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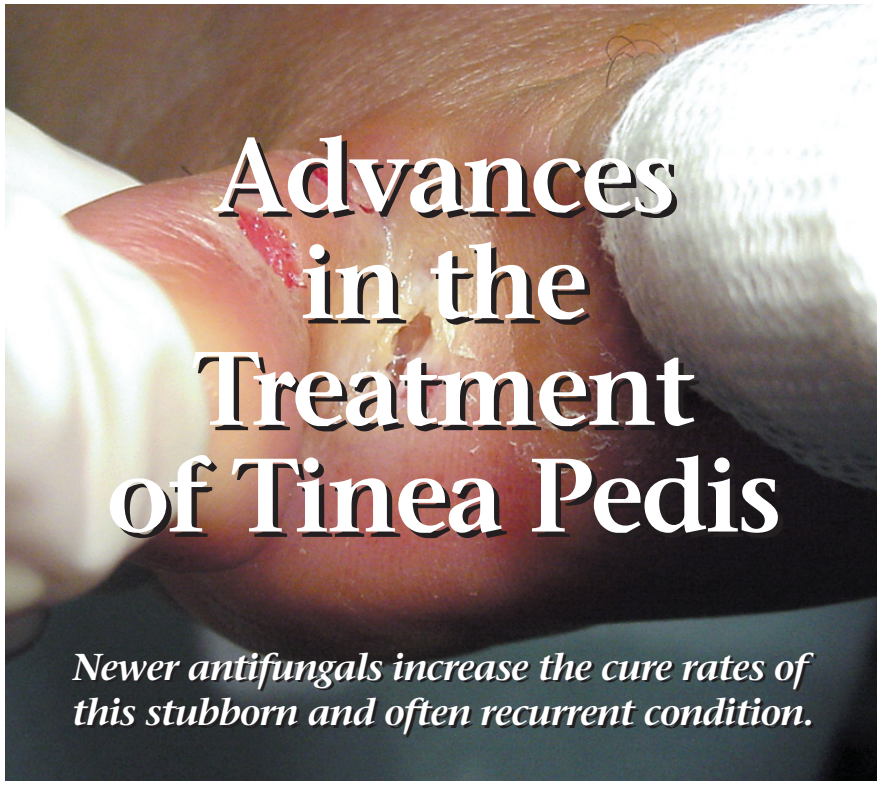

Advances in the Treatment of Tinea Pedis

Newer antifungals increase the cure rates of this stubborn and often recurrent condition.

Goals and Objectives

1) To understand the types and classifications of topical and oral anti-fungals as they relate to the treatment of tinea pedis.

2) To be able to compare the relative efficacy of each of these agents based on clinical studies.

3) To know which antifungal agents are fungistatic, which are fungicidal, and to be familiar with the usual dosing of these agents.

4) To be aware of newer treatments for tinea pedis.

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*Following this article, an answer sheet and full set of instructions are provided (p. 240).—**Editor***

By Mark Kosinski, DPM, Warren S. Joseph, DPM, and Bryan Markinson, DPM

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It is estimated that over 70% of the world's population will develop tinea pedis at some point during their lifetimes. Tinea pedis is caused by dermatophytes. Dermatophytes (which comes from the Greek words meaning "skin-plants") are pathogenic fungi that produce keratinase, an enzyme that breaks down keratin, the main constituent of hair, nails and the stratum corneum. Trichophyton rubrum (T. rubrum) is the most common dermatophyte responsible for tinea pedis, due largely to its ability to infect, its ubitquitous presence, and its ability to evade host defenses (Figure 1).

Surprisingly, although ubiquitous today, dermatomycosis of the foot is a relatively recent phenomenon in the Western world. The first cases of tinea pedis were

Continued on page 230

Tinea Pedis...

not reported until the late 1800s. Before that time, T. rubrum was initially endemic only to Sourtheast Asia, Africa and Australia. In the early 20th century, troops retuning from these countries transported T. rubrum to Europe and the United States where, once established, it spread rapidly. The purpose of this article is to review current therapeutic options in the treatment of tinea pedis.

T. rubrum is not particularly aggressive but possesses qualities that allow it to evade immune defenses. Glycoproteins found in the cell wall of T. rubrum can suppress the inflammatory response and inhibit stratum corneum turnover, allowing infection to be much more indolent. This is in contradistinction to Trichophyton mentagrophytes, which can produce a much more aggressive immune response, leading to a more aggressive bullous infection.

Patients with defective cell-mediated immunity that prevents them from mounting an effective host-response are pre-disposed to chronic infection and recurrence. T. rubrum infection shows a pattern of autosomal dominant inheritance.[1]

T. rubrum can survive off the human body as a spore. Spores desquamate and remain in human habitats, including flooring and shoe insoles. When a spore finds a warm, moist area of skin, it crowds out normal flora and grows on the stratum corneum. On average, the number of spores needed to induce a persistent infection in 50% of experimental subjects, the so-called minimum infectious dose (MID-50), has been found to be as few as six.[2]

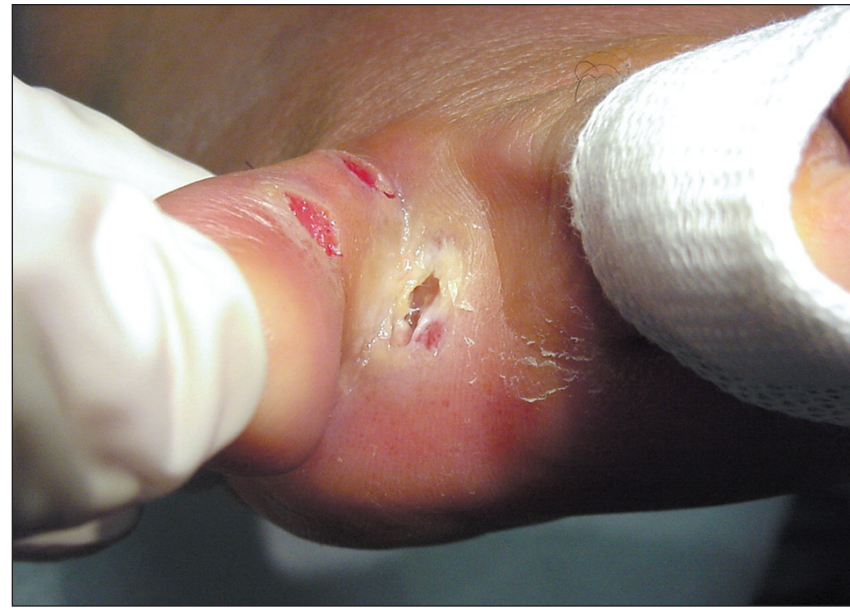

Figure 1: Interdigital tinea pedis can breach host defenses and lead to secondary bacterial infection.

