CHAPTER 23

TINEA PEDIS AND ONYCHOMYCOSIS: Overview of New Systemic Therapies

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Tinea pedis and onychomycosis are the most frequently occurring superficial fungal infections. Recently, new oral antimycotic agents have brought significant enthusiasm for the treatment of these often recalcitrant conditions. Onychomycosis was often unsuccessfully treated with topical agents prior to the introduction of these systemic agents. While tinea pedis is often treated successfully with topical agents, the author can say that in eight years of practice in podiatry, he has never successfully cleared a single case of onychomycosis with any of the topical antifungal agents promoted as treatment for this toenail infection. In the recent past, griseofulvin was the only oral agent with a satisfactory safety profile to allow its long term use for the treatment of onychomycosis. However, even this form of therapy proved to be of little value in the treatment of toenail onychomycosis. A brief overview of superficial fungal infections of the feet will be presented. Special attention is given to new forms of therapy for these conditions.

EPIDEMIOLOGY

The prevalence of fungal infections has gradually increased in the United States. Many factors are considered to contribute to this increased incidence. An aging population, combined with frequent use of systemic antibiotics are considered to be major reasons for the prevalence of these conditions. It has been estimated that 15% to 20% of those over 40 years old have onychomycosis.

The vast majority of superficial fungal infections are caused by dermatophytes. Recent emphasis has been placed on the occurrence of nondermatophytes as etiological agents in these diseases. However, Kemna found after reviewing 561 specimens, that 94.7% of the cases of tinea pedis and 81.9% of onychomycosis cases in the United States were caused by dermatophytes.[1] *Trichophyton rubrum* was the most commonly isolated organism in tinea pedis and onychomycosis, representing 78.9% and 76.2% incidence respectively. Another study, performed in Canada, reported similar results with dermatophytes causing 90.7% of tinea pedis cases and 97.1% of onychomycosis.[2]

Non-dermatophyte molds are sometimes recovered from nail, hair, and skin cultures. However, most agree that these organisms are contaminants. In fact, one investigator suggests that in order to consider a non-dermatophyte mold to be considered clinically significant, it must grow from 5 of 20 inocula.[3] However, more recent studies have suggested that nondermatophytic molds and yeasts are having an increasing role in the pathogenesis of onychomycosis.[4] Kemna[1] proposed a classification system for onychomycosis similar to that used for tinea pedis. "Onychomycosis complex" was described as a condition resulting when dermatophytic fungi create a condition favorable to the overgrowth of saprophytic molds. He also states that though the saprophyte may not have been the original pathogen, it still may represent "valid growth." In any event, it is probably reasonable to assume that as new therapies emerge so too will infections due to resistant organisms.

DERMATOPHYTOSES

Fungal infections of the superficial skin, hair, and nails are caused by keratinophilic fungi called dermatophytes. They are a small fraction of the total number of know fungi and are generally not considered normal skin flora. These organisms are found in soil and in infected animals and humans. The infection of a host occurs when an organism is deposited on the skin and secretes keratolytic enzymes that enable the fungi to invade the epidermal layers of skin. Since the organism is being sustained by keratin, it is rare that it invades deeper tissues that do not contain this food source. Host response to the invading fungi may vary depending on the organism involved, location of the infection, and the individual host's immune status.

TINEA PEDIS

Tinea pedis is very common in the shoe wearing population. Over-the-counter topical therapy is often successful in the treatment of this condition. However, in many instances the patient treats the condition incompletely, or not at all. Therefore, chronic infections and acute exacerbations are a frequent reason the patient seeks medical attention. There are three general types of tinea pedis: intertriginous, chronic hyperkeratotic, and acute inflammatory. Generally, the intertriginous type of infection is subdivided into simplex and complex, depending on the degree of superinfection and maceration of the intertriginous spaces of the toes.

