Preexisting cases of tinea pedis predispose an individual to onychomycosis. The condition usually starts when trauma weakens the seal between the nail plate and the nail bed, allowing fungal organisms to penetrate the nail unit. The increased incidence of onychomycosis, which is associated with aging, may be due to slower growth of the nail, increased trauma to the nail plate, decreased circulation, and changes in the size and width of the foot. Exposure to heat and moisture worsens the condition, and immunosuppression alters the body’s ability to combat the infection. Some investigators have suggested that estrogen exerts a protective effect against onychomycosis, as the infection is observed more frequently in postmenopausal women [14]. On the other hand, testosterone might aggravate the condition, since onychomycosis is seen more frequently in boys older than 14 years and is rarely seen in children under the age of 12 years. Indeed, increased age itself—not hormonal factors—may be a major contributor to the development of onychomycosis.

Genetic etiologic factors that predispose individuals to onychomycosis may include an autosomal dominant transmission with incomplete penetrance, leading to variable clinical expression; a selective T cell nonrecognition factor, which could lead to differences in immunologic response to infection or to atopy; or a genetic influence on the keratin itself. The presence of these genetically variant patterns alters the keratin protein within the nail structure, making the nail more susceptible to fungal invasion [15].

Clinical Manifestations of Onychomycosis

Four patterns of onychomycosis have been described: distal lateral subungual onychomycosis; superficial white onychomycosis; proximal subungual onychomycosis; and onychodystrophy, which is associated with candidal infection. The latter category is further classified as candidal paronychia, onycholysis, chronic mucocutaneous candidiasis, and distal lateral subungual onychomycosis. The clinical presentations of each form of the disease are presented in figure 1. The relative percentages of etiologic agents that cause each clinical manifestation vary according to geographic location. Total dystrophic onychomycosis is sometimes considered an additional category that is associated with an advanced stage of any of the four patterns of onychomycosis.

Distal lateral subungual onychomycosis. This manifestation of the disease begins with initial fungal penetration of the stratum corneum from the hyponychial area or from the lateral nail fold. It is characterized by yellow-brown discoloration of the nail plate, onycholysis, and subungual hyperkeratosis. It is the most common clinical presentation of onychomycosis and is most often caused by T. rubrum or T. mentagrophytes. A small percentage of cases are caused by Epidermophyton floccosum, Trichophyton tonsurans, Trichophyton violaceum, and miscellaneous Microsporum species.

Superficial white onychomycosis. Fungi directly invade the nail plate in superficial white onychomycosis, creating a white, crumbly appearance. The most common agent is T. mentagrophytes, but species of Fusarium or Acremonium may also be the etiologic agents. Superficial white onychomycosis is almost always found in toenails. The initial lesions may be randomly dispersed but will eventually coalesce to include the entire surface of the nail. This infection is capable of producing progressive dystrophy of the nails and will invade the cornified layer of the nail bed and hyponychium.

Proximal subungual onychomycosis. Proximal subungual onychomycosis is the least common clinical presentation of onychomycosis in healthy individuals. The infection penetrates the proximal portion of the nail, resulting in hyperkeratosis and onycholysis. The characteristic clinical appearance is a white hue that extends distally from under the proximal nail fold. The distal portion of the nail unit remains normal until late in the course of the disease, when the entire nail plate is affected. This infection occurs in both fingernails and toenails and is primarily caused by T. rubrum. The proximal white subungual pattern particularly affects immunocompromised patients. A recent study showed that 87.1% of 62 patients with AIDS had proximal white subungual onychomycosis [16].

Candidal onychomycosis. There are three recognized forms of nail dystrophy associated with candidal infection. Candidal paronychia results in swelling and erythema of the proximal and lateral nail folds, with secondary involvement of the nail plate; this condition is common in persons whose hands are constantly immersed in water. Onycholysis is often a result of the disease being present.

Table 1. Geographic variations in etiologic agents.