Environmental Factors

The environment is teeming with dermatophytes, including areas around swimming pools, ritual baths, spas, showers, gym floors, locker rooms, clothing, carpeting, pets, etc. Patients with chronic infection shed spores throughout their homes while walking barefoot, helping to re-infect themselves and frequently, other family members. As stated earlier, there is an inherited susceptibility to dermatophyte infection, and indeed we have seen families of five or more where every member has an ongoing infection. In that instance, treatment of the entire family is imperative in any attempt to eradicate the condition in any one member.

Patients with chronic infection shed spores throughout their homes while walking barefoot, helping to re-infect themselves and frequently, other family members.

When it comes to bathing or showering, showering is preferable as scaly, hyperkeratotic skin in standing water of a bath only becomes macerated and does not shed easily. In a shower, there is a greater tendency to shed loose scales with the lavage action of the water. In addition, the feet should actually be washed with soap and water. Upon emerging from the shower, towel drying of the areas should not be through vigorous rubbing, but rather through gentle and thorough patting. An appropriate topical antifungal cream should then be applied.

Sock Materials

Sock materials should be as close to 100% cotton as possible. Cotton keeps moisture away from the skin. Some feel that excessive moisture and chronic, dry, scaly tinea are not related, due to the fact that clinically, the rash is very xerotic. In actuality, it is the sweat (not necessarily excessive)/evaporation cycle that dries out the skin, causing fissuring and scaling that encourages the dermatophyte to harbor in the skin. So cotton materials make sense even in cases where excessive moisture is not an issue. In the same line of thinking, breathable shoe materials are very important so as to further make the local environment hostile to the fungus, by allowing air and moisture transfer which helps cool the foot. Shoes may also have to

Continued on page 231

be treated with agents such as Lysol or Formaldehyde overnight to help reduce numbers of organisms. Newer technologies are being developed to help kill fungi that are harbored in footwear, including shoe-trees with an attached ultraviolet light (Shoe Innovations, Inc.—Steri-Shoe) that kill fungal spores.

Once the infection is under control, it is the recommendation of the authors that application of topical antifungal cream and adherence to the aforementioned adjunctive measures be continued for the life of the patient, depending, of course, on the severity and frequency of recurrence.

Tinea Pedis and Diabetes

One of the authors (Markinson) keeps all diabetic patients with this problem on topical antifungal therapy for life, as well as any patient successfully treated for onychomycosis. He is convinced that this measure decreases the incidence or potential for cellulitis in diabetics and goes very far in the prevention of re-infection of the toenails in any population. Although we encourage daily use of a topical antifungal after showering, some preparations with a "reservoir effect," such as Ciclopirox, may be just as effective in clearing and preventing re-infection with every other day use, or even twice weekly use.

Tinea Pedis and Xerosis

In patients with xerosis (defined here as those patients with chronic tinea pedis who have dry skin even when the infection is cleared), aggressive management of this component alone may go a long way in preventing re-infection with tinea pedis. The use of topical urea has proven itself to be very effective in this regard, in multiple dosage forms and strengths, offering the clinician a variety of choices. Whatever you choose as a dry skin therapy, it is best applied to moist skin after showering, and it is imperative that the patient showers daily so as to make sure the desquamating skin falls away. In patients who shower infrequently, such as the infirmed elderly, patients with dementia, severe arthritis, etc., we encourage them not to re-apply emollient or moisturizing preparations, as they will be compounding the problem of adherent scale, which can become irritated and easily infected from scratching or trauma.

Dr. Markinson keeps all his diabetic patients with tinea pedis on topical antifungal therapy for life, as well as any patient successfully treated for onychomycosis.

The long-term management of tinea pedis also has to take into consideration the area of special populations. Diabetics, the elderly, group home inhabitants, the immuno-suppressed, those on chemotherapy, and those in certain occupations all have special circumstances and issues that may cause varying susceptibility to infection by dermatophytes and varying difficulties for control.

Topical Antifungals

Topical agents produce fewer adverse effects than systemic antifungals and for this reason are considered by many to be first line treatment for uncomplicated dermatophyte infections.

Why choose one topical over another? Cost, duration of therapy, efficacy, and the rate of recurrence all play a role. Improvement in the vehicle-only group may simply be the result of the alteration of the skin environment by hydration, change of pH or desquamation of infected stratum corneum.

There are a number of different classes of antifungal agents but the most popular are allylamines and imidazoles. Allylamines inhibit squalene epoxidase, while azoles inhibit cytochrome P450 14a-demethylase; both of these are essential building blocks for fungal cell structure.

Continued on page 232

TABLE 1
Topical Antifungals by Class

Imidazoles
- Clotrimazole (Mycelex, Lotrimin)
- Miconazole (Monistat)
- Econazole (Spectazole)
- Sertaconazole (Ertaczo)
- Oxiconazole (Oxistat)

Hydroxypyridones
- Ciclopirox (Loprox)

Benzylamines
- Butenafine (Lotrimin Ultra)

Allylamines
- Naftifine (Naftin)
- Terbinafine (Lamisil)

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Tinea Pedis...

Most imidazoles are fungistatic, which means they limit fungal growth, and depend on epidermal turnover to clear the organism from the skin. The one exception to this is sertaconazole, which appears to be cidal. Allylamines and benzylamines are fungicidal, meaning they kill the organism. Allylamines are less active against yeast. The azoles are best used for these types of infections.

In general, treatment times as short as one application daily for one week or less have been associated with high cure rates. This is important since many patients tend to stop treatment at the first sign of improvement, which is usually within one week. Fewer applications also translate into better compliance and lower cost.

Intuitively, an agent with the shortest treatment course and the lowest relapse rate would be most ideal. With this in mind, a review of topical and oral antifungals by class (Table 1), together with results from clinical studies, will allow the myriad of available agents to be put into perspective (Table 2).

1) Imidazoles

Clotrimazole (Lotrimin AF, Mycelex) and miconazole (Micatin, Monistat Derm, Zeasorb AF) are two of the original and hence oldest azoles and for years have been the workhorse topicals for the treatment of uncomplicated tinea pedis.

Both block ergosterol synthesis and have similar spectra of activity and efficacy[3] Since their inception, several newer imidazoles have been developed.

