Combatting Fungal

A specialist offers selected pearls for diagnosis and treatment.

By Whitney A. High, MD

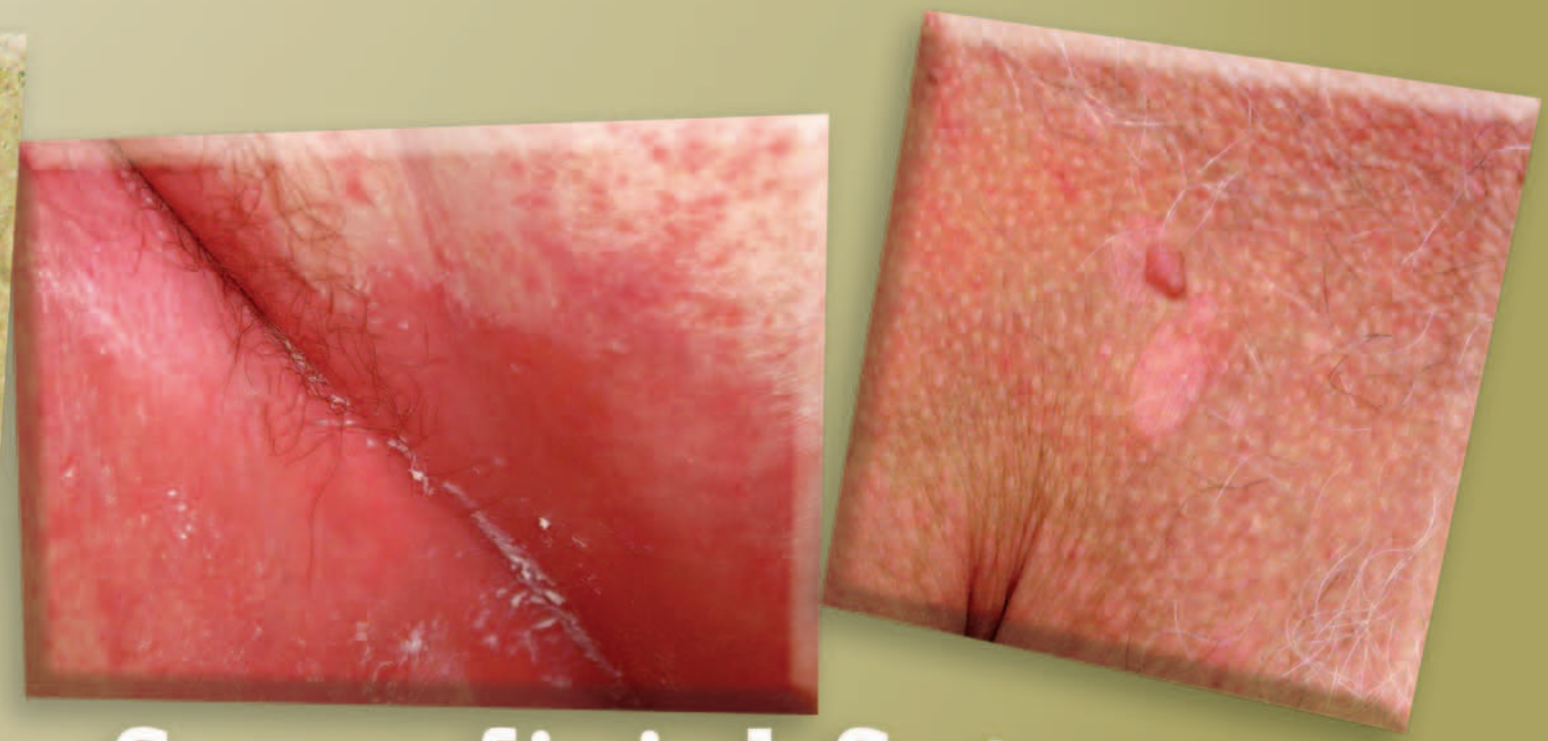
Common superficial cutaneous fungal infections include tinea, candidiasis, and pityriasis versicolor. Myriad treatment options exist to treat these infections, and it is incumbent upon the practitioner to understand general principles that guide diagnosis and management.