<table>
<thead>
<tr>
<th></th>
<th>Canada (Sumerbell; n = 3,000)</th>
<th>USA (Greer; n = 431)</th>
<th>UK (Clayton; n = 699)</th>
<th>Belgium (Willemsen; n = 700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatophytes</td>
<td>90.5</td>
<td>23</td>
<td>81</td>
<td>40</td>
</tr>
<tr>
<td>Yeasts</td>
<td>5.5</td>
<td>63</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>Nondermatophyte molds</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Mixed</td>
<td>†</td>
<td>8</td>
<td>†</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. All data are in percent. This table is reprinted with permission from the International Journal of Dermatology [12]. † Not specified.
Figure 1. Manifestations of onychomycosis. Top left: Distal lateral subungual onychomycosis. Top right: Superficial white onychomycosis. Bottom left: Proximal subungual onychomycosis. Bottom right: Candidal infection (courtesy of Dr. Gary D. Palmer, Dayton, Ohio).

Figure 2. Psoriasis of the nail (courtesy of Dr. Gary D. Palmer).

Figure 3. Chronic onycholysis (courtesy of Dr. C. Ralph Daniel III, University of Mississippi Medical Center, Jackson, Mississippi).
Diagnosis of Onychomycosis

Findings on microscopy and the results of fungal cultures confirm the diagnosis of onychomycosis. Confirmation of fungal infection of the nail is required so that appropriate therapy can be initiated, since other nail diseases such as psoriasis and lichen planus can mimic onychomycosis clinically. When culturing nails, subungual debris should be collected as proximally as possible, since the outermost debris may contain contaminants and nonviable hyphae.

Before the nail specimen is viewed, it should first be softened and cleared in 20%–30% KOH. The detection of spores and fungal hyphae can be enhanced by using stains such as Parker’s blue-black ink (1 part KOH to 1 part ink), Polychrome Multiple Stain, or fluorochromes [8]. Chlorazol black E may also be added as a counterstain because it is chitin specific and, unlike the blue-black ink, is less likely to stain other potential contaminants such as cotton or elastic fibers. Calcofluor white is a nonspecific fluorochrome stain that binds with β-configuration polysaccharides. It has been used for detecting fungi in clinical specimens and has been found to be significantly more sensitive than the KOH wet mount in observing fungal pathogens [17]. The limitation of the KOH procedure is that it is only a screening test for the presence or absence of fungi and cannot identify specific pathogens.

The identity of the pathogen can be confirmed only by fungal culture. Cultures can be done using dermatophyte test media, Mycosel (BBL Becton Dickinson Microbiology Systems, Cockeysville, MD), or Sabouraud dextrose agar. Overgrowth by nondermatophytes and bacteria is avoided by modifying the chosen medium with antibacterial agents (chlorotetracycline and gentamicin) and by using media with and without cycloheximide.

Table 2. Nail diseases that may mimic onychomycosis.

- Traumatic onychodystrophies
- Pachyonychia congenita
- Contact dermatitis
- Nail bed tumors
- Yellow-nail syndrome
- Idiopathic onycholysis

Conditions that Mimic Onychomycosis

The differential diagnosis of onychomycosis includes several nail diseases that may be clinically indistinguishable from onychomycosis (table 2). The most common of these diseases is psoriasis. A nail biopsy may be required to obtain a definitive diagnosis.

Distinguishing between onychomycosis (figure 1) and psoriasis (figure 2) can be difficult, since subungual hyperkeratosis, onycholysis, splinter hemorrhages, and diffuse crumbling are clinical signs of both conditions. The finding of a positive fungal culture does not rule out psoriasis because dermatophytes or other fungi can occasionally colonize psoriatic nails, especially when the nail plate is grossly deformed. Three clinical symptoms of psoriasis (the presence of fine pitting, the small salmon-colored oil-drop sign of onycholysis that is present in psoriasis but absent in onychomycosis, and the frequent involvement of nails in both hands in cases of psoriasis), in addition to evidence of psoriasis at another site such as the elbows and/or knees, are helpful in differentiating between the two conditions.

Lichen planus, an inflammatory skin disease, may involve the nails in ~10% of affected patients [6]. It may involve the nails on both hands and both feet. The most common manifestations are onychorrhexis (exaggerated longitudinal ridging) and “angel wing deformity” (the central portion of the nail is raised, and the lateral portion is depressed). A key clinical finding that differentiates lichen planus from onychomycosis is the presence of Wickham’s striae in typical lesions of the skin or mucous membranes. Pterygium may also be seen in patients with lichen planus but not in those with onychomycosis.