Sertaconazole nitrate (Ertaczo)

Sertaconazole is a member of the imidazole class of antifungals and inhibits ergosterol synthesis. The usual dose is twice daily for four weeks. Unlike other imidazoles, sertaconazole is fungicidal. Sertaconazole is active against yeasts and dermatophyte fungi and has shown activity against Gram-positive cocci.[4]

Sertaconazole has been shown to have anti-inflammatory activity which may help relieve pruritis and contribute to its efficacy. Ciclopirox, fluconazole, and miconazole have also been found to have anti-inflammatory activity, but the in vitro and in vivo anti-inflammatory activity of sertaconazole nitrate has been found to be greater.[5]

The first cases of tinea pedis were not reported until the late 1800s.

The use of sertaconazole in a nail patch formulation for treatment of onychomycosis has been evaluated. Concentrations of sertaconazole in nails have been shown to be well above the minimum inhibitory concentrations (MIC) values for pathogenic fungi relevant to onychomycosis.[6] Nevertheless, there are no clinical trials currently underway investigating the use of sertaconazole for the treatment of onychomycosis.

To determine the safety and efficacy of topical sertaconazole nitrate cream 2% in the treatment of tinea pedis, two randomized, multicenter, double-blinded, vehicle-controlled studies were conducted. A total of 383 subjects were randomized to treatment with sertaconazole or vehicle applied twice daily for four weeks. Improvement in symptoms was noted at week one in the active

Continued on page 233

TABLE 2
Topical Antifungals by Activity and Dosing

	Usual Dose for T. pedis	Rx or OTC
Fungistatic		
Clotrimazole (Mycelex, Lotrimin AF)	bid X 4 weeks	OTC
Miconazole (Monistat)	bid X 4 weeks	OTC
Oxiconazole (Oxistat)	qd –bid X 4 weeks	Rx
Econazole (Spectazole)	qd X 4 weeks	Rx
Fungicidal		
Sertaconazole (Ertaczo)	bid X 4 weeks	Rx
Ciclopirox (Loprox)	bid X 4 weeks	Rx
Butenafine (Lotrimin Ultra)	qd X 4 weeks	OTC
Naftifine (Naftin)	qd X 4 weeks	Rx
Terbinafine (Lamisil AT Gel)	qd X 7 days	OTC

treatment group. At week four, mycologic cure was seen in 70.3% of sertaconazole-treated subjects and 36.7% of vehicle-treated subjects. The stability of the mycologic cure rates two weeks after cessation of therapy indicates that sertaconazole protects against re-infection and recurrence at least in the short term.[7]

Econazole (Spectazole)

Econazole is a fungistatic imidazole. The usual dose is one application daily for four weeks. Econazole has been found to be a highly effective topical agent in the treatment of T. pedis with a clinical and mycological cure rate over 80% two months and over 60% three months after the cessation of four weeks of treatment.[8] Like sertaconazole, econazole has shown activity against Gram-positive bacteria.[9] Econazole is currently available only in generic form.

Using econazole in a liposomal delivery system to improve penetration and enhance accumulation has been investigated. Liposomes have been useful in parenteral agents because they reduce side effects. Animal studies have demonstrated econazole in a liposomal gel is capable of enhancing drug accumulation at the administration site and retaining the drug in the skin of mice. Liposomes may in the future be useful vehicles for topical drug delivery in the treatment of T. pedis and other skin diseases.[10]

Topical agents produce fewer adverse effects than systemic antifungals.

Oxiconazole Nitrate (Oxistat)

Oxiconazole is a fungistatic azole and has been available in the United States since 1989. It is applied once to twice daily for four weeks. Oxiconazle is highly active against a wide range of dermatophytes, including T. rubrum and T. mentagrophytes. Oxiconazole is rapidly absorbed into the stratum corneum, with maximum concentrations achieved within two hours of application. Drug levels exceeding the minimum inhibitory concentrations (MIC) of susceptible fungi have been demonstrated to be present in epidermis for over 16 hours.[11]

In studies of plantar tinea pedis caused by T rubrum, once-daily oxiconazole cream resulted in a mycologic cure in 76% of patients. In comparative clinical trials of various types of dermatophytoses, oxiconazole was shown to be as effective as, or more effective than, miconazole, clotrimazole, and tolnaftate creams, and as effective as econazole cream.[11]

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2) Hydroxypyridones

Ciclopirox (Loprox)

Ciclopirox is a broad-spectrum fungicidal medication that has activity against dermatophytes, yeast, and bacteria. It is indicated for interdigital T. pedis and moccasin tinea pedis. The usual dose of ciclopirox is twice daily X 4 weeks for T. pedis. In an 8% lacquer base, it is approved for the treatment of mild to moderate forms of onychomycosis.

Three hundred and seventy-four subjects were enrolled and randomized to one of two treatment groups: ciclopirox gel 0.77%, or ciclopirox gel vehicle, applied twice daily for 28 days. Pooled data showed that 85% of ciclopirox subjects were mycologically cured compared to only 16% of vehicle subjects at two weeks post-treatment.[12]

The use of topical antifungals with 40% urea cream for the treatment of plantar or moccasin-type tinea pedis has been studied with this and other agents with noted benefit. In a study by Elewski, et al., a total of 12 patients with moccasin tinea pedis were treated with 40% urea cream once daily and ciclopirox cream twice daily. After two to three weeks, a 100% cure rate was achieved in the 12 patients treated with topical 40% urea cream and ciclopirox cream combination.[13]

3) Benzylamines

Butenafine (Lotrimin Ultra)

Butenafine is a synthetic benzylamine derivative with a recommended application of once or twice daily for four weeks. Benzylamines are structurally related to the allylamines and are fungicidal against dermatophytes. Butenafine achieves and maintains high concentrations and long retention time in skin, with the concentration of butenafine in the skin reaching a steady state at two weeks after the application[14] The effectiveness of the drug has been noted to persist for at least four weeks following the discontinuation of therapy.[15]

Butenafine has shown anti-inflammatory activity in vivo.[16] Butenafine has shown activity against beta-hemolytic Streptococcus Group A and Corynebacterium, but no activity against Gram negatives.[17]

In the first major North American butenafine clinical trial, 40 patients with positive fungal cultures applied butenafine cream, and 40 patients applied vehicle to affected interdigital areas once daily for four weeks. There was a

Continued on page 234

mycologic cure rate of 88% in the butenafine treated group and 33% in the vehicle treated group.[18]

Comparator studies involving T. pedis are lacking; however, in a study by Singal, eighty patients with tinea cruris or localized tinea corporis were randomly assigned to one of the two treatment groups: butenafine once daily for two weeks or clotrimazole twice daily for four weeks. Butenafine recipients exhibited higher clinical cure as compared with clotrimazole at the end of one week (26.5% vs. 2.9%), as well as higher mycological cure (61.7% vs 17.6%). The difference was not statistically significant, however, at four and eight weeks after treatment.[19] Co-administration with a keratolytic ointment has been found to result in earlier clinical improvement, resulting in an almost 10% higher clinical response rate.[20]

Topical terbinafine has demonstrated good efficacy and low relapse rate with short duration of therapy.