Diagnostic Pearls

While an exhaustive review of diagnostic means is beyond this brief review, certain "pearls" merit attention. Dr. James Fitzpatrick and I have formulated our own "Ten Commandments" for diagnosing superficial cutaneous fungal infections. We often present these diagnostic pearls when traveling around the country educating providers about superficial fungal infections. These tips should function as general reminders of common clinical situations in which superficial fungal infection should be considered.

The Ten Commandments of Superficial Cutaneous Fungal Infections. Always consider fungus in…

I. Children with "Seborrheic Dermatitis": With the exception of infants, in whom maternal androgens still linger, prepubertal children lack the appropriate hormonal milieu for seborrheic dermatitis. Such a diagnosis should be held in suspicion in this population. Conversely, nearly three-quarters of



Superficial Cutaneous Infections

all tinea capitis occurs in children ages three to seven years. When scaling of the scalp occurs in a school-age child, tinea capitis should factor quite prominently in the differential diagnosis.

II. Children With Hair Loss and "Pyodermas" of the Scalp: Because tinea capitis occurs predominantly in young children, hair loss in this population should always raise suspicion for tinea capitis. In decades past, both Microsporum and Trichophyton species were often implicated in tinea capitis. Since the 1970's, however, *Trichophyton tonsurans* has achieved nearly exclusionary status in the United States, being implicated in approximately 95 percent of all cases. This impacts the clinical situation in two ways:

1. *T. tonsurans* does not fluoresce under Wood's lamp, limiting this diagnostic modality;

2. *T. tonsurans* is an endothrix and infected hairs become brittle and often break off at the scalp surface. This yields the appearance of "black dot" tinea capitis, with broken hairs and plugged follicles upon the scalp surface.

A kerion is a boggy, inflamed, purulent plaque upon the scalp which represents a vigorous inflammatory response to the presence of fungus. It is dictated both by the infecting species and the individual's degree of immune reaction. Fungal kerions may often be mistaken for bacterial infections.

Complicating matters, kerions may become secondarily infected by bacteria. A superficial culture may reveal only the secondary bacterial infection, further confounding the diagnosis. Consider tinea capitis presenting as a kerion for all purulent and inflamed plaques upon the scalp.

III. Scaly Annular Lesions: Scaling annular plaques upon the skin should always prompt consideration of fungal infection, particularly if an active scaling margin or central clearing is noted. Dermatophytes utilize keratin as an energy substrate and radial growth is often noted. When in doubt, we have a simple saying: "If it scales, scrape it!" A proper KOH examination will often confirm or refute the diagnosis of a superficial fungal infection.

Sometimes scaling may be minimized by vigorous emollient use. Application of a topical antifungal prior to testing may render a KOH examination falsely negative. Maintaining a high degree of suspicion for fungal infection is justified for any erythematous annular lesion, particularly when such an infection is suggested by the clinical history (a new pet, other involved family members, etc.).

IV. Lesions with Satellite Pustules: Unlike dermatophytes, which utilize keratin as an energy substrate, Candida species imbibe tissue fluids containing glucose. For this reason, the pseudohyphae of Candida often grow more vertically into the epidermis, often yielding a more inflammatory response than that of most forms of tinea. Satellite pustules and "beefy-red" erythema are common to cutaneous candidiasis.

V. Annular Lesions that "Fail to Tan": Pityriasis versicolor is a common superficial fungal infection caused by overgrowth of the Pityriasis/Malazzesia yeast, with conversion to the pathogenic hyphal form. This organism elaborates chemicals which block ultraviolet radiation and inhibit melanosome transfer in the skin. The result is annular lesions upon the torso which fail to tan with ultraviolet exposure. Often this failure of the affected skin to tan is what first brings the condition to the attention of the patient.

VI. Bullous Lesions of the Hands and Feet: Occasionally a vigorous inflammatory response to tinea may lead to formation of bullae. This is most common along the instep of the foot, where the skin is a bit thinner than the sole, and the resultant inflammation is more vigorous. Unroofing the blister, with microscopic examination using KOH, will reveal innumerable hyphae in bullous tinea pedis.