Contact dermatitis of the hyponychium may produce hyperkeratosis similar to that seen in onychomycosis. Contact dermatitis is usually occupation-related, and a differential diagnosis can easily be made by obtaining a careful clinical history and performing a patch test.

Repeated trauma to the nails can be responsible for onycholysis (figure 3) that resembles onychomycosis. In traumatic onychodystrophies, the onycholytic space can be colonized by microorganisms that produce pigmentation of the onycholytic area. A differential diagnosis can be made by clipping the onycholytic nail. In cases of onychomycosis, clipping the onycholytic nail reveals a hyperkeratotic nail bed. In cases of traumatic onychodystrophy, clipping the onycholytic nail reveals a normal nail bed unless the trauma is chronic.
Nail bed tumors should also be considered in the differential diagnosis of onychomycosis and can be ruled out by obtaining a radiograph. Melanomas of the nail can be differentiated from onychomycosis by biopsy.

An uncommon nail disease that sometimes needs differentiation from onychomycosis is yellow-nail syndrome. This condition exists in conjunction with primary lymphedema and chronic obstructive pulmonary disease. Clinical manifestations of yellow-nail syndrome include an absence of cuticles, yellow pigmentation, an excessive curve in the nail, and cessation of nail growth.

Management of Onychomycosis

Once a diagnosis of onychomycosis is established, management may include topical therapy, surgical intervention, or systemic antifungal therapy, either alone or in combination with a topical agent. Patients should also be instructed in the proper care of their nails (table 3).

When topical agents have been used for the treatment of onychomycosis, either alone or in conjunction with other therapies, the outcome has been disappointing; however, limited disease or superficial white onychomycosis may occasionally respond to this form of treatment. Nevertheless, topical agents may be useful for preventing relapse of chronic tinea pedis, which often accompanies onychomycosis. Because topical agents lack efficacy, administration of oral agents such as griseofulvin, ketoconazole, and (more recently) itraconazole, fluconazole, and terbinafine has been the treatment of choice.

The results of conventional therapy with griseofulvin and ketoconazole for onychomycosis have been less than satisfactory. Prolonged therapeutic regimens, poor results, and significant adverse effects have all contributed to less than optimal compliance of patients as well as to frustration of physicians. The newer antifungals fluconazole, itraconazole, and terbinafine are more efficacious and can be administered for shorter periods than the older agents.

Traditional Oral Antifungal Therapy

Griseofulvin. The limited efficacy of griseofulvin was found to result in part from incomplete absorption from the gastrointestinal tract [18]. Thus, improved formulations have been devised with micronized preparations. [19] When micronized griseofulvin is administered, 27%-72% of the drug is absorbed, and peak serum levels are reached ~4 hours after administration [20].

Allergic reactions to griseofulvin occur in 5%-7% of cases [21]. Other common side effects include headache and nausea, both of which decrease in severity when griseofulvin is given with a meal. Less common side effects include vomiting, diarrhea, photosensitivity, urticaria, fatigue, fever, and menstrual irregularities. Biochemical changes include neutropenia, monocytosis, liver function abnormalities, albuminuria, and, rarely, granulocytopenia.

Drug interactions that occur when griseofulvin is administered include reduced efficacy of birth control pills, decreased absorption of griseofulvin with the concomitant administration of phenobarbital, and inhibition of warfarin’s effect with the concomitant administration of griseofulvin. In addition, the combination of alcohol and griseofulvin may cause a disulfiram-like reaction [22].

Griseofulvin therapy for onychomycosis of the fingernails should be continued for 4–6 months, and therapy for infected toenails should be continued for 10–18 months or until the nail has grown out. The mycologic cure rate with griseofulvin varies from study to study but is usually between 40% and 80% for infected fingernails and between 3% and 38% for infected toenails [23]. There is continued controversy regarding laboratory monitoring while patients are receiving the drug; some clinicians recommend that a baseline complete blood count and liver function tests be performed and be repeated periodically. However, other clinicians do not believe that such testing is necessary.