4) Allylamines

Naftifine (Naftin)

Naftifine is a broad spectrum agent active against dermatophytes. It works by inhibiting squalene[2,3] epoxidase, decreasing ergosterol production, and disrupting the stability of the fungal membrane. Naftifine is applied twice daily for 7 days or once daily for four weeks. In vivo, naftifine gel and cream, econazole, and clotrimazole cream were equally effective against T. rubrum and T. metagrophytes.[21]

Topical naftifine gel has been studied for the treatment of onychomycosis, albeit of the fingers. In a small, open-label study of naftifine gel for the treatment of distal subungual onychomycosis, ten patients with culture-proven distal subungual onychomycosis were treated twice daily for six months with naftifine 1 percent gel. After six months of therapy, eight of ten patients showed negative results of fungal culture and eight of ten patients showed clinical improvement. There have been no follow-up studies on onychomycosis of the toenails.[22] Naftifine has been shown to inhibit polymorphonuclear leukocyte (PMN) chemotaxis, which may explain part of its anti-inflammatory effect.[23]

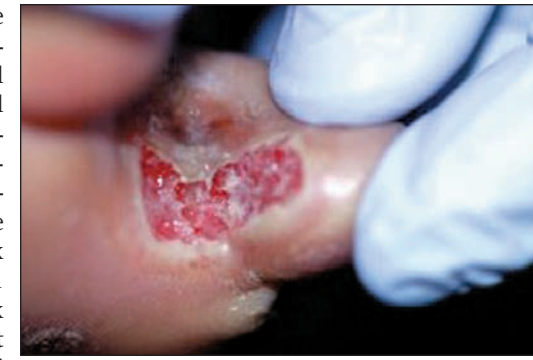

Figure 2: This is a classic example of interdigital bullous T. pedis following deroofing of the lesion

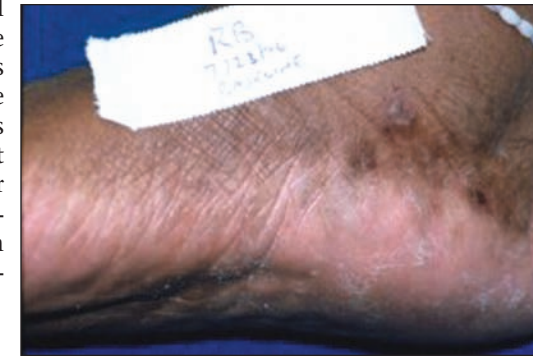

Figure 3: Tinea pedis in the characteristic moccasin distribution.

(Figures 2 and 3 have been supplied courtesy of Dr. Joseph.)

Terbinafine (Lamisil)

Terbinafine is a lipophilic, keratophilic, orally and topically active allylamine, which has fungicidal activity against dermatophytes, molds and certain dimorphic fungi. It is static against Candida albicans. One-week application of terbinafine cream has shown results equivalent to four-week application of terbinafine cream for the treatment of T. pedis.[24] Therefore, a shorter duration of terbinafine cream is equally effective as a longer duration of treatment.

In a study of 15 species of clinically important dermatophytes, susceptibilities ranged between 94% for terbinafine, 87.6% for sertaconazole, 86.4% for clotrimazole, 81.6% for econazole, 78.4% for itraconazole, 74.4% for ketoconazole and 73.3% for miconazole.[25]

Terbinafine 1% cream applied once daily for seven days in adult patients with interdigital tinea pedis has been shown to be significantly more effective than its vehicle in achieving and maintaining mycological cure for seven weeks: 91.4% vs. 37.1%.[26] The labeled dose for the treatment of interdigital tinea pedis is twice daily for one week (Figure 2).

Topical terbinafine cream has been shown to be at least as active as miconazole cream and naftifine gel for the treatment of tinea pedis, and more effective than clotrimazole cream and oxiconazole lotion. Clinical improvement generally continues after the treatment period ends, underscoring the drug's reservoir effect.[27]

Terbinafine in an emulsion gel has demonstrated good efficacy and low relapse rate with short duration of therapy. Because it is applied only once daily, it requires the fewest number of applications as compared to other topical antifungals. For the treatment of interdigital T. pedis, pharmacokinetic studies have shown AUC values significantly greater for gel than for cream. Skin penetration is greater and occurs sooner with the emulsion gel compared with 1% cream, and remains in high concentrations for several months after seven days of application.[28]

In a multi-center, randomized

Continued on page 235

vehicle-controlled trial 101 patients with culture confirmed tinea pedis were randomized to receive either terbinafine 1% emulsion gel or vehicle. Each was applied once daily for 7 days. At the end of week 8 (7 weeks after the last application) the terbinafine group showed a 59% clinical cure and a 81% mycological cure, versus 29% and 33% respectively for the vehicle treated group.[29]

In a similar study involving tinea corporis, terbinafine emulsion gel showed an 83% mycological cure compared to 27% for the vehicle comparator.[30]

Summary

As discussed above in great detail, the topical antifungal agents are the most commonly used for the treatment of most cases of tinea pedis. They are relatively inexpensive, are easy to apply, are generally efficacious and carry no concerns about systemic toxicity. Furthermore, patients may feel more "actively involved" with the treatment since they are applying the medication directly to the affected area, forcing the patient to regularly observe the site for progress. In many cases, the vehicle alone has been shown to be effective by directly changing the environment of the skin (i.e., moisturizing if dry, drying if wet and macerated).

Topical Antifungal Issues

However, there are some potential issues regarding the use of topical antifungal agents. Because of limited mobility or flexibility, the patient may have difficulty reaching the affected site. They may be viewed as cosmetically inelegant, if not downright "messy" to apply. Adherence to treatment plans may be difficult for patients, especially with drugs that need to be applied twice daily for up to four weeks. In fact, most patients never complete a full treatment course and rather unilaterally stop therapy when symptoms improve.

This can be an issue for drugs that are primarily fungistatic since the organism may simply begin growing once the residual antifungal is out of the skin. Finally, since most of the studies examined the treatment of interdigital fungal infections, we have little knowledge of their efficacy against the more common, dry-type moccasin variety of tinea pedis (Figure 3). For these reasons, oral antifungals may play a role in the treatment of tinea pedis.