VII. Unexplained Follicular Abscesses: It is not uncommon for dermatophytes to extend down terminal hair follicles yielding a fungal folliculitis referred to as "Majocchi's granuloma." This is particularly true when the infection has been misdiagnosed and mistakenly treated with potent topical steroids. These errantly prescribed topical steroids will often yield temporary relief of symptoms, due to anti-inflammatory properties, followed by prompt worsening. In simple terms, potent topical steroids act as "fertilizer" for tinea infections.

VIII. "Dermatitis" of the Groin: Tinea cruris is quite common in men, but relatively rare in women. Epidemics often occur among athletic teams, prisoners, military recruits, or others living in close quarters. Tinea cruris, as opposed to candidiasis, tends to spare the scrotum. This is because the dermatophytes prefer the heavily-cornified, keratin-rich skin of the inner thighs to the thin, lightly-cornified skin of the scrotum.

IX. "Dermatitis" or Scale of Toe Webs: Tinea pedis is the most common fungal infection in mankind, and it is a direct result of one benefit of civilization: shoes. The warm and moist environment within shoes fosters growth of fungus. Tinea pedis should always be chief in the differential when scaling toewebs or scaling feet are noted.

X. *One Scaling Hand With Two Scaling Feet:* For reasons that are unclear, tinea manum (hand) and tinea pedis (feet) often present as the "one hand, two feet syndrome." It has never been firmly established why just one hand is preferentially involved, but the clinical correlation is undeniable. In my clinic, the examination of a single scaling hand must always include examination of both feet!

Treatment Selection and Patient Management

Topical Versus Oral Antifungal Treatment. With these diagnostic tips established, thoughts turn to treatment of superficial fungal infections. The proper approach to treatment depends upon both the nature of the infection and the anticipated efficacy of treatment. For limited infections of glabrous skin, topical agents tend to be the best initial treatment. However, in patients with extensive or recalcitrant disease, or in those with involvement of terminal hairs or nails, systemic agents may be necessary. Co-morbid conditions or potential drug interactions may also influence treatment selection.

Pearls: Topical Medications. Topical medications offer various benefits over systemic agents including: lesser side effects, fewer drug interactions, localization of treatment, and generally lower cost. Most topical antifungals may be placed into one of three classes: imidazoles; allylamines and benzylamines; and polyenes. Some useful antifungals, such as ciclopirox olamine, do not fit well into these classes and must be addressed separately.

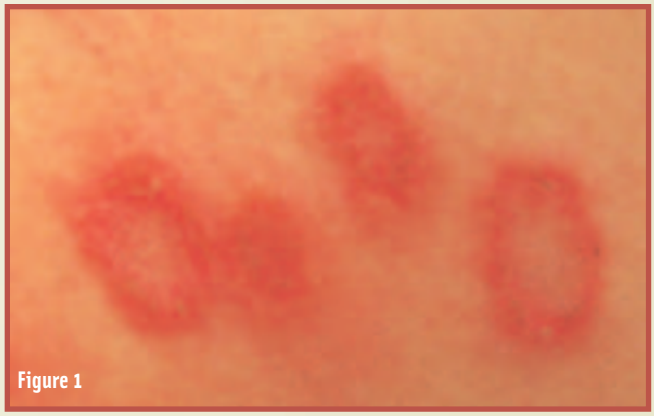
Imidazoles represent a broad class of antifungal medications that inhibit sterol synthesis in fungi. These agents are fungistatic in action. Imidazoles are both affordable and efficacious. In fact, many of the older agents are available as over-the-counter or generic formulations. There is no compelling

evidence of significant differences in cure rate or relapse rate among the various topical imidazoles, yet other considerations may guide product selection.

Econazole, ketoconazole, and oxiconazole are approved for once-daily dosing. Twice-daily dosing is recommended for the others. This convenience in dosing may foster improved compliance. Furthermore, some topical imidazoles are available as either a cream or lotion. Lotions are often better suited for use over large areas or upon hair-bearing skin, but limited data may suggest that creams are marginally more effective. In studies performed by the manufacturer, oxiconazole cream yielded a clinical and mycological cure in 52 percent of tinea pedis cases, while oxiconazole lotion yielded the same cure in just 41 percent of cases.[1] Finally, the potential for irritancy must be considered. In one study of topical clotrimazole for treatment of tinea cruris, erosive reactions developed in four of 27 patients, yet sulconazole did not yield any erosions in the same population.[2] In a similar study, severe irritant reactions were reported with miconazole use but not with sulconazole use.[3] Until formal studies of irritancy are performed, I often recommend use of sulconazole in areas of sensitive skin, like the groin.

