Topical antifungal agents are medications utilized to combat cutaneous fungal infections. Our goals in this lesson are to describe various cutaneous conditions, and to discuss the appropriate topical therapy. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. The ACPE program ID # for this lesson is 707-000-04-009-H01. Our CE Provider Registered # with CE Broker.com is 50-3170-1.

Pharmacists completing this lesson by September 30, 2007 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Illinois, Alaska and Hawaii phone 1-847-945-8050). Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Describe the pathogenesis of cutaneous fungal infection.
2. List the genera that cause superficial mycoses.
3. Identify the various types of Tinea (ringworm) infections.
4. Discuss the various types of topical antifungals.
Topical antifungal agents are medications utilized to combat cutaneous fungal infections. There are two types of topical antifungals: fungistatics and fungicidals. A fungistatic drug is an agent that stops the growth of fungi, whereas a fungicide is one that kills fungi and its spores. Fungi are widely distributed in nature, and their spores are found in the air, soil and water. They grow in single cells, as in yeast, or as multicellular filaments, as in mold or mushrooms. The cell structure of the unicellular fungi consists of protoplasm, a nucleus, a cell wall, granules, carbohydrates and nitrogenous materials. The cell of the multicellular filamentous type consists of an actively growing vegetative section on a thread-like portion of each branching filament that projects into the air. The aerial portion acts as a reproductive organ, while the remaining part absorbs food and water. Unlike plants, fungi do not need light for growth; in fact, sunlight may inhibit growth. Fungi are nonphotosynthetics and contain no chlorophyll, and, thus, are incapable of providing their own food. They exist by parasitizing living organisms, or feed on dead or decaying organic matter. They are capable of invading dead human tissue such as keratin, hair, and nails, as well as living tissue of individuals who suffer from debilitating conditions such as diabetes, lymphoma, or rheumatoid arthritis. Individuals whose immune system has been compromised as a result of HIV or the intake of drugs such as corticosteroids, antibiotics, antimetabolites or immunosuppressive agents, are susceptible to fungal infections. Some fungi are capable of invading the keratin of the skin by producing keratinolytic enzymes (keratinase). These proteolytic enzymes, as well as the metabolites produced by the fungi, diffuse into the living tissue that lies under the keratin of the skin. Sensitivity to these substances develops, and the skin becomes inflamed and covered with tiny pruritic vesicles that produce itching. If left untreated, the infected area enlarges and assumes a radially shaped lesion with a scaly center. Occasionally, fungi may infect subcutaneous tissue of the skin. However, these microorganisms usually invade the upper layers and are unable to penetrate deeper tissue or organs. It has been postulated that this manifestation is due to either the inhibition of fungal keratinase or the presence of inhibiting substances in the blood. Because of the ring-like appearance of the lesions, cutaneous fungal infections are known as ringworm. Fungi may invade the hair follicle, as well as the hair shaft, resulting in brittleness and different appearance of the shaft. Nails may become distorted and painful if invaded by fungi.

The vast majority of fungi are not pathogenic and, in fact, the normal flora of the skin consists of many species. Of the thousands of fungi that are in existence, only about 50 species are potentially infectious to humans, and only about 25 can cause cutaneous infections. The skin surface is contaminated by a variety of microorganisms that include bacteria and fungi. Some of these microorganisms reside on the skin continuously, whereas others are deposited on the skin temporarily and can be removed by scrubbing and with disinfectants. Both the resident and transient microflora are potential pathogens. However, favorable conditions, such as decreased host resistance and changes in integrity of the skin, may trigger an infection. Species of Candida and Cryptococcus, as well as the genus Pityrosporum with two species of P. ovale and P. orbiculare are the most commonly encountered fungi of the skin microflora.

SUPERFICIAL MYCOSES

Mycoses and dermatophytes (phyto means plants or something that grows) are two terms used to indicate fungal infections. There are two types of infections caused by fungi: superficial or cutaneous mycoses, and deep or systemic mycoses. In this lesson, focus will be placed on the former. The 25 species
of dermatophytes that cause superficial infection in humans belong to three genera: 1) *Trycophyton*, which affects skin, hair and nails; 2) *Epidermatophyton*, which invades skin and nails, but not hair; and, 3) *Microsporum*, which is common on the hair and skin, particularly on the scalp. It rarely involves the nails. Tinea is a term used to describe fungal infections caused by dermatophytes.