Adherence to treatment plans may be difficult for patients, especially with drugs that need to be applied twice daily for up to four weeks.

The Role of Oral Antifungals for the Treatment of Tinea Pedis

While topical antifungals are the first line of treatment for tinea pedis, there are instances when oral antifungals are indicated (Table 3).

The concept of using oral antifungals for tinea pedis is not new. A Medline search reveals articles on the use of griseofulvin for tinea pedis dating back as far as 1959. Griseofulvin, in both its microsized and ultramicrosized formulations, is specifically FDA-approved for the treatment of tinea pedis. Ketoconazole, another older oral agent, while not specifically labeled for tinea pedis, is approved for use in "recalcitrant cutaneous dermatophyte infections which have not responded to topical therapy or oral griseofulvin..."[36]

In the past, neither of these older oral agents really had widespread usage for tinea pedis. Ketoconazole has been considered by most podiatrists as too risky of a drug to use for this indication with "black-box" warnings of liver toxicity including fatalities along with multiple drug-drug interactions. Griseofulvin, on the other hand, while a considerably safer drug than ketoconazole, in the past was primarily marketed for the treatment of onychomycosis. It generally received a "bad rap" when used to treat onychomycosis because of the need for prolonged therapy of up to 18 months, relatively low cure rates and high recurrence rates.

There has also been confusion over the different formulations of the drug. Furthermore, because of the prolonged therapy, there were mostly unfounded concerns about toxicities involving the liver, white blood cell and headache. These are not much of a problem with the shorter courses used in the treatment of tinea pedis. Recently, in the past two to three years, ultramicrosized griseofulvin has found resurgence in the profession and is being marketed for the oral therapy of this infection.

At least one in vitro study from Singapore of the susceptibility of various dermatophytes to griseofulvin, ketoconazole, and intraconazole found that the antifungal activity against the dermatophytes of all three agents were similar. The investigators concluded that "Griseofulvin may be given as the first-line drug for treating such infections..."[37]

It is theorized that the ultramicrosized (ums) form of griseofulvin may have better absorption from the gastrointestinal tract and

Continued on page 236

TABLE 3
Oral Antifungals Used to Treat Tinea Pedis

Ketoconazole (Nizoral)
Itraconazole (Sporanox)
Fluconazole (Diflucan)
Terbinafine (Lamisil)
Griseofulvin (Gris-Peg)

reach higher levels at the target tissue. In an older, multinational, multicenter study that looked specifically at the ums form of griseofulvin, 73 patients were treated with either ums griseofulvin alone, topical clotrimazole alone, or the combination of the two. The patients were also divided by disease state into those with moccasin-type tinea pedis and those with interdigital disease. Patients were then followed for three months after the end of therapy. In the moccasin-type, patients at the three month follow-up for those on ums griseofulvin alone demonstrated a 68% cure rate, clotrimazole alone an 18% cure, and a 64% cure with the combination. In those patients with interdigital tinea pedis, the cure rates at three months were 43%, 20%, and 84% respectively.[38]

Off-Label Use of Antifungals

There has been increased interest in itraconazole, fluconazole and terbinafine for the treatment of tinea pedis. It should be noted that none of these drugs are currently FDA indicated for this use; however, there are both practitioner clinical experience and good medical evidence that point to their efficacy.

The thought that these drugs may be useful in the treatment of tinea pedis arose in the minds of many podiatrists while they were using these drugs when first marketed for onychomycosis. Patients would complain about "dry skin" on the soles of their feet that they had unsuccessfully treated for years with various moisturizers. This was, of course, undiagnosed dry-type moccasin tinea. Treatment would be initiated for their concomitant onychomycosis (Figure 4). At the time of the first follow-up appointment, usually scheduled at four to six weeks for subsequent blood testing, the first comment of many of these patients was that their skin never looked so good. In fact, on examination, most of the previous signs of scaling and flaking were all but gone long before any changes in the nails could be appreciated. For this reason, despite the lack of a formal indication, many podiatrists began using short courses of these oral drugs specifically for more severe cases of tinea pedis. Unfortunately, there has never been a consensus on the length of that course, with variations of one to four weeks of either continuous or intermittent ("pulse") therapy being attempted.

Oral ketoconazole has been considered by most podiatrists as too risky of a drug to use for this indication with "black-box" warnings of liver toxicity, including fatalities along with multiple drug-drug interactions.

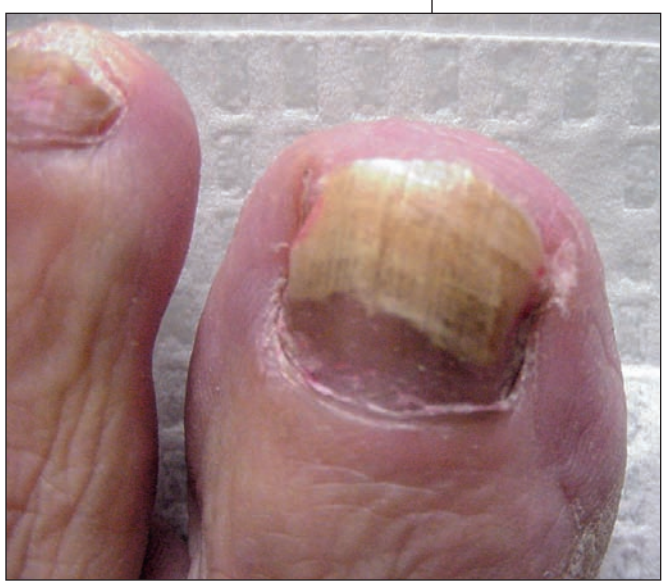

Figure 4: Dry, scaling tinea pedis characteristic of Trichophyton rubrum, coexisting in a patient with onychomycosis.