Allylamines and benzylamines represent a second class of topical antifungal medications. Both of these agents interrupt sterol synthesis at an earlier point than imidazoles and are fungicidal in nature. It is unclear exactly what clinical benefit this cidal action affords. Limited evidence suggests that topical allylamines or benzylamines may be preferred over topical imidazoles for certain tinea infections. Repeated trials for treatment of tinea pedis indicate that one week of topical terbinafine is as effective as four weeks of topical imidazoles, with a cure resulting in 53 to 95 percent of cases.[4-7] Use of this abbreviated treatment with terbinafine has been confirmed in other trials comparing the active agent versus vehicle alone.[8] In some instances, resolution of tinea pedis using terbinafine has occurred with as few as three doses.[9]

Ultimately, economics may dictate the relevance of these studies. Currently, a 30gram tube of terbinafine cream is roughly three times more expensive than a 30gram tube of clotrimazole cream.[10] Considering the frequency of application, the amount of medication required, the likelihood of patient compliance and ease of use, and the rapidity of results, some experts now recommend topical terbinafine over topical imidazoles for treatment of tinea pedis.[11,12] Nevertheless, a consensus does not yet exist. Other experts, using the same data, recommended initial use of imidazoles, with reservation of allylamines and benzylamines for treatment failures.[13] For the time being, a patient's prescription-plan benefits or formulary restrictions may serve as the ultimate guide in selecting a topical antifungal.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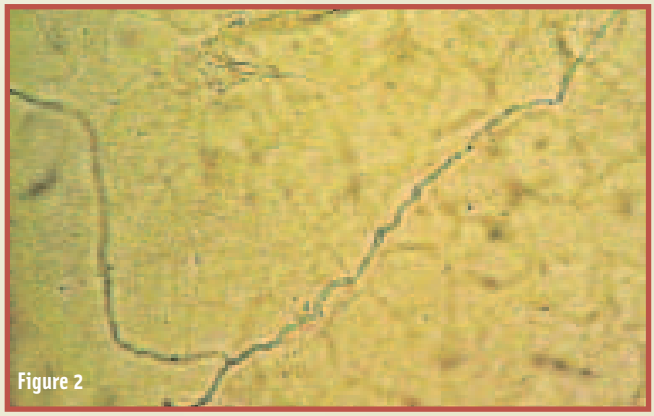
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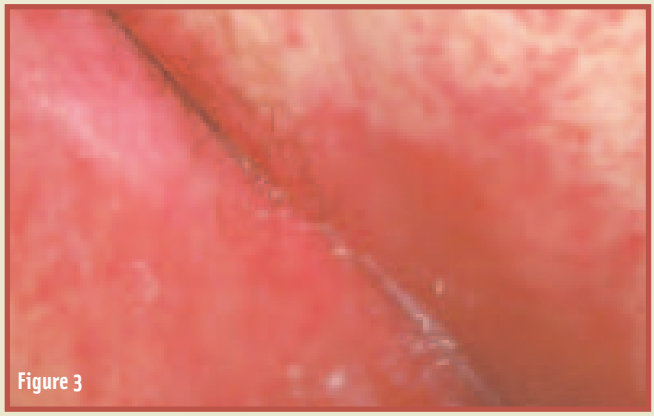


Figure 3

Figure 1. Tinea Corporis. Note the active scaling margin with central clearing common to tinea corporis. This classic appearance led to the common parlance of "ringworm" to describe these lesions.

Figure 2. KOH Examination. A microscopic view of the actual KOH preparation performed on the clinical lesions noted in Figure 1. The long branched hyphae that crosses the faint keratinocyte boundaries in the background is definitive evidence of a dermatophyte infection. (KOH preparation, magnification 400x)

Figure 3. Candidiasis. "Beefy-red" erythema with satellite lesions is highly suspicious for cutaneous candidiasis in the moist folds of this man's axilla. KOH examination revealed yeast and short pseudohyphae.

Seborrheic Dermatitis: A fungal infection? Yes and No.