In general, superficial fungal infections occur in separate phases of eruptions. The acute phase represents the initial primary lesion. The eruption may range from asymptomatic lesions to inflamed oozing areas accompanied by itching. The acute stage ends when the inflammation ceases to exist and the lesion becomes dry. The subacute stage begins at the end of the acute stage, and is terminated when the skin forms a scab and eventually becomes scaly. The chronic stage occurs when the skin thickens and the lesions become hyperkeratotic. Infection of the nails is one of the most chronic types of superficial mycoses. The chronic stage may never emerge if the infection is properly treated.

The following information describes the various types of superficial fungal infections, characteristics and manifestations of the infections, and the causative fungi.

**Tinea pedis (ringworm of the foot or athlete’s foot)**

**Causative Fungi**
- *T. mentagrophytes*
- *T. rubrum*

**Characteristics**
This is the most common fungal infection worldwide. It has been estimated that about half the world population will contract athlete’s foot at least once during their lifetime. It comprises about 25% of all dermal disease in the warmer regions of the world and about 6% in colder regions. The infection usually begins in the toe web (interdigital) and is often characterized by maceration, soggy, scaly periphery and accompanied by itching that provokes scratching. Fissures and blisters may be conducive to pyogenic secondary bacterial infection that may result in the formation of vesicopustules. This variety is persistent and is aggravated by warm weather. Another type, that affects the instep, is characterized by intense itching, but the lesions appear dry and scaly with brownish discoloration. Athlete’s foot is transmitted either directly by human contact or indirectly by exposure to contaminated objects. Walking barefooted on infected moist floors such as swimming pools or locker rooms, and household objects such as floor mats may result in the spread of infection.

**Tinea cruris (Jock itch, ringworm of the groin)**

**Causative Fungi**
- *E. Floccosum*
- *T. rubrum*
- *T. mentagrophytes*

**Characteristics**
Tinea cruris primarily affects males. The lesions usually involve the groin, perineum and perianal areas, and appear symmetrical with sharply defined margins and slightly scaly surfaces. In severe cases, the infection may spread to the buttocks and lower abdomen. Moderate to intense itching is a common symptom, and the condition can be aggravated by obesity, friction, excessive perspiration, and inadequate personal hygiene. To prevent relapse and reinfecion, wearing loose-fitting cotton underwear, weight reduction, and the use of absorbent powder are helpful.

**Tinea barbae (ringworm of the beard)**

**Causative Fungi**
- *T. verrucosum*
- *T. mentagrophytes*
- *T. rubrum*
Characteristics
Bearded areas of the face and neck are involved. The lesions appear annular with elevated margins and some vesicles and papules. It may be transmitted from animals. It usually triggers moderate pruritus. Hair, that may be affected, becomes loose, dry and brittle. Alopecia may appear at the site of the infection.

Tinea capitis (ringworm of the scalp)

Causative Fungi
- *M. audouini*
- *M. canis*
- *T. tonsurans*

Characteristics
This type of fungal infection affects children of school age, and occasionally infants and adults. It can be transmitted from one child to another. In the USA, the disease is rare, but it appears in epidemic proportions in some parts of the world. The fungi flourish on hair and keratin. The most common site is the scalp. Circular, erythematous, scaly or pustular patches in which the hair becomes loose and breaks off just above the skin surface characterize the lesions. In severe cases, the lesions may become suppurative, and, form an inflammatory swelling. The variety caused by *T. tonsurans* is characterized by black dot ringworm. For unknown reasons, the infection disappears spontaneously at puberty. It has been postulated that the increased secretions by the sebaceous glands of the scalp, which contain fatty acids that possess fungi-static activity, are responsible for this.

T. corporis (ringworm of the body)

Causative Fungi
- *T. rubrum*
- *M. audouini*
- *T. mentagrophytes*

Characteristics
The infection results in lesions that are papulosquamous, inflammatory and scaly. Non-hairy parts of the body are usually affected, and the lesions have a slightly elevated border that spreads peripherally with areas of central healing. The lesions appear in different sizes. Some may reach a diameter of several inches. The eruptions cause mild to moderate pruritus.

