MAR 9 1999

LABELING REVIEW OF NDA

NDA 20-980

Submission Date:	3/27/98	**Review Date:**	5/3/98
Amendment Date:	6/15/98		8/12/98
	10/27/98		12/8/98
	11/24/98		2/19/99
			3/9/99

Applicant: Novartis Consumer Health, Inc.

Representative: Christine Babiuk, Ph.D.
Associate Director, Regulatory Affairs
(908) 598-7816

Drug: Terbinafine Hydrochloride Cream, 1%
Lamisil $^{AT\ TM}$ Cream

Pharmacologic Category: Antifungal

Reviewed:

1. Draft labeling for the 2, 12, and 24 gram cartons and tubes for tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm) indications
2. Educational package inserts for 2 , 12, and 24 gram products
3. The labeling for the 2 gram jock itch product is distinct from the athlete's foot product and is consistent with the 12 gram carton, tube wrap and the consumer educational package.

Reviewer's Comments:

Background - This NDA is submitted in support of the switch of Terbinafine hydrochloride cream, 1% to non-prescription status. Terbinafine hydrochloride cream, 1% was approved on December 30, 1992, for prescription use for interdigital tinea pedis (athlete's foot), plantar tinea pedis (moccasin type), tinea cruris (jock itch) and tinea corporis (ringworm) under NDA 20-192. The over-the-counter (OTC) formulation is identical to the approved NDA 20-192. Terbinafine hydrochloride is the first topical antifungal of the allylamine class to be marketed without prescription. The applicant proposed to maintain plantar tinea pedis (moccasin type) as a prescription indication; however, this request was later changed to part of the OTC switch. Thus,

the only remaining prescription (Rx) indication is for this product is tinea versicolor.

Revised carton labeling and a labeling comprehension study were received on November 24, 1999.

Labeling review - The proposed labeling for terbinafine hydrochloride, 1% marketed OTC is different from the Rx label as follows:

a. The proposed OTC indications are tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm).
b. The proposed OTC label states that the cream is to applied twice a day (athlete's foot) for 1 week for interdigital tinea pedis and for 2 weeks for moccasin; whereas the current Rx label states 1 to 4 weeks treatment.
c. The proposed OTC label states that the cream is to be applied once a day (jock itch and ringworm) for 1 week of treatment.

Many of our comments are based on the proposed rule for the labeling requirements for OTC drug products published in the Federal Register of February 27, 1997 (62FR9024). The background text is identical to applicant's submission of March 27, 1998. Reviewer recommended additions are identified by redline. Reviewer recommended deletions are identified by a ~~single strike out line~~.

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

Recommendations:

1. It is recommended that all the headings on the back panel, ***Active ingredient***, ***Purpose***, ***Uses***, ***Warnings***, and ***Directions***, be in bold print and italic. Only the first letter of the word is capitalized. The subheaders should be bolded, but not placed in italic. The heading "**Active ingredient**" should appear immediately adjacent and to the left of the heading "**Purpose**" (§ 201.66(d)(6)).
2. Bulleted sentences should have initial capitals and end with a period when the bullet is a complete sentence (as under the heading "**Directions**"). Bulleted phrases and words that are not complete sentences (as under the heading "**Warnings**") should not use initial capitals and should not end with periods.
3. The applicant should be reminded that the word "New" may only be used for six months.
4. Under the subheading "When using this product,: the following may be used as an alternative: "**When using this product** do not get in the eyes. If eye contact occurs, rinse thoroughly with water."
5. Under the headings "**Directions**" on the carton and tube labels and "**How should I apply Lamisil AT™ Cream?**" on the consumer educational brochure, the colored text should be replaced by bolded black and white text and similarly the colored diagrams should appear in black and white.
6. Please make the following changes on product labeling as in the accompanying attachments:

/S/ (For NM-R)

Nahid Mokhtari-Rejali, Ph.D.

cc:NDA
HFD-560 3/9/99
HFD-560/Bowen/Katz/Aurecchia/Lipnicki/Mokhtari
HFD-540
HFD-540/Wilkin/Vaughan/Cross/Kozma-Fornaro

R/D:Mokhtari/2-19-99/2-23-99
Revised:Lipnicki/2-19-99/2-23-99
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Noted, comments via e-mail to OTC on 3/2/99