Although seborrheic dermatitis is a common skin disease, affecting three to five percent of the general population, the etiology of the disease has remained a matter of debate. Many investigators favor a pathogenic role for the liphophilic yeast Pityrosporum/Malassezia. In this regard, it might be properly classified as a superficial fungal infection, but only with the caveat that there exists an aberrant immunologic response that contributes to pathogenesis. Still others believe that any observed yeast overgrowth is merely a consequence of a larger immunodysregulatory process.

Two patient populations are predisposed to severe and/or recalcitrant seborrheic dermatitis; specifically those with HIV/AIDS and those with Parkinson's disease or related neurological conditions.[32,33] Worsening of seborrheic dermatitis with immunosuppression in the setting of HIV/AIDS may be easy to rationalize if seborrheic dermatitis is in fact a fungal "infection," yet the reasons for this worsening with Parkinson's are more cryptic – explanations have focused on alteration of sebum production.

Many treatment options for seborrheic dermatitis exist, including low potency topical steroids, topical antifungals or even immunomodulators, such as pimecrolimus or tacrolimus.[34] The simple fact that multiple treatment options exist is testimony to the multifactorial nature of the disease.

Finally, in limited situations, there may be a role for oral antifungal medication in the treatment of seborrheic dermatitis. While certainly not "standard," in cases of severe seborrheic dermatitis, or in disease recalcitrant to topical management, I have used a seven to 10 day course of intraconazole 100mg by mouth twice daily, followed by a maintenance dose of 100mg by mouth twice daily for the first two days of each following month. Typically, this therapy allows for a great reduction in disease activity, with daily exacerbations treated by the addition of hydrocortisone 1% cream. While many dermatologists–myself included–have used this regimen for a number of years, recent published investigations confirmed the efficacy of this treatment.[35,36]

Finally, like imidazoles, topical allylamines and benzylamines are effective against Candida or Pityrosporum/Malazzesia infections. However, given the cost of these agents relative to imidazoles, polyenes, ciclopiroxamine, and even over-the-counter selenium sulfide, there is often no compelling reason to turn away from these more affordable options.

Polyenes represent the final major class of topical antifungal medications. In the United States, nystatin is the only actively-marketed topical polyene. Nystatin binds irreversibly to membrane sterols located on susceptible specifics of Candida. Importantly, however, nystatin exerts no effect against dermatophytes, and it is useful only for cutaneous candidiasis, but not tinea infections. Nystatin is available as a cream, ointment, powder or solution for the skin, and as a solution, lozenge or troche for treating oral candidiasis (thrush). In one study, use of clotrimazole for oral candidiasis resulted in a measurable alteration of systemic tacrolimus levels in renal transplant patients, and oral nystatin may be preferred in this population.[14]

Finally, some useful topical antifungal agents do not fit well into any major class. For example, ciclopirox olamine is a hydroxypyridone antifungal agent with a unique structure and mode of action. Unlike most other topical antifungals, ciclopirox olamine does not interfere with sterol synthesis, but instead it interferes with active membrane transport of essential cellular precursors, particularly trivalent cations. Ciclopirox olamine is indicated for the treatment of tinea and onychomycosis, candidiasis, pityriasis versicolor, seborrheic dermatitis, and even cutaneous infections with unusual saprophytes.

Ciclopirox olamine is available in a multitude of forms including a cream, gel, solution, and a medicated shampoo. Cutaneous candidiasis, dermatophytoses, and pityriasis versicolor should be treated twice daily for two weeks to one month, but treatment for tinea pedis should continue one month or longer. When using ciclopirox olamine shampoo for seborrheic dermatitis, treatment may occur twice-weekly for an indefinite duration, with improvement usually noted in two to four weeks. Ciclopirox olamine also demonstrates significant permeation of the nail plate, and this has been exploited to develop an antifungal nail lacquer (see below).