Tinea unguium (onychomycosis, ringworm of the nails)

Causative Fungi
- *T. rubrum*
- *T. mentagrophytes*
- *E. floccosum*

Characteristics
This is a chronic fungal infection, characterized by paronychial (skin fold surrounding the nail) inflammation, thickened, discolored, distorted, grooved and pitted nails. The initial infection usually takes place at the lateral nail borders. The nail and affected area appear white or yellow. In later stages, the nail plate separates from its bed, and the tip may clip off. Toenail involvement is more common than that of the fingernails. Because of its chronic nature, *T. unguium* may serve as a source of fungal infection of the hands and feet. The infection is very resistant to topical treatment, but positive results can be achieved with systemic medications.
Tinea versicolor (Pityriasis versicolor)

Causative Fungus
- Malassezia furfur

Characteristics
Tinea versicolor is a chronic, but mild, fungal infection that may cause mild itching. It is only of cosmetic concern. It primarily involves the smooth skin of the upper trunk, chest and shoulders. It is most common among young adults. The lesions are annular, fawn-yellow or brown, with yellow or pink scales. The lesions become more noticeable in summer, when the surrounding skin is exposed to the sun, becoming tanned.

TOPICAL ANTIFUNGAL AGENTS
Topical antifungal therapy is the preferred treatment for common cutaneous fungal infections because of the low risk for side effects. Additionally, factors such as immunity status of the patient, the nature of the causative fungus, site and magnitude of the infection, and cost can play important roles in determining the choice between systemic or topical treatments. Systemic administration may be required for treating chronic or recurrent cases of tinea capitis, tinea pedis, and tinea unguium. Frequently, topical medications may be used concurrently with systemic ones.

To achieve an optimal therapeutic effect, topical antifungal agents should be applied over the site of infection as well as on an area that is at least one inch from the outer periphery of the lesion. It is essential that the patient apply the medication regularly and at a frequency and duration prescribed by the physician or recommended by the pharmacist. The patient should be counseled not to discontinue use of the medication when initial improvement takes place. Prompt treatment is important, since infection in the early stages is likely to respond more positively and thoroughly than advanced stages. Symptomatic relief usually occurs within one week. If clinical improvement does not occur after recommended treatment, the patient should seek medical advice.

Tolnaftate
Tolnaftate is a thiocarbamate that exerts its fungicidal activity by blocking sterol biosynthesis in fungal cells via inhibition of squalene epoxidase. It is effective against fungal infections caused by T. rubrum, T. mentagrophytes, T. tonsurans, E. floccosum, and M. canis. Tolnaftate 1% is available in cream, powder, aerosol powder, solution or aerosol. The medication should be applied twice daily for 2 to 6 weeks. It is used primarily for dry, scaly type of athlete’s foot rather than the soggy, macerated type. Mild irritation may occur following application. The drug has a low index of sensitization.

Haloprogin
Haloprogin is a halogenated phenolic ether that possesses a broad-spectrum fungicidal activity as well as antibacterial activity against certain gram-positive bacteria. It is available in 1% solution or cream. It is as effective as tolnaftate in treating fungal infections. Adverse effects are minimal and include burning, irritation and scaling. It should be applied twice daily for 2 to 4 weeks.

Undecylenic acid and its Salts
Undecylenic acid possesses a fungistatic activity especially at acidic pH. It is used in combination with zinc or calcium undecylenate because these salts possess astringent activity. It is applied in the form of ointments, creams, liquids, dusting powder or aerosol. A common combination is 5% undecylenic acid and 20% zinc undecylenate.

Ciclopirox
Ciclopirox is a broad-spectrum fungicidal agent with antibacterial activity against many gram-positive and gram-negative bacteria. It acts by interfering with the uptake of substances needed for the formation of cell membrane. It is available as 1% cream, and 0.1% solution.
**Triacetin**

Triacetin is a fungistatic agent whose activity is due to the formation of acetic acid that results from the hydrolysis of triacetin by fungal esterase enzymes. The resultant acidic environment of the infected area tends to retard the growth of fungi. It is available in cream, solutions and spray.

**Butenafine**

Butenafine is a benzylamine antifungal that is believed to act by inhibiting fungal squalene epoxidase and depletion of ergosterol, resulting in altering the cellular membrane. It acts as a fungistatic against *C. albicans* and as a fungicide in vitro against dermatophytes. The medication is effective against *T. pedis*, when applied as a 1% cream, once daily for 4 weeks. It is more effective than theazole derivatives (e.g., ketoconazole, econazole) against dermatophytes, but less active against *Candida*.