3/9/99

Noted 03/09/99

Teleconference Date: April 15, 1998 Time: 1330 Location: N229

NDA 20-980, Lamisil (terbinafine cream) Cream, 1% - Rx to OTC Switch

Applicant: Novartis Pharmaceuticals Corporation

CMC Meeting

Meeting Chair: Wilson DeCamp, Ph.D., Chemistry Team Leader

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., LCDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Jim Vidra, Ph.D., Chemist, DNDCIII, HFD-540
Frank H. Cross, Jr., M.A., LCDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Christine Babiuk, Ph.D., Associate Director, Regulatory Affairs, Novartis Consumer Health Inc.
Robert Clark, Associate Director, Chemistry, Manufacturing and Controls, Novartis Pharmaceuticals, Inc.

Meeting Objective:

Clarification of CMC Issues.

Discussion:

Agency:

1. Is there any change in the CMC of the Lamisil Cream, 1%, from the approved NDA 20-192? The Sponsor said no.

2. Does the Sponsor anticipate any new CMC supplements for Lamisil? The Sponsor said it plans to file a CMC supplement in the next 3 months. This supplement will provide for a change in the tube sealant. The Sponsor requested guidance on bracketing from the Agency. The Agency said that it will get back to the Sponsor to determine whether stability bracketing on the 2 oz tube used for samples, is required.

3. Before any change is anticipated to any of the approved Lamisil products, the Agency should be consulted. The Sponsor agreed.

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: /S/
Concurrence Chair (or designated signatory): /S/, Ph.D.
Attachment/Handouts: None.

cc:

Division Files
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Ko
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Mainigi
HFD-540/CHEM TL/DeCamp WS 4/16/98
HFD-540/CHEM/Vidra/4.16.98
HFD-725/BIOSTAT TL/Srinivasan
HFD-725/BIOSTAT/Thomson
HFD-880/BIOPHARM TL/Bashaw
HFD-520/MICRO TL/Sheldon
HFD-520/MICRO/Altaie
HFD-160/MICRO TL/Cooney
HFD-540/PROJ MGR/Cross
Drafted by: fhc/April 15, 1998
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Initialed by:
final:

MEMORANDUM OF TELECONFERENCE

PRESENTED AT THE "INTERNATIONAL SUMMIT ON CUTANEOUS ANTIFUNGAL THERAPY," SUPPORTED BY EDUCATIONAL GRANTS FROM JANSSEN PHARMACEUTICA; ORTHO PHARMACEUTICAL CORPORATION—DERMATOLOGICAL DIVISION; ROERIG—A DIVISION OF PFIZER; AND SANDOZ PHARMACEUTICALS CORPORATION.

Tinea pedis pathophysiology and treatment

James L. Leyden, MD *Philadelphia, Pennsylvania*

Fungal infections of the foot can be divided into three major varieties, all of which have differing pathophysiologic aspects with therapeutic implications. Interdigital infections involve an ecological interplay between dermatophytes and bacteria. Simple scaling types of infection are caused by dermatophyte invasion of the stratum corneum, whereas macerated, erosive infections are caused by selection and overgrowth of bacteria, particularly *Brevibacterium epidermidis, Micrococcus sedantarius*, and various gram-negative species. Bacterial production of methanethiol and other sulfur compounds leads to inhibition of dermatophytes and accounts for the lower recovery of dermatophytes from the most severe cases. Plantar surface infections consist of widespread, moccasin-type infection caused by *Trichophyton rubrum* and localized scaling infections with episodes of intense inflammation caused by *Trichophyton mentagrophytes*. The former is particularly associated with an atopic background. Therapy is difficult because of poor immune responses and difficulty in delivering a sufficient quantity of drugs to the lower layers of a thick stratum corneum. Intense inflammation in *T. mentagrophytes* infections is the result of an immune, contact allergic response to fungal antigens. (J AM ACAD DERMATOL 1994;31:S31-S33.)

Tinea pedis, commonly known as athlete's foot, is the most common form of dermatophytosis. This disorder can generally be classified into three categories: (1) interdigital infections, (2) scaling hyperkeratotic moccasin-type infections of the plantar surface, and (3) highly inflammatory vesiculobullous eruptions.