Combination Topical Antifungal/Corticosteroid Treatments. Some topical antifungal medications are manufactured and packaged in combination with topical corticosteroids. One example is the combination of clotrimazole and betamethasone dipropionate. During development of this

combination agent, many assumed that the addition of the steroid would more rapidly relieve inflammation, scaling, and pruritus. While early studies demonstrated the combination was indeed more effective than clotrimazole alone in resolving symptoms, betamethasone dipropionate is a potent topical steroid, and soon after release, striae and other cutaneous side effects from the steroid component were reported.[15-17] Furthermore, long-term studies have reported a higher relapse rate (up to 36 percent) with use of this combination product.[18-19]

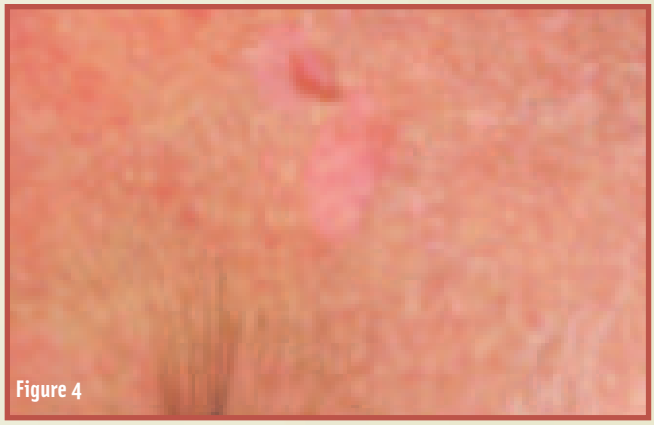
A recent study demonstrated that clotrimazole/betamethasone dipropionate may comprise 50 percent or more of antifungal expenditures prescribed by primary care providers, compared to less than seven percent among dermatologists.[20] Presumably, overuse by non-specialists occurs under a mistaken assumption that either the steroid agent is mild—which it is not—or that the combination will be a "better choice" when the differential diagnosis is unresolved. In fact, the FDA has twice revised the product warnings for clotrimazole/betamethasone dipropionate, discouraging use upon thin skin, use for prolonged periods, or use when the diagnosis is in doubt. Personally, I do not use combination antifungal and corticosteroid combinations except in rare and exceptional circumstances.

Pearls Regarding Oral Treatment

Oral antifungal medications are indicated whenever terminal hairs are infected, when a large areas is so extensively involved that topical regimens are impractical, or in the treatment of onychomycosis.

For treatment of tinea capitis, oral griseofulvin remains the first-line recommendation of dermatologists and pediatricians alike.[21,22] Oral absorption of the griseofulvin liquid is increased by coadministration with a fatty food, such as whole ice cream. However, shorter treatment courses with fluconazole or terbinafine, coupled with generally declining costs, may lead to a revision of this recommendation in the future. For young children, terbinafine tablets must be crushed and placed in food. Itraconazole suspension is often avoided in the treatment of tinea capitis, mostly for theoretical concerns, because the active ingredient is dissolved in cyclodextrin, an agent that has induced pancreatic neoplasms in laboratory rats given large doses. The itraconazole capsules may be opened and the granules mixed with ice cream or applesauce if use of this medication is desired.

In the past, either itraconazole or terbinafine was used for treatment of onychomycosis. However, recent evidence indicates that terbinafine represents a superior treatment, and use of itraconazole has waned somewhat.[23,24] When using oral terbinafine or itraconazole, there exist two major complications with which to be particularly aware: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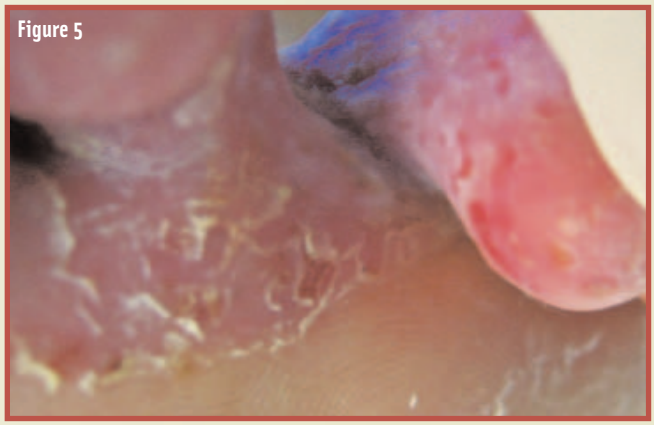
Figure 5

Figure 4. Pityriasis Versicolor. Faint, fawn-colored, thin plaques with light scale is the typical appearance for pityriasis versicolor. These lesions on this man's chest "failed to tan" when he received exposure to the sun.