**Selenium Sulfide**

A 2.5% lotion of Selenium Sulfide is utilized in treating *T. versicolor*. It has antibacterial with cytostatic antiseborrheic and mild antifungal activity. The pure drug has a reddish brown to bright orange color. Its mechanism of action is unknown, but it is especially active against *Pityrosporon ovale*, a yeast-like fungus that is believed to cause dandruff and seborrheic dermatitis. In addition, its cytostatic activity tends to reduce the rate of cell turnover in the scalp. The drug may cause irritation to the skin and, consequently, patients should be advised to rinse the affected areas and lather with a small amount of water. Allow to remain on the skin for 10 minutes and then lotion should be rinsed thoroughly. This process should be repeated once daily for a week.

**Zinc Pyrithione**

Zinc pyrithione possesses antifungal and antibacterial properties. A 1% shampoo is used for treating dandruff, but it is effective in treating *T. versicolor* when applied daily for 2 weeks.

**ALLYLAMINE DERIVATIVES**

**Naftifine**

Naftifine is an allylamine derivative that structurally and pharmacologically resembles terbinafine. It is considered a fungicidal agent against dermatophytes, but fungistatic in action against *Candida*. It has been postulated that its action is due to interference with sterol biosynthesis. In addition to its antifungal activity, it possesses anti-inflammatory effects. It has been estimated that 3 – 6% of a topically applied naftifine 1% cream or gel to intact skin is absorbed systemically. Sufficient effective concentrations remain in the upper layers of the skin 24 hours following application. The drug is well tolerated and has a low toxicity. Burning, pruritus, rash, local irritation, and skin tenderness have been reported. Naftifine is available as a 1% cream or gel and should be applied once daily for 2 to 6 weeks, depending on the type of dermatophyte infection.

**Terbinafine**

This allylamine derivative antifungal agent is active in vitro against many fungi, including dermatophytes, yeast, *Aspergillus, Blastomyces*, and *Histoplasma*. It has fungicidal activity against all the aforementioned microorganisms, but is only fungistatic against *Candida*. Terbinafine is more effective than the imidazole derivatives (e.g., ketoconazole, terconazole) against dermatophytes, and less effective than these derivatives against *Candida*. Its mechanism of action is similar to that of naftifine. It is available as a 1% cream, and a 1 – 2 week topical therapy appears to be more effective than a 4-week course of topical clotrimazole 1% cream. Terbinafine is reported to have a more rapid antifungal action than the imidazoles. The cream is recommended to be applied twice daily for a minimum of 1 week for treating *T. pedis*. The duration of therapy may be extended for 2 weeks.
THE AZOLES

The imidazole-derivative antifungals are widely used in treating dermatophytes and other fungi. They act by inhibiting the biosynthesis of ergosterol via inhibition of the enzyme. They act by inhibiting the biosynthesis of ergosterol via inhibition of the enzyme lanosterol 14-a-demethylase, a cytochrome P450-dependent enzyme. Ergosterol is necessary for the formation of the fungal cell membrane. Altering cellular membranes results in increased permeability and loss of potassium and other cellular constituents. Theazole antifungals include: clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sulconazole, and terconazole. Terconazole is a triazole derivative. Imidazole-derivative azoles, as well as the allylamine derivatives are considered the drugs of first choice for topical treatment of dermatophytes, even though other agents such as tinactin, tolnaftate, ciclopirox, undecylenic acid, and butenafine are effective.

Clotrimazole

Topical preparations of clotrimazole, that are available as 1% lotions, creams or solutions, are effective in treating T. pedis, T. cruris, T. corporis, and Pityriasis versicolor. In vitro, the drug inhibits Trichophyton, Microsporum and Epidermatophyton. Additionally, it retards the growth of Candida and certain strains of gram-positive bacteria. The preparation used should be rubbed gently on the cleansed affected area and the surrounding skin twice daily. Clotrimazole has no serious adverse reactions. Occasionally, mild burning, erythema, or pruritus may occur.

Econazole

Econazole has broad-spectrum antifungal activity. It acts as a fungistatic agent, but in high concentrations, it exerts fungicidal activity. The nitrate salt of econazole is used in topical preparations. The drug is available in 1% cream, lotion or solution. The main side effects of such preparations include burning, stinging sensations and itching. A one-month treatment for T. pedis may be required, whereas other fungal infections should be treated for two weeks.

Ketoconazole

It is available in 2% cream and shampoo. It possesses a broad-spectrum antifungal activity. The preparation should be used once daily for treating T. pedis, T. cruris, and T. corporis. To prevent recurrence of infection, the duration of treatment should be at least 2 weeks.

Miconazole

This phenethyl imidazole inhibits the growth of common dermatophytes when applied topically. It is available in 2% aerosol, aerosol powder, and cream. Adverse reactions include burning and stinging.