Multiple clinical trials support this usage. A Cochrane database review of this topic published in 2002 looked at twelve trials, involving 700 participants. The two trials comparing terbinafine and griseofulvin produced a "pooled risk difference of 52% (95% confidence intervals 33% to 71%) in favor of terbinafine's ability to cure infection. No significant difference was detected between terbinafine and itraconazole; or between fluconazole and either itraconazole or ketoconazole." It was the reviewers' conclusion that "The evidence suggests that terbinafine is more effective than griseofulvin, and that terbinafine and itraconazole are more effective than no treatment."[39]

A few studies/reports can be found that looked at the use of intraconazole against tinea pedis. A single clinical case of a 40 y/o woman with recalcitrant tinea pedis, which had failed to respond to topical therapy and oral griseofulvin, was successfully treated with a four-month course of intermittent itraconazole. It was published in 1996, fairly early in this era of newer oral antifungals.[40]

Continuous itraconazole, 100 mg. for four weeks, was compared to 500 mg. of griseofulvin in a trial of 20 patients with culture proven tinea pedis or tinea manus. After four weeks therapy, 50% of itraconazole-treated patients, and 30% of griseofulvin-treated patients had negative microscopy. Interestingly, six patients reported mild adverse events, with five caused by the itraconazole and only one by the griseofulvin.[41]

Terbinafine

Terbinafine has been studied both against placebo and against other active agents. In one study, 53 patients were treated with ei-

Continued on page 237

ther two weeks of daily 250 mg. terbinafine versus placebo. At the end of the study, 71% of terbinafine-treated patients for moccasin tinea pedis and tinea manum were judged to have received effective therapy vs. 0% of the placebo patients.[42]

In a large study of 366 patients comparing two weeks of 250 mg. terbinafine to 100 mg. itraconazole for tinea pedis, terbinafine showed statistically greater absence of clinical symptoms than itraconazole (94.1% vs. 72.7%).[43]

Yet another study that compared these two drugs looked at the intermittent dose of 200 mg of itraconazole given for one week vs. 250 mg daily of terbinafine for 14 days. This study of 304 patients found results that were much closer than the previously cited trial with a positive clinical response of 93% for itraconazole vs. 91% for terbinafine.[44]

The bottom line results of these data show that all of the above oral antifungal drugs can play a significant role in the treatment of tinea pedis despite the lack of an FDA indication for some of the agents. Because of the outside risk of systemic adverse reactions or drug-drug interactions, many practitioners still prefer to attempt topical therapy as first line. In patients with severe dry-type moccasin disease or significant, fissuring, bullous tinea pedis, or in those patients who may not be adherent to treatment recommendations for the use of topical therapy, the use of oral agents may be a useful alternative or adjunct.

Long-Term Management and Prevention of Re-infection

Tinea pedis of the chronic, dry, scaly type is much harder to eradicate in the long term than the acute vesicular and interdigital types. In patients with onychomycosis, especially the total dystrophic type, it is very rare to not be able to find a focus of tinea pedis on the skin, and indeed, the moccasin type distribution is very common in this scenario. After successful clearing of chronic, dry, scaly tinea pedis, patients must be educated as to the virtual certainty of re-infection if preventive measures are not taken.

The long-term management of tinea pedis also has to take into consideration the area of special populations. Diabetics, the elderly, group home inhabitants, the immuno-suppressed, those on chemotherapy, and those in certain occupations all have special circumstances and issues that may cause varying susceptibility to infection by dermatophytes and varying difficulties for control.

With diligent podiatric management and patient adherence to the principles outlined above, and the use of newer topical and systemic antifungals, long term cure, long-term control, and prevention of re-infection are certainly achievable. ■

71% of oral terbinafine-treated patients for moccasin tinea pedis and tinea manum were judged to have received effective therapy vs. 0% of the placebo patients.

References

[1] Zaias N, Tosti A, Rebell G, Morelli R, Bardazzi F, Bieley H, Zaiac M, Glick B, Paley B, Allevato M, Baran R.. Autosomal dominant pattern of distal subungual onychomycosis caused by Trichophyton rubrum.. J Am Acad Dermatol. 1996 Feb;34(2 Pt 1):302-4.

[2] Jones HE, Reinhardt JH, Rinaldi MG. Acquired immunity to dermatophytes. Arch dermatol 1974:109: 840-8.

[3] Ernest JM. Topical antifungal agents. Obtet Gnecol Cin North Am 1992;19;587-607.

[4] Pfaller MA, Sutton DA. Review of in vitro activity of sertaconazole nitrate in the treatment of superficial fungal infections. Diagn Microbiol Infect Dis. 2006 Oct;56(2):147-52.

[5] Liebel F, Lyte P, Garay M, Babad J, Southall MD. Anti-inflammatory and anti-itch activity of sertaconazole nitrate. Arch Dermatol Res 2006 Sep;298(4):191-9.

[6] Susilo R, Korting HC, Greb W, Strauss UP. Nail penetration of sertaconazole with a sertaconazole-containing nail formulation. Am J Clin Dermatol. 2006;7(4):259-62.

[7] Savin R, Jorizzo J. The safety and efficacy of sertaconazole nitrate cream 2% for tinea pedis. Cutis 2006 Oct:78(4) 268-74.

[8] Cullen SI, Millikan LE, Mullen RH. Treatment of tinea pedis with econazole nitrate cream. Cutis. 1986 May;37(5):388-9.

[9] Kokjohn K, Bradley M,Griffiths B, Ghannoum M.Evaluation of in vitro activity of ciclopirox olamine, butenafine HCl and econazole nitrate against dermatophytes, yeasts and bacteria. Int J Dermatol. 2003 Sep;42 Suppl 1:11-7.

[10] Qi X. R. ; Liu M. H. ; Liu H. Y. ; Maitani Y. ; Nagait T. Topical econazole delivery using liposomal gel. STP pharma sciences . 2003, vol. 13, no4, pp. 241-245.

[11] Jegasothy BV, Pakes GE.. Oxiconazole nitrate: pharmacology, efficacy, and safety of a new imidazole antifungal agent. Clin Ther. 1991 Jan-Feb;13(1):126-41.

[12] Aly R, Fisher G, Katz I, Levine N, Lookingbill DP, Lowe N, Menter A, Morman
M, Pariser DM, Roth HL, Savin RC, Shavin JS, Stewart D, Taylor JR, Tucker S,Wortzman M. Ciclopirox gel in the treatment of patients with interdigital tinea pedis Int J Dermatol. 2003 Sep;42 Suppl 1:29-35

[13] Elewski BE, Haley HR,Robbins CM. The use of 40% urea cream in the treatment of moccasin tinea pedis Cutis. 2004 May;73(5):355-7.

[14] Tanuma H, Doi M, Ohta Y, Abe M, Kume H, Mukai H, Katsuoka K Butenafine hydrochloride (Mentax) cream for the treatment of hyperkeratotic type tinea pedis and its transfer into the horny layer, with or without concomitant application of 20% urea ointment (Keratinamin). Mycoses. 2001;44(7-8):287-99.