Figure 5. Scaling, erosions and severe pruritus in the moist toewebs should always suggest a diagnosis of tinea pedis. A KOH preparation taken from these areas was definitively positive of hyphae indicative of dermatophyte infection.

Terbinafine. Cases of drug-induced lupus erythematosus caused by terbinafine are well-recognized. Before prescribing oral terbinafine, it is important to question the patient about any family history of lupus or a personal history of sun sensitivity.

Itraconazole. As a negative inotrope, itraconazole can decrease the contractility of cardiac muscle. For this reason there is a "black box" warning against use of oral intraconazole in patients with congestive heart failure.

Also, both oral terbinafine and oral itraconazole have rarely been implicated in inducing fulminant hepatic necrosis. The risk of this side-effect has been estimated to be around

1:54,000 patients for terbinafine,[25] and approximately 1:500,000 patients for intraconazole.[26] It is always appropriate to question patients regarding any prior episodes of hepatitis or known liver disease. Baseline liver function tests should be obtained in all patients anticipating a four week or longer course of oral antifungal medications that have not had such an evaluation in the last three to six months or in any patient with a possible change in liver function. Routine mid-course liver function testing is no longer recommended during treatment for onychomycosis, unless there exist indications of liver toxicity, such as abdominal distress, acholic stools, darkening urine, frank jaundice, or the patient begins a second hepatotoxic or conflicting medication.

Finally, topical treatment for onychomycosis is definitely inferior to oral management. Ciclopirox olamine lacquer has only around an eight percent clinical cure rate,[27,28] but it remains an option for those with contraindications to oral treatment (such as hepatitis C) but a desire to "do something." Recent investigations have also examined combined treatment using oral terbinafine in conjunction with topical ciclopirox olamine lacquer to decrease the rate of the long-term recurrence in onychomycosis.[29,30] This development is exciting, as the five-year recurrence using oral treatment alone has been as high as 50 percent in some studies. Expect further developments in the arena of combination oral and topical management to improve long-term clearance in onychomycosis.

Conclusion

Because of lesser side effects, fewer drug interactions, localization of treatment, and generally lower cost, topical antifungals are preferred for most superficial fungal infections of limited extent. Use of oral agents is indicated when a superficial fungal infection covers a large surface area, involves terminal hair or nails, or is recalcitrant to topical management. Imidazoles are both efficacious and affordable and are useful for tinea infections, candidiasis, and pityriasis versicolor. Despite higher cost, allylamines and benzylamines may be advantageous in some cases of tinea pedis. Topical nystatin is useful in treating candidiasis but is ineffective for treating tinea or pityriasis versicolor, while ciclopirox olamine is a topical antifungal with a broad range of indications. For the time being, oral griseofulvin remains the treatment of choice for tinea capitis, while terbinafine has emerged as the preferred agent for treatment of onychomycosis. When employing systemic antifungal agents, the patient's overall health, baseline liver function, and existence of any co-morbid conditions must always be considered.

1. Oxistat Prescribing Information (4130405). Glaxo Smith Kline Consumer Health Care: Pittsburg, Pennsylvania; 2002.

2. Tanenbaum L et al: Sulconazole nitrate cream 1 percent for treating tinea cruris and corporis. Cutis 1989; 44: 344.

3. Tanenbaum L et al: Sulconazole nitrate 1.0 percent cream: A comparison with miconazole in the treatment of tinea pedis and tinea cruris/corporis. Cutis 1982; 30:105.

4. Leenutaphong V et al: Double-blind study of the efficacy of 1 week topical terbinafine cream compared to 4 weeks miconazole cream in patients with tinea pedis. J Med Assoc Thai 1999; 82:1006.

5. Patel A: Topical Treatment of interdigital tinea pedis: terbinafine compare with clotrimazole. Australa J Dermatol 1999; 40:197.

6. Schopf R et al: Efficacy and tolerability of terbinafine 1% topical solution used for 1 week compared with 4 weeks of clotrimazole 1% topical solution in the treatment of interdigital tinea pedis: a randomized, double-blind, multi-centre, 8-week clinical trial. Mycoses 1999; 42:415.