Ketoconazole. This agent was the first broad-spectrum oral antifungal developed. It is well absorbed in individuals with normal gastric acidity. Ketoconazole is metabolized by the liver, and the major route of excretion is through the bile into the intestinal tract. About 13% of the drug is excreted in the urine; of this quantity, 2%-4% is excreted as unchanged drug [24].

Significant drug interactions during ketoconazole therapy include potentiation of warfarin’s effect and decreased absorption of rifampin. Concomitant administration of both rifampin and isoniazid may decrease serum levels of ketoconazole. Ketoconazole may also increase levels of cyclosporine, and an interaction with terfenadine that leads to cardiac dysrhythmia has been described. Ingestion of alcohol during therapy with ketoconazole may produce a disulfiram-like effect [22].

The side effects of ketoconazole may include nausea, vomiting, abdominal pain, diarrhea, pruritus, and headache. The nausea and headache may be relieved if the drug is given with a meal. Hepatic reactions characterized by transient abnormalities in liver function occur in <10% of patients receiving ketoconazole [25]. Risk factors for the development of hepatic reactions include age of >40 years, prolonged courses of therapy (>6 months) with the drug, female sex, prior treatment.

<table>
<thead>
<tr>
<th>Table 3. Recommended nail care for patients with onychomycosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Keep nails short and clean</td>
</tr>
<tr>
<td>• Clip toenails straight across to prevent ingrown toenails</td>
</tr>
<tr>
<td>• File hypertrophic nails</td>
</tr>
<tr>
<td>• Avoid trauma and irritants, especially when onychomycosis is</td>
</tr>
<tr>
<td>present</td>
</tr>
<tr>
<td>• Use cotton gloves for dry manual work</td>
</tr>
<tr>
<td>• Use vinyl gloves for wet work</td>
</tr>
<tr>
<td>• Change instruments between care of normal and infected nails</td>
</tr>
<tr>
<td>• Discourage use of community nail instruments at beauty salons</td>
</tr>
<tr>
<td>• Avoid high heels and narrow-toed shoes</td>
</tr>
<tr>
<td>• Encourage daily use of antifungal foot and shoe powder</td>
</tr>
</tbody>
</table>
with griseofulvin, and a history of other drug allergies. The worldwide experience has shown that hepatic injury occurs in ~1 of 70,000 cases [25]. This change from the originally reported incidence (1 of 10,000 cases) [26] may be due to the fact that ketoconazole is now given in short courses rather than long courses of therapy.

Rates of treatment success are similar to those for griseofulvin (i.e., mycologic cure rate, 15%–30% for toenails and 50%–70% for fingernails) [21]. Ketoconazole is seldom used for onychomycosis because of the long course of treatment (200 mg/d for 4–6 months for fingernails and 200 mg/d for 10–18 months for toenails) required for mycologic cure, which increases the risk of hepatic reactions.

Newer Oral Antifungals

Fluconazole. Fluconazole is a triazole with a high bioavailability; it is not currently approved by the FDA for the treatment of onychomycosis in the United States. More than 90% of an ingested dose of fluconazole is absorbed [22]. Peak plasma levels are reached within 1–2 hours of oral administration, and steady-state levels are reached in 6–10 days [22]. Fluconazole’s half-life of 22–30 hours may result in accumulation of the drug in serum with multiple dosing. Fluconazole has been detected in skin and nails within 3 hours and 2 weeks, respectively, after the initiation of therapy [22].

The results of in vitro studies suggest that fluconazole may be effective in treating dermatophytic infections and C. albicans infections of the nail [27, 28]. Clinical cure rates of 100% for infected fingernails and 90% for toenails have been reported when fluconazole and 40% urea ointment are used concomitantly [29, 30]. However, published clinical data on the use of fluconazole for treatment of nail infections are limited.

Side effects associated with fluconazole were reported in a study of 4,000 patients who received the drug [31]. The side effects that occurred at the highest rate (8.6%) were related to the gastrointestinal system. Others included headache and rashes. Drug interactions may occur and are listed in table 4.