Intertriginous Tinea Pedis

The typical intertriginous infection of tinea pedis can be subdivided into two types. Dermatophytosis simplex is the condition that produces dry, scaly lesions of the intertriginous areas, often spreading to the dorsum of the foot (Fig. 1). KOH will be positive for dermatophyte. *Trichophyton,* or less frequently, *Epidermophyton* are the organisms most likely encountered. If the conditions exist for progression of the disease process, the organism causes skin damage and build up of macerated desquamated skin. This "media" of detritus can allow the overgrowth of other organisms to occur, specifically, cocci, diptheroids, and gram negative organisms that are not inhibited by the penicillin-like substances secreted by the dermatophytes. This condition of "superinfection" is called dermatophytosis complex. Usually severe overgrowth with gram negative organisms such as *Pseudomonas, Corynebacterium minutissimum,* or *M. sedentarius* cause a pungent malodor that aids in the diagnosis of this condition (Fig. 2).

Treatment of the simplex condition is often successful with various over-the-counter or prescription antifungal agents. However, as the simplex condition gives way to the complex form of dermatophytosis, treatment may need to be altered to reduce bacterial growth and remove macerated tissue. The author has found that improved foot hygiene combined with Castellani's paint (carbolfushin dye and phenol) is very helpful in drying the webspaces, and as a keratolytic to reduce desquamated cells that have become infected. Eventually, treatment of the dermatophyte on a long-term basis is generally required to prevent recurrent infections.

Chronic Hyperkeratotic Tinea Pedis

This form of tinea pedis is generally caused by the organism *Trichophyton rubrum* or *T. mentagrophytes.* In general, this form of tinea pedis is restricted to the soles of the feet. In some cases, the palm of the hand can become involved. This two feet one hand presentation is sometimes helpful in distinguishing tinea from psoriatic lesions that are usually bilateral symmetrical. The thickness of the soles of the feet act as a barrier to the fungus, while allowing a dry scaly infection to occur without causing the host to mount an immune response. Moccasin foot distribution is used to describe the typical presentation of this infection.

The treatment of this condition can at times be difficult. Prolonged topical therapy may be curative, however, many practitioners have found

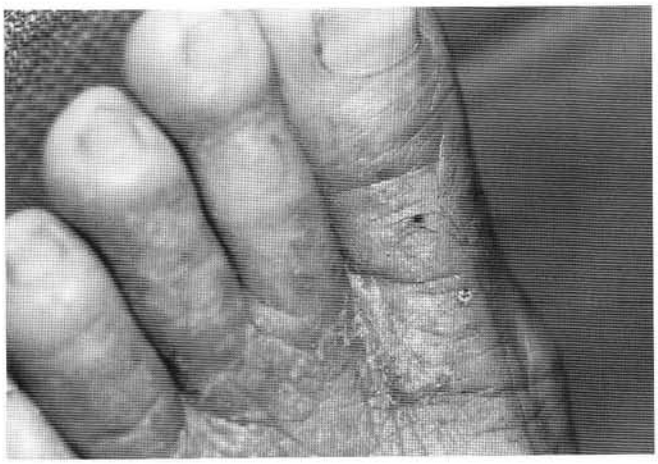

Figure 1. Dry, scaly, intertriginous tinea pedis. Dermatophyte was cultured. One month course of topical terbinafine successfully cleared this infection.

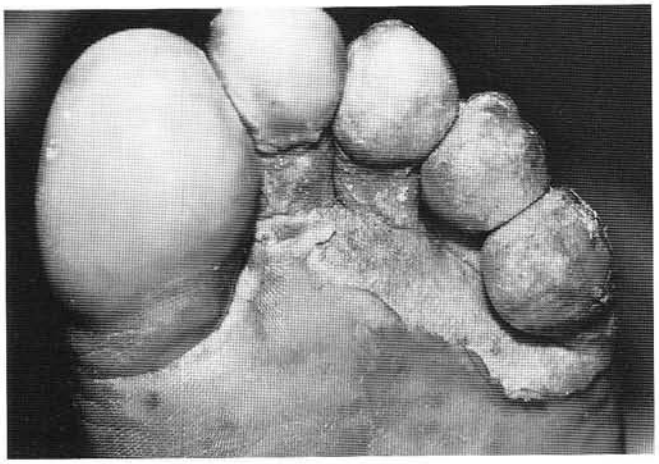

Figure 2. This patient suffered a painful intertriginous infection of the left foot. The infection cleared with oral ciprofloxacin. However, he presented with recurrent infections with the same organism intermittently until antifungal therapy followed clearing of the bacterial superinfection.