INTERDIGITAL INFECTIONS

Historically, interdigital toe web infections have usually been categorized as fungal diseases. They usually start as a dermatophyte infection with scaling, and when the bacteria proliferate, maceration occurs. However, toe web infections can now be best viewed as an ecological interplay between dermatophytes (*Trichophyton rubrum* and *Trichophyton mentagrophytes*), various bacterial species, and, although rare, *Candida* species.[1] The two polar extremes feature a simple fungal infection associated with scaling and, at times, fissures and a highly macerated, leukokeratotic symptomatic process in which dermatophytes can be recovered in only one third of patients. This variety of interdigital infection is mainly caused by an overgrowth of a variety of bacterial species, especially *Micrococcus sedantarius, Brevibacterium epidermidis, Corynebacterium minutissimum*, and gram-negative species including *Pseudomonas* and *Proteus*.[2] We have proposed the terms *dermatophytosis simplex* and *dermatophytosis complex* for these two forms of interdigital infection.

Our studies and those of others have demonstrated that the recovery of dermatophytes from macerated, symptomatic interspaces is low (most studies recovered fungi in less than half of cultured interspaces) and that dermatophytes can be recovered from up to 11% of normal, nondiseased interspaces.[3-9] These seemingly paradoxic findings have become better understood in terms of bacterial-fungal interactions. The recovery of dermatophytes from clinically normal interspaces can be explained by two factors: first, fungal spores can survive in low numbers without germinating and producing invasive hyphal elements, and second, the stratum corneum of the plantar surface, including the interspace, is 30 to 50 times thicker than that of other areas of the body (except the palm). It is possible that small numbers of dermatophytes exist on the surface of an interspace but do not penetrate deeply

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0190-9622/94 $3.00 + 0 16/0/57450

enough to evoke a host response or even superficial scaling.

The inability to culture dermatophytes from symptomatic, macerated interspaces is now understood in terms of the dynamic interplay between fungi and bacteria. Many years ago we conducted a series of experiments with volunteers in which an asymptomatic, potassium hydroxide-positive and culture-positive interspace could be converted into a macerated, symptomatic interspace simply by occluding the interspace with an impermeable plastic film and tape.[1] Fungi could not be recovered from the interspace. On removal of the occlusive dressing, the macerated, symptomatic interspace persisted. Similarly, occluded fungal-positive interspaces in which bacterial proliferation was prevented by a topical antibiotic resulted in transient low-grade excessive hydration. These treated interspaces quickly reverted to pretreatment conditions after removal of the occlusive dressing. Further experiments using similar occlusive dressings in patients with normal interspaces (free of dermatophytes) resulted in hydrated, somewhat malodorous interspaces, but no maceration or leukokeratosis developed. On the basis of these findings, we proposed the term *dermatophytosis simplex* for the uncomplicated, relatively asymptomatic fungal type of scaling athlete's foot and *dermatophytosis complex* for the macerated, symptomatic, often malodorous process from which a variety of bacteria were recovered and dermatophytes were infrequently cultured.

During the past 15 years, advances in bacterial taxonomy have clarified which bacterial species proliferate in macerated symptomatic interspaces.[2] In macerated interspaces, there is an increased prevalence of *Staphylococcus aureus, M. sedantarius, B. epidermidis, C. minutissimum*, the multiple antibiotic-resistant *Corynebacterium jeikeium* and *Pseudomonas* and *Proteus* species. An important piece of the puzzle of understanding why these bacteria proliferate was revealed with the demonstration that dermatophytes produce penicillin- and streptomycin-like substances.[10,11] *S. aureus, M. sedantarius, B. epidermidis*, and gram-negative species are routinely resistant to penicillin. Proliferation of these bacteria appears to be secondary to the ecological advantage provided by dermatophyte growth and penicillin production. These ecologically advantaged bacteria also possess the ability to produce a variety of proteolytic enzymatic substances capable of digesting a variety of proteins. In the setting of a weakened stratum corneum caused by dermatophyte invasion, these bacteria can produce tissue damage with maceration and leukokeratosis. Normal interspaces without dermatophyte invasion appear to resist damage from these bacteria, presumably because of the thickness of the stratum corneum and its barrier properties.