Itraconazole. This drug has recently been approved by the FDA for the treatment of onychomycosis. It is a broad-spectrum triazole that is effective against dermatophytes, yeasts, and many molds. Itraconazole is well absorbed when administered orally with food, and it is distributed extensively throughout tissue.

The pharmacokinetic properties of itraconazole are mainly related to its pronounced lipophilic properties. Its plasma half-life varies between 15 and 25 hours; the peak plasma concentration is reached within 2–4 hours after a single 100-mg dose is administered [32]. Itraconazole binds strongly (99.8% of drug) to protein and has a marked avidity for lipids [32]. The slow elimination of itraconazole from tissue may explain its continuing therapeutic effect after treatment is discontinued. Itraconazole’s strong affinity for keratinized tissues results in high concentrations of the drug in the nails and explains its effectiveness in the treatment of onychomycosis.

In a study of the pharmacokinetics of itraconazole, detectable levels of the drug were found in nail clippings after 7 days of treatment [33]. Evidence of itraconazole’s penetration into the nails so soon after treatment has begun suggests that it acts rapidly on the fungus in the nail plate not only by incorporating itself into the nail matrix but also by diffusing from the nail bed into the nail plate. Detectable levels of itraconazole in the nail plate, with no evidence of the drug in plasma, demonstrate its affinity for keratinous material and thus efficacy in the treatment of onychomycosis. Results of clinical studies that support the diffusion of itraconazole from the nail bed into the nail plate are limited because the invasive procedures required to measure drug levels are undesirable to patients.

A subsequent study supported the theory that itraconazole penetrates the nail bed as well as the nail matrix [34]. Nineteen patients with onychomycosis were treated with itraconazole (100 mg/d) for up to 7 months. After the first month, mean concentrations of the drug were about three times higher in the fingernails (42 ng/g) than in the toenails (16 ng/g). The faster distribution of itraconazole into fingernails than into toenails may be due to differences in the structure and thickness of the two types of nail and the faster outgrowth of the fingernails. The detection of itraconazole in distal nail clippings before full outgrowth of the fastest-growing nail shows that the nail matrix is not the only means by which this drug penetrates the nail [34].

In a dose-response study designed to examine the kinetics of itraconazole in the nails in relation to therapeutic outcome, 39 patients with onychomycosis received a daily dose of either 100 mg or 200 mg of the drug for 3 months [35]. Itraconazole levels in distal nail clippings were determined during a 6-month posttherapy period. The intergroup difference reached significance at the follow-up, with a mean drug concentration of 35 ng/g in the 100-mg group and 141 ng/g in the 200-mg group 6 months after the completion of therapy (P < .05) [35]. These concentrations were well within the therapeutic range for the most common fungal nail pathogens [36]. The mycologic cure rates were 79% for the 200-mg group and 26% for the 100-mg group [35]. The early attainment of extratherapeutic drug levels and the persistence (>6 months) of these levels after treatment suggest the potential for shorter courses of therapy with itraconazole.

On the basis of the pharmacokinetic properties found in this study, the use of intermittent or "pulse" dosing regimens of itraconazole has been explored. In an investigation of the pharmacokinetics and pharmacodynamics of the drug, 50 patients with confirmed onychomycosis of the toenails were randomly assigned to receive three or four pulses of itraconazole therapy for 1 week (200 mg twice daily each month) [36]. Clinical and mycologic evaluation of the infected toenails and determination of drug levels in the distal ends of the fingernails and toenails were performed at the end of each month for ≤6 months, and then every 2 months for ≤1 year. Endpoint analysis of the follow-up findings showed that 80% of the patients in both treatment groups had negative cultures. The rates of mycologic cure, as defined by negative cultures and negative KOH prepa-
Table 4. Systemic antifungal drugs and potential drug interactions.