that a combination of oral and topical therapy is the most successful. In the author's experience, a 4 week course of terbinafine with a 3 month, once a day application of a topical agent such as naftifine or ciclopirox has been for the most part successful. In addition to this therapy, the author recommends (but rarely witnesses compliance) discarding old shoes worn prior to the therapy. Certainly, treatment of the shoes with a antifungal powder can be helpful in controlling excess moisture and reducing the colony count of infectious organisms. Fungal spores, however, are not eliminated by this treatment. Finally, once the active infection appears under control and the antimycotic therapy is complete, the author finds that continuous long term treatment with Lactinol or Lachydrin 12% is an effective keratolytic that helps prevent recurrent infection.

Acute Inflammatory Tinea Pedis

This form of tinea pedis is caused by the more antigenic organism *T. mentagrophytes*. An allergic response or id reaction to the organism is considered the reason for the dramatic presentation of this form of tinea pedis. The distinguishing feature of this infection is vesicular or bullous eruptions, pruritus, and occasionally pain (Fig. 3). Treatment is therefore targeted at the inflammatory component of the condition rather than the ablation of the organism itself. Systemic corticosteroids may be necessary in severe cases. The author has found that deroofing the larger bulli and clusters of vesicles followed by the application of topical compresses with Burrow's paste is very helpful for many patients. Burrow's paste consists of 1 part Burrow's solution, 2 parts aquaphor, and 3 parts Lassar's zinc paste. The acute reaction can be quite painful in weight-bearing areas and may require several weeks to completely resolve. Secondary infection is fairly common and bacterial culture should be performed and broad spectrum antibiotics initiated if this is suspected. Long term preventive therapy with topical antifungal agents is recommended to prevent recurrence.

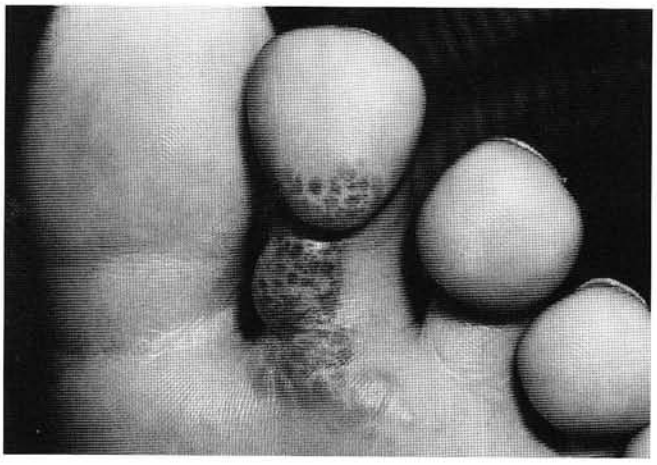

Figure 3. Acute inflammatory tinea pedis in a teenage female. Note the coalesced vesicles of the plantar aspect of the toe.

ONYCHOMYCOSIS

Infection of the nail plate and nail bed is termed onychomycosis. There are four basic types of onychomycosis: white superficial onychomycosis, proximal subungual, distal subungual, and candidal. Any of previously mentioned infections may vary in severity and extent of nail plate involvement.

Superficial White Onychomycosis

Superficial white onychomycosis describes infection of the surface of the nail plate with dermatophytic fungi. It is a relatively common form of onychomycosis, and may be present in combination with the other types fungal nail infections. Mechanical debridement combined with topical antifungal therapy are usually successful forms of therapy.