A probable mechanism by which dermatophyte-positive interspaces can be converted into macerated interspaces from which fungi cannot be recovered involves the production of a variety of sulfur compounds such as methanethiol, ethanethiol, dimethyl sulfide, and others.[12] These sulfur compounds are potent antifungal agents and are produced by *M. sedantarius* and *B. epidermidis*.

The studies of experimentally manipulated interspaces, coupled with data from patients with interspace infections ranging from simple scaling to maceration, support the conclusions that dermatophytes promote the selection of antibiotic-resistant bacteria through the protection of penicillin- and streptomycin-like antibiotics and that these bacteria damage the interspace, producing a symptomatic, macerated condition while also suppressing dermatophytes through the production of a variety of sulfur compounds.

The therapeutic implication of these findings is that antifungal therapy alone will not be successful in the most severe forms of interdigital infections. The use of agents that have broad-spectrum antibacterial action is needed to supplement antifungal drugs. Aluminum chloride, Castellani's paint, and various tinctures of dyes are particularly useful. Because dermatophytes are the primary instigating factor, the use of a fungicidal agent, such as an allylamine, is preferable to minimize survival of dermatophyte spores that can subsequently germinate, penetrate the stratum corneum, and select growth of bacteria that damage tissue. Likewise, any other reservoir of fungi (e.g., toenails) must be addressed.

PLANTAR MOCCASIN-TYPE INFECTION

The plantar moccasin-type of infection results in diffuse hyperkeratotic scaling of the plantar surface and is often associated with nail involvement. Many patients have an atopic history. These patients appear to have a defect in their cell-mediated immune reactivity and are unable to mount a delayed-type hypersensitivity to certain dermatophytes, although other antigens evoke a normal

response. Negative reactions to intradermal *Trichophyton* are common. Immediate wheal and flare responses indicate the presence of IgE antibodies.[13, 14] These antibodies, however, are not helpful in ridding the skin of dermatophytes.

Because the plantar surface has such a thick stratum corneum, delivery of topical and systemic drugs in a sufficient quantity to have a fungicidal effect is difficult. In in vitro studies in which cadaver skin was used as a substrate, we found that certain topical antifungal agents penetrate more quickly to exert a greater antifungal activity than other agents. Terbinafine, an allylamine, and ketoconazole, an imidazole, appear to penetrate the most efficiently. Our approach is to initially combine one of these agents with oral ketoconazole for 1 month if nails are not involved or for 3 months if nails are involved. Subsequently, topical therapy for an indefinite period is needed to prevent relapse.

VESICULOBULLOUS TINEA PEDIS

Acute, highly inflammatory eruptions, particularly on the arch and side of the foot, occur with *T. mentagrophytes* infection. The intense inflammatory reaction represents a T-cell immune host response.[15, 16] Patients with recurrent episodes often have low-grade scaling between bouts of acute inflammation. Presumably, differing environmental factors such as seasonal temperature, sweating from physical activities, and type of shoewear influence the growth of the fungus, and when sufficient proliferation and penetration of the stratum corneum occur, the epidermis comes into contact with fungal antigens and a T-cell–mediated immune reaction occurs, that is, an allergic contact dermatitis appears. This type of response has been shown to be important in the natural history of fungal infections and is a primary means of shedding fungi from skin.[15]

Compresses and topical or systemic corticosteroids in conjunction with antifungal agents are used with acute attacks. The choice of topical or systemic agents depends on the extent and severity of the process. Steroid therapy is withdrawn once the cell-mediated immune response is curtailed, but continued topical therapy is desirable in an attempt to eradicate residual fungus. The allylamines, which are fungicidal, appear to be the best choice.

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Tinea Pedis

James J. Leyden and Raza Aly

Tinea pedis is a term used to encompass several clinically distinctive infections of the skin of the foot. Dermatophytic fungi are primarily responsible for these infections. Several nondermatophytes have been implicated in some patients, particularly for nail infections. The major clinical variants are (1) interdigital infections in which dermatophytes initiate the process by damaging the stratum corneum while the subsequent maceration and leukokeratosis results from overgrowth of bacteria such as *Micrococcus sedantarius, Brevibacterium epidermidis, Corynebacterium minutissimum* and gram-negative organisms; (2) plantar mocasin type of hyperkeratosis due to *T rubrum* and found primarily in those with an atopic background; (3) vesiculo-bullous infections in the arch and side of the foot due to an immune response of delayed hypersensitivity to *T mentagrophytes*.