<table>
<thead>
<tr>
<th>Griseofulvin</th>
<th>Fluconazole</th>
<th>Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Barbiturates</td>
<td>• Rifampin</td>
<td>• Cimetidine</td>
</tr>
<tr>
<td>• Warfarin</td>
<td>• Coumarin</td>
<td>• Rifampin</td>
</tr>
<tr>
<td>• Coumarin</td>
<td>• Sulfonylureas</td>
<td></td>
</tr>
<tr>
<td>• Oral contraceptives</td>
<td>• Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyclosporine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hydrochlorothiazoles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Valproic acid</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>• Terfenadine</td>
<td></td>
</tr>
<tr>
<td>• Cyclosporine</td>
<td>• Astemizole</td>
<td></td>
</tr>
<tr>
<td>• Rifampin</td>
<td>• Cimetidine</td>
<td></td>
</tr>
<tr>
<td>• Isoniazid</td>
<td>• Digoxin</td>
<td></td>
</tr>
<tr>
<td>• Phenytoin</td>
<td>• Rifaximin</td>
<td></td>
</tr>
<tr>
<td>• Sulfonylureas</td>
<td>• H₂ antagonists</td>
<td></td>
</tr>
<tr>
<td>• Coumarin</td>
<td>• Isoniazid</td>
<td></td>
</tr>
<tr>
<td>• Terfenadine</td>
<td>• Coumarin</td>
<td></td>
</tr>
<tr>
<td>• Astemizole</td>
<td>• Sulfonylureas</td>
<td></td>
</tr>
</tbody>
</table>

Therapy with itraconazole is well tolerated; side effects are reported for ~7% of patients with dermatologic conditions who are treated with the drug [37]. The adverse reactions are mostly minor and primarily consist of gastric upset and headache [37]. Drug interactions can occur with itraconazole, as is shown in table 4.

**Terbinafine.** Terbinafine is an allylamine that is effective against dermatophytes and some molds. It has recently been approved by the FDA for the treatment of onychomycosis. Unlike the azoles, oral terbinafine is not very effective against C. albicans. It is well absorbed after oral administration and binds strongly to plasma proteins. When patients were given oral terbinafine at a dose of 250 mg/d, the drug was detected in plasma as early as 24 hours after the initiation of treatment [38]. Therapeutic levels persist in the nail for 3–6 months after therapy is discontinued.

In a randomized study, terbinafine was administered for periods of 6 weeks, 12 weeks, and 24 weeks; complete cure of toenail onychomycosis was achieved in 67%, 82%, and 85% of patients, respectively. After an additional 24 weeks of follow-up, cure rates were 40% for patients in the 6-week group, 71% for those in the 12-week group, and 79% for those in the 24-week group [39].

In a randomized, double-blind study by Hanecz and colleagues [40], terbinafine (250 mg/d) was compared with griseofulvin (500 mg/d in micronized form) in 180 patients with dermatophytosis of the fingernails. The cure rates were 76% in the terbinafine group and 39% in the griseofulvin group at the end of the study [40]. The recommended dosage is 250 mg daily for 12 consecutive weeks for treatment of toenail onychomycosis and 6 consecutive weeks for fingernail onychomycosis.

Terbinafine has a generally favorable safety profile; most side effects are characterized as minor and transient (such as taste disturbances), although there have also been reports of patients who developed neutropenia, pancytopenia, and hepatotoxic reactions while receiving the drug [41]. Terbinafine does not activate cytochrome p-450 enzyme; therefore, its potential for interacting with drugs metabolized through this pathway is minimal (table 4).

**Surgical Treatment of Onychomycosis**

Surgery can be a useful therapeutic adjuvant in the treatment of onychomycosis. However, surgical avulsion is painful and disfiguring, and it must generally be restricted to one or a few nails in selected cases. General indications for surgical treatment include pachyonychia associated with pain; contraindications to the administration of oral antifungals; the presence of onychomycosis due to drug-resistant nondermatophytic fungi; and the desire to limit the duration of drug therapy and/or reduce costs and the incidence of side effects. For optimal results, a combination of surgical, systemic, and/or topical treatment may be used.