[15] Butenafine: an update of its use in superficial mycoses. Gupta AK. Skin Therapy Lett. 2002 Sep;7(7):1-2)

[16] Syed TA, Maibach HI. Butenafine hydrochloride: for the treatment of interdigital tinea pedis. Expert Opin Pharmacother. 2000 Mar;1(3):467-73)

[17] Kokjohn K, Bradley M,Griffiths B, Ghannoum M.Evaluation of in vitro activity of ciclopirox olamine, butenafine HCl and econazole nitrate against dermatophytes, yeasts and bacteria. Int J Dermatol. 2003 Sep;42 Suppl

Continued on page 238

Tinea Pedis...

1:11-7.

[18] Tschen E, Elewski B, Gorsulowsky DC, Pariser DM. Treatment ofinterdigital tinea pedis with a 4-week once-daily regimen of butenafine hydrochloride 1% cream. J Am Acad Dermatol. 1997 Feb;36(2 Pt 1):S9-14.

[19] Singal A, Pandhi D, Agrawal S,Das S.Comparative efficacy of topical 1% butenafine and 1% clotrimazole in tinea cruris and tinea corporis: a randomized, double-blind trial. J Dermatolog Treat. 2005;16(5-6):331-5).

[20] Tanuma H, Doi M, Ohta Y, Abe M, Kume H, Mukai H, Katsuoka K Butenafine hydrochloride (Mentax) cream for the treatment of hyperkeratotic type tinea pedis and its transfer into the horny layer, with or without concomitant application of 20% urea ointment (Keratinamin). Mycoses. 2001;44(7-8):287-99.

[21] (Stoughton RB, sefton J, Zeleznick L. In vitro and in vivo cutaneous penetration of antifungal activity of naftifine.. cutis 44:333-335. 1989).

[22] Meyerson MS, Scher RK, Hochman LG, Cohen JL, Pappert AS, Holwell JE. Open-label study of the safety and efficacy of naftifine hydrochloride 1 percent gel in patients with distal subungual onychomycosis of the fingers. Cutis. 1993 Mar;51(3):205-7).

[23] Choi TS, Solomon B, Nowakowski M, Lee WL,Geen S, Suntharalingam K, Fikrig S, Shalita AR. Effect of naftifine on neutrophil adhesion. Skin Pharmacol. 1996;9(3):190-6).

[24] Sugiura M, Hata Y, Fukuda T, Ishizaki S, Hanyaku H,Naka W, Harada T, Nishikawa T.[One-week application of terbinafine cream compared with four-week application in treatment of Tinea pedis] Nippon Ishinkin Gakkai Zasshi. 2001;42(4):223-8.

[25] Carrillo-Munoz AJ, Guglietta A, Palacin C, Casals J, del Valle O, Guardia C, Rodriguez V, Quindos G.In vitro antifungal activity of sertaconazole compared with nine other drugs against 250 clinical isolates of dermatophytes and Scopulariopsis brevicaulis. Chemotherapy 2004 Dec;50(6):308-13.

[26] Korting HC, Tietz HJ, Brautigam M, Mayser P, Rapatz G, Paul C. One week terbinafine 1% cream (Lamisil) once daily is effective in the treatment of interdigital tinea pedis: a vehicle controlled study. LAS-INT-06 Study Group.Med Mycol. 2001 Aug;39(4):335-40).

[27] McClellan KL, Wiseman LR,Markham A. Terbinafine. An update of its use in superficial mycoses.Drugs. 1999 Jul;58(1):179-202).

[28] Denouel Jannick , Burtin Pascale, Kshatraya Bahakti, Snoddy, Andrew Pharmacokinetics of 1% terbinfine emulsion gel in healthy volunteersn and in helthy patients with tinea cruris/corporis. 2006 Annual Meeting, American College of Clinical Pharmacy. October 26-29, St Louis, MissouriPoster 249.

[29] Hollmen KA, Kinnunen T, Kiistala U, Vaananen A, Saarelainen IO, De Cuyper C, DeCroix J, Broeckx W, Karvone J. Efficacy and tolerability of terbinafine 1% emulsion gel in patients with tinea pedis. Jol Europ Acad Dermatol and Venereology 2002 16:81-84.

[30] Van Heerden JS, Vismer HF. Tinea corporis/crusis" New Treatment options. Dermatology 1997: 194(supl 1):14-18.

[31] Ortonne JP, Korting HC, Viguie-Vallanet C, Larnier C, Savaluny E Efficacy and safety of a new single-dose terbinafine 1% formulation in patients with tinea pedis (athlete's foot): a randomized, double-blind, placebo-controlled studyJ Eur Acad Dermatol Venereol. 2006 Nov;20(10):1307.

[32] Watanabe S, Takahashi H,Nishikawa T, Takiuchi I, Higashi N, Nishimoto K, Kagawa S, Yamaguchi H, Ogawa H A comparative clinical study between 2 weeks of luliconazole 1% cream treatment and 4 weeks of bifonazole 1% cream treatment for tinea pedis Mycoses. 2006 May;49(3):236-41.

[33] del Palacio A, Ortiz FJ, Perez A, Pazos C, Garau M, Font E.A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections.Mycoses. 2001;44(5):173-80.

[34] Watanabe S, Takahashi H, Nishikawa T, Takiuchi I,Higashi N, Nishimoto K, Kagawa S, Yamaguchi H, Ogawa H. Dose-finding comparative study of 2 weeks of luliconazole cream treatment for tinea pedis—comparison between three groups (1%, 0.5%, 0.1%) by a multi-center randomised double-blind study, Mycoses. 2007 Jan;50(1):35-40.

[35] Koga H, Tsuji Y, Inoue K,Kanai K, Majima T, Kasai T, Uchida K, Yamaguchi H In vitro antifungal activity of luliconazole against clinical isolates from patients with dermatomycosis J Infect Chemother. 2006 Jun;12(3):163-5.

[36] (Nizoral® package insert).

[37] Goh CL, Tay YK, Ali KB, Koh MT, Seow CS. In vitro evaluation of griseofulvin, ketoconazole and itraconazole against various dermatophytes in Singapore. Int J Dermatol. 1994 Oct;33(10):733-72.

[38] Zaias N, Battistini F, Gomez-Urcuyo F. Treatment of tinea pedis with griseofulvin and a topical antifungal cream. Cutis August 1978 Vol 22, pp196-199.

[39] Bell-Syer SE, Hart R, Crawford F, Torgerson DJ, Tyrrell W, Russell I. Oral treatments for fungal infection of the skin of the foot. Cochrane Database Syst Rev. 2002;(2).

[40] Del Rosso JQ. Treatment of onychomycosis and tinea pedis with intermittent itraconazole therapy J Am Osteopath Assoc. 1996 Oct;96(10):607-9.