INFECTIONS of the feet and toenails are the most common form of superficial fungal infections and are most often caused by either *Trichophyton rubrum, Trichophyton mentagrophytes*, or *Epidermophyton floccosum*. The general term tinea pedis encompasses three clinically distinctive syndromes; viz, interdigital toe web infections, scaly hyperkeratotic moccasin type of infection of the sole of the foot, and a highly inflammatory vesicular/bullous variety.[1] These three varieties have differences in terms of the site of infection, the causative organisms, host immune response, and microbial ecological interactions which have important implications for therapy.

NONDERMATOPHYTES AND TINEA PEDIS

Several nondermatophytes have been implicated in foot and nail infections, but it is often difficult to establish their etiology. The criteria to establish pathogenicity by nondermatophytes suggested by Zaias are: (1) the presence of hyphae in the infected subungual debris, (2) the persistent failure to culture recognized dermatophytes, and (3) the regularity of positive cultures of these nondermatophytes.[2] In recent years, *Nattrassia mangiferae* (*Hendersonula toruloidea*) and *Scytalidium hyalinum* have been reported as agents of recalcitrant foot and nail infections.[3-6]

Today, *Nattrassia mangiferae* is one of the most frequently isolated fungi from patients with tinea pedis and/or onychomycosis in Great Britain.[3] Hay and Moor described the clinical appearance of infection caused by the *N mangiferae* and *S hyalinum* in 128 patients.[3] The clinical features noted with *Nattrassia* and *Scytalidium* were mostly those that are seen in *Trichophyton rubrum* infection of the feet. Another distinctive feature noted with this type of tinea pedis was the absence of dorsal infection on the feet. The fungi and combination of fungi isolated in Great Britain are shown in the Table 1.

Nattrassia mangiferae is a recognized plant pathogen and most likely is a soil organism. *Scytalidium*, on the other hand, has never been isolated from the environment. In reviewing the geographical distribution of *Nattrassia* and *Scytalidium*, Moore found that all the patients originated from the tropics or subtropics of the Caribbean or West Africa.[7] Frankel and Rippon reported 40 cases of infection related to *Nattrassia* in the Chicago area.[6] The largest contributor to this patient population was the Indian subcontinent, accounting for 40%. In direct microscopic examination of infected scales, hyphae of *Nattrassia* are scarcely distinguishable from dermatophytic hyphae. Greer reported typical dermatophyte type of hyphae associated with the above fungus when examined directly under the microscope.[8] Cultures of *Nattrassia* should show a white colored, velvety to cottony, rapidly growing colony, which often darkens with age, developing a grey or brown pigment. *S hyalinum* is white colored with cottony like growth and is the asexual form (anamorph) of *N mangiferae*. In culturing a suspected infection of tinea pedis, it is important to remember that both *Nattrassia* and *Scytalidium* are sensitive to the presence of cycloheximide. Because of their susceptibility to cycloheximide, many cases related to

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0278-145X/9311204-0012$5.00/0

Table 1. Fungi Isolated From 128 Patients With Tinea Pedis

Fungi isolated	Number of Patients	Percent (nondermatophyte)
N mangiferae alone	52	40.6
S hyalinum	14	10.9
N mangiferae and *S hyalinum*	10	7.8
N mangiferae + dermatophyte*	39	30.5
S hyalinum + dermatophyte*	12	9.3
N mangiferae + *S hyalinum* and dermatophyte*	1	0.8
	128	

* Dermatophyte species isolated: *Trichophyton rubrum* 28 patients; *T mentagrophytes-interdigitale* (17 patients); *Epidermophyton floccosum* (6 patients); *T soudanese* (1 patient).
(Adapted from Hay and Moore.[3])

this type of tinea pedis may be misdiagnosed as recalcitrant dermatophytosis. Confirming the diagnosis of either *Nattrassia mangiferae* or *S hyalinum* can be made by the findings when (potassium hydroxide (KOH) is positive but no growth on cycloheximide containing agar.