Before the newer antifungal agents had become available, Baran and Hay [42] treated 12 patients with distal lateral subungual onychomycosis of the toenail, which was caused by a dermatophyte. These investigators used a combination of surgical avulsion, a 3-month course of oral ketoconazole, and topical treatment with an imidazole preparation. The mycologic cure rate was 50% at 12 months. In another study [43], surgical nail avulsion followed by daily application of ciclopirox olamine for 4 months cleared fingernail onychomycosis due to Scytal-
Onychomycosis is a common fungal infection that, until recently, has been difficult to treat. If left untreated, it may eventually lead to total destruction of the nail plate. The clinical manifestations of the infection have both physical and psychological consequences for the patient. It is essential to make an accurate diagnosis before instituting systemic therapy for onychomycosis. Examination of a specimen with use of a KOH preparation and culture constitute the diagnostic gold standards.

Surgical nail plate avulsion is an ambulatory procedure done under local anesthesia. Since it is advisable to remove only the diseased part of the nail plate, partial avulsions are always preferred. Total nail plate avulsion and distal transversal nail plate hemiavulsion should be avoided because these procedures may result in secondary distal embedding of the nail plate.

It is mandatory to obtain a preoperative history and perform a clinical examination in order to eliminate contraindications to local anesthetics and/or nail surgery. Adequate anesthesia, hemostasis, and sterile technique are prerequisites to surgery. The nail folds are loosened from the nail plate, and nail bed and nail plate attachments are freed with a nail elevator. The diseased nail plate, including a margin of normal-appearing nail, is cut with an English nail splitter or a heavy-duty nail nipper and removed with forceps. Hemostasis is achieved by topical application of Monsel’s solution. The digit is wrapped, and postoperative care is continued until the pain and exudation have stopped. Analgesics are helpful for the first few days. Simple nail trimming is useful for managing onycholysis. It is performed with a heavy-duty nail nipper at the most proximal part of the diseased nail plate; no anesthesia is administered. Primary onychomycosis and secondary onychomycosis due to Candida species are the most frequent indications, but trimming is also useful for the management of onycholysis due to dermatophytic and nondermatophytic molds.

Conclusion

Onychomycosis is a common fungal infection that, until recently, has been difficult to treat. If left untreated, it may eventually lead to total destruction of the nail plate. The clinical manifestations of the infection have both physical and psychological consequences for the patient. It is essential to make an accurate diagnosis before instituting systemic therapy for onychomycosis. Examination of a specimen with use of a KOH preparation and culture constitute the diagnostic gold standards. Treatment includes a combination of topical therapy, surgical or chemical nail avulsion, and systemic therapy. The systemic agents fluconazole, itraconazole, and terbinafine are now being administered with great success. Of these newer antifungals, itraconazole and terbinafine have been approved by the FDA for the treatment of onychomycosis. The higher cure rates and shorter courses of treatment associated with this new generation of antifungal drugs may improve patient compliance, produce more favorable therapeutic outcomes, and reduce relapse rates.

References


Downloaded from https://academic.oup.com/cid/article-abstract/23/2/305/367004 by guest on 01 January 2018
29. Coldiron B. Recalcitrant onychomycosis of the toenails successfully
3:115–7.
31. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic
and pharmacokinetic properties, and therapeutic potential in superficial
32. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn
JG. Pharmacokinetics of itraconazole following oral administration to
Haeverans K. Pharmacokinetic profile of orally administered itracona­
the nail via the nail matrix and the nail bed—an investigation in onycho­
levels in the nail: new implications for treatment in onychomycosis. J
onychomycosis: a pharmacokinetic and pharmacodynamic investigation
of monthly cycles of 1-week pulse therapy with itraconazole. Arch
reaches the stratum corneum. Journal of Dermatological Treatment
ment duration–finding study of terbinafine in onychomycosis. Br J
40. Hanke E, Tausch I, Bräutigam M, Weidinger G, Welzel D, the LAGOS
III Study Group. Short-duration treatment of fingernail dermatophytosis:
a randomized, double-blind study with terbinafine and griseofulvin. J
41. Kovacs MJ, Alshammari S, Guenther L, Bourcier M. Neutropenia and
pancytopenia associated with oral terbinafine. J Am Acad Dermatol
1994; 31:806.
42. Baran JR, Hay R. Partial surgical avulsion of the nail in onychomycosis.
43. Rollman O, Johansson S. Hendersonula toruloidea infection: successful
response of onychomycosis to nail avulsion and topical ciclopiroxolam­