Proximal Subungual Onychomycosis

Proximal subungual onychomycosis is the least common form of nail infection. The nail plate becomes involved proximal to the eponychium, and grows distally as the infection continues. Onychomadesis (separation of the proximal nail plate from the underlying soft tissue) may occur, with complete onycholysis and shedding of the entire nail plate frequently resulting. This form of onychomycosis has been associated with immune compromise and is sometimes seen in patients with AIDS. Careful history taking is needed when diagnosing this condition. A nail plate that has shed, following total involvement of the nail from another form of onychomycosis, or an infected nail that has been traumatized may mimic proximal subungual onychomycosis. Treatment with systemic agents is generally less protracted than with distal nail involvement.

Distal Subungual Onychomycosis

Distal subungual onychomycosis is the most common form of fungal nail infection. In this form of onychomycosis, the fungi enter the subungual area through the distal aspect of the nail bed (Fig. 4). The infection is generally caused by dermatophytes, or in rare instances by non-dermatophytic molds. Many patients present to the physician with a history of "ugly toenails" that have been present for several years. Some have tried over-the-counter treatment without success. A large number have not sought therapy until symptoms of pain or discomfort arose. Many embarrassed elderly patients are seen each year in physicians' offices with extreme elongation and neglect of the toenails due to this condition. New and relatively safe forms of therapy have recently become available that should make treatment of this condition more successful.

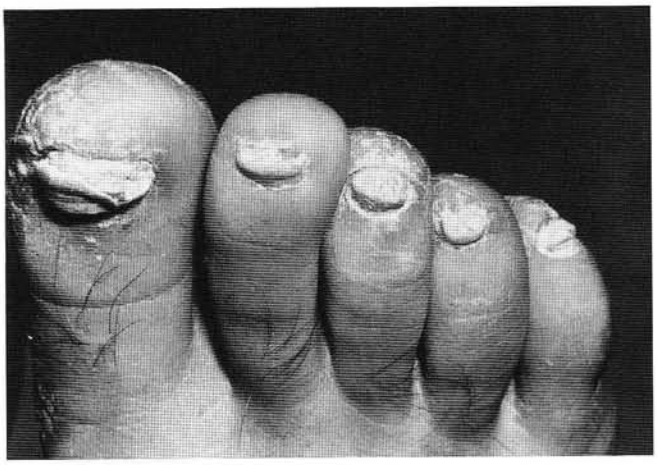

Figure 4. Severe distal subungual onychomycosis involving all toes in this 49-year-old patient.

Candidal Onychomycosis

Candida is sometimes isolated from cultures of nail infections. Kemna found *Candida albicans* in 26 of 561 positive nail cultures.[1] Although the importance of candida as a pathogen in onychomycosis is not well understood, it does appear to have a role in certain individuals.

ANTIFUNGAL AGENTS

Antifungal agents can be divided into two categories based on their method of administration. Topical and oral agents can be subdivided into one of five groups of agents: polyenes, azoles, allylamines, morpholines, and miscellaneous agents. Topical agents are generally successful in the treatment of tinea pedis. However, systemic antifungals have typically been required to treat hair and nail infections with any degree of fruition. Topical amorolfine nail lacquer has shown some degree of success, but appears to have a primary role as an adjunct to systemic therapy and as a prophylactic agent following successful clearing of the infection. Newer imidazole and allylamine agents have provided significant enthusiasm for the successful treatment of fungal hair and nail infections.

Recently, FDA guidelines for over-the-counter topical agents in the treatment of fungal infections have been issued.[5] One of the major rulings discussed by these guidelines is that only one active ingredient, or single-entity antifungal products are considered appropriate for over-the-counter use. Combinations of antifungal agents with antiperspirants, hydrocortisone, broad-spectrum antibiotics, salicylic acid and/or topical anesthetics are considered to have no increase in efficacy or added relief of symptoms. In addition to this ruling, approved labeling for over-the-counter antifungal products must include the statement: "This product is not effective on the scalp or nails."

Systemic antifungals used for the treatment of superficial mycotic infections of the feet include griseofulvin, older imidazole antifungals such as ketoconazole, and the newer triazoles-fluconazole and itraconazole. Finally, a new class of antifungal agents called allylamines are now available in the form of the drug terbinafine. While some uses for the older agents may still exist for tinea versicolor or tinea capitis, the newer agents specifically terbinafine, itraconazole, and fluconazole are the best suited for treatment of onychomycosis or resistant tinea pedis.