Oxiconazole

In addition to being active against common dermatophytes, Candida and M. furfur, oxiconazole possesses antibacterial activities against some Gram-positive bacteria. The application of oxiconazole 1% cream, once daily, is sufficient for treating tinea pedis, tinea corporis and tinea cruris. The recommended duration for treating T. corporis and T. cruris is 2 weeks and for T. pedis, is one month to prevent recurrence.

Sulconazole

Sulconazole is available as a 1% cream or solution that acts primarily as a fungistatic agent against most dermatophytes and yeast. However, at higher concentrations, it acts as a fungicidal drug due to its direct action on the fungal cell membrane. Similar to some imidazole-derivative azoles, it possesses some antibacterial properties. The most frequent side effects include pruritus, stinging, tingling, dryness of skin, and erythema. Symptomatic relief is usually achieved within days to one week of initiation of treatment.

Terconazole

Terconazole acts as an antifungal by inhibiting cytochrome P-450-a-demethylase in fungi that in turn causes the increased level of C-14 methylated steole and a decrease in concentration of ergosterol. It
possesses mild antibacterial activities against some gram-positive and gram-negative organisms. It is effective against yeast and dermatophytes especially T. mentagrophytes, T. rubrum, T. tonsurans, T. verrucosum, and T. floccosum.

**SUMMARY**

Cutaneous fungal infections such as T. pedis, T. cruris, T. barbae, T. capitis, T. corporis, T. unguium, and T. versicolor are common occurrences. These infections are caused by three genera of dermatophytes: tricophyton, epidermatophyton and microsporum. Treatment should be based on identification of the causative fungus. There are a number of antifungal preparations that can effectively be used for treating these infections. They are available in various dosage forms. To achieve an optimal therapeutic effect, these preparations should be applied over the site of infection, as well as on the immediate surrounding healthy area. In some chronic cases, systemic antifungals may be used. In general, T. cruris and T. corporis are treated for 2 weeks, whereas T. pedis is treated for 4 weeks withazole derivatives and 1 to 2 weeks with allylamine derivatives. It is essential that the patient be advised to use the medication regularly at the prescribed frequency and duration. Treatment should continue at least one week after the infection subsides. If clinical improvement does not occur after recommended treatment, medical advice should be sought. A number of nonprescription topical antifungals are effective in treating these infections.

**REFERENCES**

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1. Relevance of topic to practice.
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3. Author’s knowledge of topic.
   1 2 3 4 5 6 7
   1 2 3 4 5 6 7

5. Do you have any further comments about this lesson? ____________________________________________________________________
   ____________________________________________________________________________

Please Select the Most Correct Answer

1. Which statement is CORRECT concerning T. pedis?
   A. Only affects children, and the infection disappears spontaneously at puberty
   B. Is not contagious
   C. Responds only to systemic treatment
   D. Is the most common fungal infection worldwide

2. Keratinase is:
   A. Enzyme that softens or dissolves keratin
   B. Capable of dissolving fatty tissue
   C. Precursor to keratin
   D. Essential element for skin protection

3. Which one of the following does NOT cause cutaneous fungal infections?
   A. Epidermatophyton
   B. Microsporum
   C. Trycophyton
   D. Nocardia asteroids

4. Tolnaftate:
   A. Is a fungistatic agent
   B. Is a fungicidal agent
   C. Acts by stimulating the production of squalene epoxidase
   D. Is a very sensitizing agent

5. Triacetin:
   A. Upon application to the skin, it undergoes hydrolysis to acetic acid
   B. Is a fungistatic agent
   C. Is the drug of choice for T. versicolor
   D. Is an imidazole derivative azole

6. Which of the following is the drug of choice against Pityrosorum ovale?
   A. Undecylenic acid
   B. Econazole
   C. Selenium sulfide
   D. Haloprogin

7. Which of these antifungals is an allylamine derivative?
   A. Terbinafine
   B. Ketoconazole
   C. Haloprogin
   D. Ciclopirox

8. Which one of the following drugs has cytostatic properties?
   A. Econazole
   B. Tolnaftate
   C. Undecylenic acid
   D. Selenium sulfide

9. When using a topical antifungal, if clinical improvement does not occur after recommended treatment, the patient should continue the application indefinitely.
   A. True
   B. False

10. Which statement is FALSE about fungi?
    A. Capable of invading dead tissue
    B. Do not need light for growth
    C. Can invade tissue of individuals whose immune system has been compromised
    D. All fungi grow as multicellular filaments

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