Infection caused by *Nattrassia* and *Scytalidium* do not respond to griseofulvin and oral ketoconazole treatment.[3] Therapy with topical bifonazole, clotrimazole, or econazole for 4 weeks was not effective.[8] A single case of mycotic verrucose dermatitis caused by *Nattrassia* was cleared with amphotericin B.[9] Half-strength Whitfield ointment showed very limited success—only 2 of 93 patients were cured.[5] Newer drugs, intraconazole and terbinafine, are being investigated for nondermatophyte infections.

CLINICAL VARIANTS OF TINEA PEDIS

Interdigital Toe Web Infections

Interdigital toe web infections have been traditionally categorized as caused solely by invasion of the skin by dermatophytic fungi. Clinically, toe web infections, range from relatively asymptomatic mild scaling to exudative, macerated, malodorous conditions. Surprisingly the recovery of fungi from toe web infections has been low and rarely exceeds 30% in many large series.[10-12] This apparent paradox has been at least partially clarified by new insights into the microbial ecology of the toe web after invasion by a dermatophyte.[13,14] In macerated, malodorous, highly symptomatic infected interspaces, there is an overgrowth of various bacterial species, including *Brevibacterium epidermidis*, *Corynebacterium minutissimum*, *Micrococcus sedantarius*, *Pseudomonas*, and *Proteus* species, and *Staphylococcus aureus*. Many of these bacteria are resistant to penicillin and penicillin derivatives, and their proliferation may be caused by the production of penicillin- and streptomycin-like antibiotics by dermatophytes.[15-17] In the presence of a stratum corneum damaged by dermatophyte invasion, these bacteria proliferate and induce inflammation. *M sedantarius* and *Brevibacterium epidermidis* also produce a variety of thioesters which have an extremely pungent malodor and are fungicidal.[18] This ecological interaction explains the transition from a simple scaling process (dermatophytosis simplex) in which fungi are readily recovered into a macerated, malodorous, symptomatic process (dermatophytosis complex) in which the fungus is recovered in only a small percentage of cases.

Moccasin-Type Infections

Diffuse scaling with hyperkeratosis involving the entire sole and heel and often associated with onychomycosis is the characteristic clinical picture. At times, one hand will be similarly involved with this diffuse scaling process. The reason why only one hand is involved is not known but may reflect differences in sweating from one hand to the other. The causative organism is *T rubrum*. A major obstacle to therapy is the thickness of the plantar stratum corneum which makes it difficult to achieve a suitable concentration of drug even when both topical and systemic therapy is used in combination. *T rubrum* also appears to be less efficient in eliciting the T-cell, delayed-type immune response which is the host mechanism by which fungi are eliminated.[19,20] This inherent difference in inducing immune responses, coupled with the organism being relatively sequestered from the body in the thick plantar stratum corneum, accounts in part for the chronicity of *T rubrum* moccasin infections. Another important factor in the chronicity of these infections is the association with atopic disease states. There is some evidence to suggest that IgE antibody response to *T rubrum* may block T-cell receptor access to fungal antigen on the surface of antigen-presenting cells.[21]

Vesicular/Bullous Tinea Pedis

This syndrome consists of episodes of acute, highly inflammatory vesicular and bullous lesions which can involve the interdigital area, dorsum of the foot, instep, and even the heel. Commonly, thickening of the soles and secondary bacterial infection develop. This variant of tinea pedis is caused by *Trichophyton mentagrophytes* and is associated with a brisk T-cell immune response which produces in effect a contact allergic dermatitis to the organism.[22] Between attacks of acute inflammation, a more or less low-grade scaling exists. Presumably when local factors such as increased sweating occur, the fungus proliferates, further invades the skin, and then elicits a T-cell immune response.

TREATMENT

In recent years, there has been a rapid increase in the number of topical and systemic antifungal agents. These agents work primarily by interfering with the formation of the fungal cell membrane. This is true for the major classes of antimycotic agents such as the azoles, which include the imidazoles and triazoles, as well as the recently introduced allylamines (Table 2). The importance of the systemic azoles is the fact that their mode of action involves one of the nitrogen atoms in the azole binding to heme iron of cytochrome P-450 which can lead to inhibition of cytochrome activation and function. This can be important in terms of metabolism of other drugs, as well as being important in steroid synthesis resulting in decreased testosterone and cortisol production.[23] The azoles and allylamines work differently than griseofulvin, which inhibits microtubule formation and blocks mitosis.