Mechanisms of Action

Systemic antifungal agents generally target inhibition of sterol synthesis crucial to fungal cell membrane formation. Unfortunately, human cholesterol synthesis is not very dissimilar from that of fungi, and therefore, developing antifungal agents specific for the pathogen versus the host has been difficult. Lack of specificity can cause endocrinologic, hypolipidemic, or hematologic changes. The newer systemic antifungals have significantly improved their specificity for fungal cholesterol synthesis thereby improving their safety in clinical use.

Azoles

The azole antifungals have been improved by the addition of a third nitrogen atom to the azole ring. These newer triazole antifungal agents show improved specificity for fungal enzyme inhibition compared to the imidazole ketoconazole. This has resulted in less hepatotoxicity, increased potency and shorter courses of therapy. While azole antifungals at high concentrations can be fungicidal, these agents are generally considered fungistatic at levels achieved with therapeutic dosing.

Itraconazole. Itraconazole (Sporonox) was discovered in 1980 and is currently being used in the United States for the treatment of superficial fungal infections. It has a high affinity for keratin with drug levels 3 to 10 times that of plasma found in the skin. Excretion of intraconazole in the sebum increases the level of the drug reaching the stratum corneum. Itraconazole is metabolized in the liver and excreted in the urine and feces primarily as inactive metabolites. Fortunately, renal disease and the age of the patient appear to have little effect on the pharmacokinetics of the drug.

Itraconazole has proven to be a relatively safe and effective drug for the treatment of superficial fungal infections. The incidence of untoward effects are reported to be approximately 13% with durations of therapy greater than one month. The side effects most commonly encountered in order of frequency include nausea, headaches, abdominal pain, and rash. In addition to these, elevated liver function tests have occurred in .3% to 5% of patients. Rarely, intraconazole may cause symptomatic drug-induced hepatitis. In the reported cases, liver function tests returned to normal following cessation of therapy. Liver function studies are recommended for patients receiving continuous itraconazole therapy for greater than one month or in any patient with history of hepatic dysfunction. Signs and symptoms of hepatic disease must be carefully monitored.[6]

Unfortunately, several significant drug interactions are associated with concomitant therapy with itraconazole. Some severe reactions can occur such as life-threatening cardiac dysrhythmia when itraconazole is combined with terfenidine (Seldane) or astemizole (Hismanol). Contraindicated drug combinations prevent itraconazole from being considered first line therapy for most long term treatment of superficial fungal infections such as dermatophytic onychomycosis. Drug combinations that should be avoided or monitored very closely include itraconazole with terfenidine (Seldane), astemizole (Hismanol), lovastatin (Mevacor) and niacin, simvastatin (Zocor) and cyclosporine, midazolam (Valium), alprazolam (Xanax), triazolam (Halcion) and cisapride (Propulsid). Drugs inducing hepatic enzymes including rifampin, isoniazid, carbamazepin, phenytoin and others may result in increased metabolism of itraconazole with subsequent failure of antifungal therapy. *Clinicians are cautioned to review the package insert for complete list of drug interactions before prescribing this or any drug.*

The approved dosing regime for itraconazole for the treatment of onychomycosis is 200 mg/day for 3 months, with a cure rate at 18 month follow-up of 67%. Tinea pedis is treated with 100 mg/day for 30 days with a cure rate after 4 weeks of 79%. Pulse therapy is described and used with itraconazole although FDA approval is still pending for this method of dosing. Generally, itraconazole 200 mg taken twice daily for 7 days with 21 days off is the most commonly reported dosing regimen. A recent investigation of itraconazole pulse therapy for onychomycosis reported a clinical cure rate at 12 months between 76% and 84%.[7] Therefore, an insignificant difference in cure rates appears to be present with continuous versus pulse therapy of itraconazole.