[41] Wishart JM. A double blind study of itraconazole vs. griseofulvin in patients with tinea pedis and tinea manus. N Z Med J. 1994 Apr 13;107(975):126-8.

[42] White JE, Perkins PJ, Evans EG. Successful 2-week treatment with terbinafine (Lamisil) for moccasin tinea pedis and tinea manuum. Br J Dermatol. 1991 Sep;125(3):260-2.

[43] De Keyser P, De Backer M, Massart DL, Westelinck KJ. Two-week oral treatment of tinea pedis comparing terbinafine (250 mg/day) with itraconazole (100 mg/day): a double-blind, multicentre study. Br J Dermatol. 1994 Apr;130 Suppl 43:22-5.

[44] Tausch I, Decroix J, Gwiezdzinski Z, Urbanowski S, Baran E, et al. Short-term itraconazole versus terbinafine in the treatment of tinea pedis or tinea manus. Int J Dermatol. 1998 Feb;37(2):140-2.

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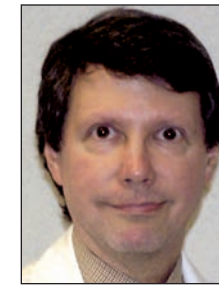

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EXAMINATION

Continuing Medical Education

See answer sheet on page 241.

1) The most common dermatophyte causing tinea pedis is
- A) T. rubrum
- B) T. mentagrophytes
- C) Candida albicans
- D) T. tonsurans

2) On average, the number of spores needed to induce a persistent infection in 50% of experimental subjects has been found to be
- A) One hundred thousand
- B) Ten thousand
- C) One thousand
- D) As few as six

3) Which of the following classes of antifungals inhibit cytochrome P450 14a-demethylase, an essential building block for fungal cell structure?
- A) Imidazoles
- B) Allylamines
- C) Pyridones
- D) Benzylamines

4) Which of the following is an imidazole ?
- A) Ciclopirox
- B) Econazole
- C) Butenafine
- D) Terbinafine

5) Which of the following is an allylamine?
- A) Ciclopirox
- B) Econazole
- C) Butenafine
- D) Terbinafine

6) Which of the following is a hydroxypyridone ?
- A) Ciclopirox
- B) Econazole
- C) Butenafine
- D) Terbinafine

7) Which of the following is a benzylamine?
- A) Ciclopirox
- B) Econazole
- C) Butenafine
- D) Terbinafine

8) Allylamines are:
- A) Fungicidal
- B) Fungistatic
- C) Highly active against yeasts
- D) Do not inhibit squalene epoxidase

9) Terbinafine is:
- A) Fungicidal against T. rubrum
- B) Fungistatic against T. mentagrophytes
- C) Cidal against Candida albicans
- D) Does not inhibit squalene epoxidase

10) Clotrimazole belongs to what class of antifungal ?
- A) Imidazoles
- B) Hydroxypyridones
- C) Benzylamines
- D) Allylamines

11) Ciclopirox belongs to what class of antifungal ?
- A) Azoles
- B) Hydroxypyridones
- C) Benzylamines
- D) Allylamines

12) Butenafine belongs to what class of antifungal?
- A) Azoles
- B) Hydroxypyridones
- C) Benzylamines
- D) Allylamines

13) Naftifine belongs to what class of antifungal?
- A) Azoles
- B) Hydroxypyridones
- C) Benzylamines
- D) Allylamines

14) Terbinafine is:
- A) Lipophilic
- B) A benzylamine
- C) An azole
- D) Fungistatic

15) Which of the following is considered to be an "upside" of topical antifungal therapy for tinea pedis?
- A) Relatively inexpensive
- B) Little or no systemic side-effects
- C) No interaction with systemic drugs
- D) All of the above

16) Which of the following is considered to be an "issue" of topical antifungal therapy for tinea pedis?
- A) The patient may have limited flexibility, making application difficult.
- B) Topicals may be viewed by the patient as "messy" to apply.
- C) Adherence to treatment plans may be difficult, especially with drugs that need to be applied twice daily for up to four weeks.
- D) All of the above

17) Which of the following is true?
- A) Dermatophytes are

Continued on page 240

Continuing Medical Education

EXAMINATION

(cont'd)

pathogenic fungi that produce keratinase.
B) Glycoproteins found in the cell wall of T. rubrum can suppress the inflammatory response.
C) T. rubrum infection shows a pattern of autosomal dominant inheritance.
D) All of the above

18) Which of the following is false?
A) Griseofulvin, in both its microsized and ultramicrosized formulations, are FDA approved for the treatment of tinea pedis.
B) Ultramicrosized (ums) form of griseofulvin may have better absorption from the gastrointestinal tract.
C) Ultramicrosized (ums) form of griseofulvin may reach higher levels at the target tissue.
D) Oral terbinafine has received FDA approval for the treatment of tinea pedis.

19) Which of the following is false?
A) Tinea pedis of the chronic dry scaly type is much easier to eradicate in the long-term than the acute vesicular and interdigital types.
B) Trichophyton mentagrophytes can produce a much more aggressive immune response than Trichophyton rubrum.
C) Infection with Trichophyton mentagrophytes may lead to a more aggressive bullous infection compared to Trichophyton rubrum.
D) Patients with defective cell-mediated immunity are pre-disposed to chronic infection and recurrence of tinea pedis.

20) Which of the following is true?
A) Aggressive management of xerosis may go a long way to preventing re-infection with tinea pedis.
B) The application of urea cream in conjunction with a topical antifungal has been shown to increase the cure rate of tinea pedis.
C) Treatment of the entire family may be necessary in any attempt to eradicate the condition in any one member.
D) All of the above are true.

See answer sheet on page 241.

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EXAM #5/07

Advances in the Treatment of Tinea Pedis (Kosinski, Joseph, and Markinson)

Circle:

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2.	**A**	**B**	**C**	**D**	**12.**	**A**	**B**	**C**	**D**
3.	**A**	**B**	**C**	**D**	**13.**	**A**	**B**	**C**	**D**
4.	**A**	**B**	**C**	**D**	**14.**	**A**	**B**	**C**	**D**
5.	**A**	**B**	**C**	**D**	**15.**	**A**	**B**	**C**	**D**
6.	**A**	**B**	**C**	**D**	**16.**	**A**	**B**	**C**	**D**
7.	**A**	**B**	**C**	**D**	**17.**	**A**	**B**	**C**	**D**
8.	**A**	**B**	**C**	**D**	**18.**	**A**	**B**	**C**	**D**
9.	**A**	**B**	**C**	**D**	**19.**	**A**	**B**	**C**	**D**
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