Table 2. Major Classes of Antifungal Treatment of Tinea Pedis

Antifungal Agent	Mode of Action
Azoles	
Imidazoles	
Miconazole	Inhibit ergosterol synthesis
Clotrimazole	Block demethylation of lanosterol
Ketoconazole	Cytochrome P-450 involved
Econazole	
Sulconazole	
Allylamines	
Terbinafine	Block conversion of squalene to squalene epoxide
Naftifine	Cytochrome P-450 not involved
Griseofulvin	Blocks microtubule formation in the nucleus, inhibits mitosis
Triazoles	
Itraconazole	
Fluconazole	

The relation of antimycotic mechanism of action to clinical efficacy is not a direct one. In addition to how these drugs work, the questions of concentration of drug needed to kill fungi and the delivery of the drug to the infected compartment are extremely important. Furthermore, in vitro testing antifungal agents is a technically complicated business, and variances in results from one laboratory to another are common. Most testing, however, shows that the allylamine terbinafine is more active against dermatophytes than naftifine, the azoles, and griseofulvin. Griseofulvin usually seems to be the least effective, but this is in part because of its poor solubility which complicates in vitro testing. Terbinafine seems to have an additional advantage in that this agent is fungicidal in vitro, and the rapid response and high cure rate without remission after a brief course of therapy suggests in vivo fungicidal activity.

With the proliferation of the azoles and the appearance of the allylamines, the clinician has an extensive menu from which to select a treatment. No in vivo comparisons of all of these agents exist, nor are they ever likely to be done in view of the extremely large numbers of subjects that would be needed to have a statistically sound study. However, direct in vivo comparisons in extremely difficult to treat infections, such as the moccasin variety, could be done and would help the relative clinical merits of these agents.

Treatment of Interdigital Toe Web Infections

Interdigital toe web infections involve both fungi and bacteria in the macerated, symptomatic varieties.[13,14] Pure antifungal therapy is successful only in the relatively asymptomatic scaling variety. Of the various antifungal agents available, econazole nitrate has the most effective (although limited) antibacterial spectrum in in vitro testing. This agent has also been shown to have in vivo antibacterial effects.[24] Agents which are both drying or astringent and have broad-based antibacte-

rial and antifungal activity, such as 20% to 30% aluminum chloride, gentian violet, and other dyes, are effective particularly in more extensive infections. Treatment should be continued beyond the point of symptomatic relief. Surviving dermatophyte spores can initiate a relapse once environmental conditions favor their proliferation.

Treatment of Moccasin Type Tinea Pedia

Treatment of this variety of infection is complicated by the thickness of the stratum corneum, the relatively low immunogenicity of *T rubrum*, and the frequent association with atopic disease states which tend to blunt T-cell immune responsiveness. At the present time, combined systemic and topical therapy followed by long-term use of topical therapy can contain the process. True cures are extremely rare.

Vesicular/Bullous Tinea Pedis

During the phase of acute inflammation, compresses and topical corticosteroids coupled with systemic antifungal therapy is usually sufficient to abort the acute attack. At times, systemic corticosteroids are needed. Once the acute contact dermatitis has been suppressed, topical and/or systemic antifungal therapy should be continued until the skin is free of any evidence on culture or examination of scrapings.

A common problem with the treatment of tinea pedis is that recurrences are common. This raises the question of relapse versus reinfection. It is our opinion that relapses are more common than is generally perceived. By relapse we mean that treatment was not continued to the point of eradication of the fungus, even though clinical signs are no longer present. Patients will commonly discontinue therapy once symptoms have abated. The analogy between treatment of streptococcal pharyngitis and urinary tract infections is useful. Partial eradication of pathogens is associated with symptomatic relief only to be followed by proliferation of the surviving organisms and recurrence of symptoms. This problem of failure to eradicate the causative organism is further complicated in the case of tinea pedis by the presence of spores under toenails and in clinically normal-appearing skin where low numbers of spores can survive and subsequently proliferate when conditions favor growth.[10,11,12,14] Successful therapy requires compliance by the patient and diligent search for evidence of surviving spores after symptomatic relief and apparent clinical cure has occurred.

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