7. Evans EGV: A Comparison of teribinafine (Lamisil) 1% cream given for one week with clotrimazole (Canestan) 1% cream given for four weeks in the treatment of tinea pedis. Br J Dermatol 130:2, 1994

8. Korting HC et al: One week terbinafine 1% cream (lamisil) once daily is effective in the treatment of interdigital tinea pedis: a vehicle controlled study. Med Mycol 2001; 39:335.

9. Evans EG et al: Short-duration therapy with terbinafine 1% cream in dermatophyte skin infections. Br J Dermatol 1994; 130:83.

10. Prices for Lamisil ATTM (30 gm) versus generic clotrimazole (30 gm). Drugstore.com. www.drugstore.com. Belleview WA. Last accessed July 1, 2006.

11. Bedinghaus JM et al: Over-the-counter foot remedies. Am Fam Physician 2001; 64:791.

12. Finlay AY: Skin and nail fungi - almost beaten. BMJ 1999; 319:71.

13. Crawford F et al: Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Database Syst Rev 2000; 2:CD001434.

14. Vasquez E et al: Clotrimazole increases tacrolimus blood levels: a drug interaction in kidney transplant patients. Clin Transplant 2001; 15:95.

15. Lotrisone' package insert. Kenilworth, NJ: Schering Corp., 1994.

16. Katz HI et al: SCH 370 (clotrimazole-betamethasone dipropionate) cream in patients with tinea cruris or tinea corporis. Cutis 1984; 34:183.

17. Barkey WF: Striae and persistent tinea corporis related to prolonged use of betamethasone dipropionate 0.05 percent; cream/clotrimazole 1 percent; cream (Lotrisone cream). J Am Acad Dermatol 1987; 17:518.

18. Smith EB et al: Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. J Am Acad Dermatol 1992; 26:125.

19. Alston SJ et al: Persistent and recurrent tinea corporis in children treated with combination antifungal/ corticosteroid agents. Pediatrics 2003;111:201.

20. Greenberg HL et al: Clotrimazole/betamethasone diproprionate: a review of costs and complications in the treatment of common cutaneous fungal infections. Pediatr Dermatol 2002; 19:78.

21. Fleece et al. Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. Pediatrics 2004; 114:1312.

22. Roberts BJ et al: Tinea capitis: a treatment update. Pediatr Ann 2005; 34:191.

23. Gupta AK et al: Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. Br J Dermatol 2004; 150:537.

24. Sigurgeirsson B et al: Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. Arch Dermatol 2002; 138:353.

25. Gupta AK et al: Hepatitis associated with terbinafine therapy: three case reports and a review of the literature. Clin Exp Dermatol 1998; 23:64.

26. Caputo R: Itraconazole (Sporanox®) in superficial and systemic fungal infections. Expert Rev Anti Infect Ther 2003; 1:531.

27. Epstein E: Fungus-free versus disease-free nails. J Am Acad Dermatol 2004; 50:151.

28. Gupta AK, et al: Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. J Am Acad Dermatol 2000; 43:S70.

29. Avner S, et al: Combination of oral terbinafine and topical ciclopirox compared to oral terbinafine for the treatment of onychomycosis. J Dermatolog Treat 2005; 16:327.

30. Gupta AK et al: Management of onychomycosis: examining the role of monotherapy and dual, triple, or quadruple therapies. Cutis 2004; 74:5.

31. Plewig G et al: Seborrheic dermatitis. In: Freedberg, et al, editors. Fitzpatrick's dermatology in general medicine. 6th ed. New York: McGraw-Hill; 2003.

32. Mathes BM et al: Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. J Am Acad Dermatol 1985; 13:947.

33. Fischer M, et al: Skin function and skin disorders in Parkinson's disease. J Neural Transm 2001; 108:205.

34. High WA, et al: Pilot trial of 1% pimecrolimus cream in the treatment of seborrheic dermatitis in African American adults with associated hypopigmentation. J Am Acad Dermatol 2006; 54:1083.

35. Kose O, et al: Oral itraconazole for the treatment of seborrhoeic dermatitis: an open, non-comparative trial. J Eur Acad Dermatol Venereol 2005; 19:172.

36. Baysal V, Yildirim M, Ozcanli C, Ceyhan AM. Itraconazole in the treatment of seborrheic dermatitis: a new treatment modality. Int J Dermatol 2004; 43:63.