Fluconazole. Fluconazole (Diflucan) is a triazole antifungal agent. This agent has not been studied or promoted as extensively as itraconazole for the treatment of onychomycosis. However, preliminary studies report low incidence of adverse reactions and similar cure rates with both pulse and continuous therapy. In a pilot study, Assaf and Elewski reported successful treatment of eleven patients with onychomycosis utilizing fluconazole in various pulse dosing regimens.[8] Efficacy is generally believed to be equal to or better than itraconazole for the treatment of dermatophytic onychomycosis.

Drug interactions with fluconazole are basically the same as those reported for itraconazole. Again, liver enzyme levels are monitored throughout continuous therapy.

Allylamines

Allylamines have very successfully achieved specificity for fungi by acting at the squalene epoxidase level of ergosterol synthesis. This has two important beneficial effects. First, the

cytochrome P-450 isoenzymes do not mediate squalene epoxidase inhibition. This results in improved safety profile having little interaction with other pharmacologic agents that are acted on by the P-450 system. Second, the inhibition at this level causes fungicidal levels of squalene to accumulate within the organism. This fungicidal activity is achievable at normal therapeutic levels, and is the reason for the reported lower relapse rates following treatment of onychomycosis.

Terbinafine. The newest systemic antifungal agent is terbinafine (Lamisil). It is classified as an allylamine antifungal and demonstrates unique and advantageous pharmacokinetics. It is the first systemic antifungal agent considered fungicidal rather than fungistatic. It has a broad spectrum of activity against dermatophytes, *Sporotrix schenckii, aspergilli, Schopulariopsis brevicalis* and *Candida parapsilosis.* Terbinafine has fungistatic activity for *Candida albicans.*

Terbinafine has proven to be the most effective form of systemic antifungal therapy for onychomycosis in several comparison studies. DeBacker et al. performed a double-blind study comparing itraconazole 200 mg a day to 250 mg of terbinafine daily for the treatment of onychomycosis.[9] Both drugs were dosed for 12 weeks. At 48 weeks follow-up, clinical cure rates were compared. The terbinafine treated group revealed a cure rate of 76.3% versus 58.1% for itraconazole.

In another double-blind study, 195 patients were treated for clinically diagnosed onychomycosis. Half of the patients received terbinafine and half received itraconazole. Again, both groups were treated for 12 months. At 52 weeks follow up mycologic cure rates (negative microscopy and culture result) were determined for the two groups. The terbinafine cure rate was 81% and the itraconazole rate was 63%.[10]

Drug interactions are much less likely for terbinafine than triazole antifungal agents. At therapeutic levels no clinically significant drug interactions are reported. At 250 mg per day, no clinically significant endocrinologic, hypolipidemic or hematologic changes have been reported. A single case of neutropenia and pancytopenia has been associated with oral terbinafine. Liver enzymes are monitored at 6 weeks, midway through the therapy. Baseline studies are suggested as the medical history warrants.

Side effects are usually gastrointestinal, and include dyspepsia, gastritis, nausea, and diarrhea. The second most frequently reported untoward effect is cutaneous eruptions. The majority of these reactions are mild, and reverse with cessation of therapy. Acute generalized exanthematous pustulosis has recently been reported in two patients taking 250 mg daily for suspected superficial fungal infections. Patients should be informed of the side effects before instituting therapy and instructed to discontinue therapy if signs of skin rash or pruritus occur.

CONCLUSION

Systemic therapy for fungal infections of the foot has significantly improved with the recent development of triazole and allylamine agents. Most skin infections are probably best treated with topical agents. However, the treatment of onychomycosis requires systemic therapy. Grisofulvin would appear to no longer have a role in the treatment of onychomycosis. Terbinafine, with its relative lack of drug interactions and greater degree of efficacy is considered the drug of choice for onychomycosis caused by sensitive organisms. More investigation is needed to determine if pulse terbinafine therapy provides the same efficacy and safety profile. Pulse dose therapy with itraconazole or fluconazole provide an alternative treatment method in patients that may not tolerate continuous therapy with terbinafine. Significant drug interactions prevent itraconazole and fluconazole from being considered first line therapy for onychomycosis.

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