“Superficial Fungal Infections & Their Therapy”  

Superficial fungal infections are common worldwide. Our goal in this lesson is to review significant information that can be shared with patients. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

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

1. Differentiate between the parts of the skin.
2. List the most common superficial fungal infections.
3. Describe the signs and symptoms of these conditions.
4. State the three stages in which fungal infections occur.
5. List the types of topical antifungal medications and their adverse effects.

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BACKGROUND
Superficial fungal infections of the skin, hair and nails, known as dermatophytes (skin plants), are common worldwide. Their incidence is on the increase. Dermatophytes include the following groups: *Trichophyton*, *Epidermophyton* and *Microsporum*. These fungi thrive on keratin of the skin, hair and nails and are transmitted from an infected person to a healthy one through direct or indirect contact. The infected keratin may be found in clothing, combs, hair brushes, bedding, socks, shoes, towels, public bathrooms and locker room floors. Exposed skin increases the probability of acquiring infections. Out of the thousands of fungi that exist, only about 25 species potentially can cause these infections in humans.

Fungi are parasitic or saprophytic microorganisms that are incapable of synthesizing their own food. Consequently, they attack keratin of living tissues or saprophytize plants or animal remains. Fungi invade dead parts of the body such as keratin of the skin, hair or nails, and are additionally able to invade normal tissue of persons suffering from debilitating systemic diseases like diabetes, AIDS, lymphoma, rheumatoid arthritis, or patients whose immune systems have been compromised following the intake of corticosteroids, immunosuppressive agents or antimetabolites.

Metabolites of fungi living in keratin or proteolytic enzymes, such as keratinase, produced by the fungi, can diffuse into living tissue beneath the keratin to trigger sensitivity reactions provoking itching and inflammation. Unlike plants, fungi do not need light for growth. In fact, sunlight may inhibit their growth. If left untreated, the infected area of the skin enlarges and assumes a radially shaped lesion with a scaly center. Because of this ring-like appearance, cutaneous fungal infections are sometimes known as ringworm. When fungi invade the hair follicle and shaft, the hair becomes brittle and rough. The nails become distended, painful, and may assume varying colors.

Superficial fungal infections occur in stages. The acute phase represents the initial, primary lesion. The eruption may be asymptomatic or may cause inflamed oozing areas accompanied by itching. This acute period ends when the inflammation ceases to exist and the lesion becomes dry. The subacute phase follows and terminates when the skin forms a scab and eventually becomes scaly. The chronic phase occurs when the skin thickens, and the lesions become hyperkeratotic. Infection of the nails is in the most chronic stage, and presents a resistant fungal infection.

THE SKIN
The skin is the outer covering of the body. It is the largest organ and protects the underlying tissues from pathogens, injuries, radiation from the sun, dehydration, assists in maintaining proper body temperature, and makes patients aware of external stimuli via touch receptors located in the skin. The skin may be divided into three layers: epidermis, dermis, and subcutaneous tissues.

Epidermis
The epidermis is the outermost layer of the skin and consists of stratified squamous epithelium. It is devoid of blood vessels. It receives nutrition by diffusion from the underlying layers, which are supplied with blood vessels.

The epidermis consists of several parts: the stratum corneum, which is a layer composed of dead, keratinized cells; the stratum germinativum, which replaces the dead keratinized cells of the stratum corneum with new cells. It is the deepest layer. As the newly formed cells leave the stratum germinativum and move upward toward the surface, nourishment becomes
Dermis
The dermis, which is made of connective tissue, is a continuation of the epidermis and lies between the epidermis and subcutaneous tissue. It contains numerous blood vessels, lymphatics, nerves, hair follicles, sweat and sebaceous glands.

Subcutaneous Tissue
This is also known as the hypodermis. It consists of elastic and fatty tissue and acts as a cushion, heat insulator, and energy source.

TOPICAL ANTIFUNGALS
The majority of superficial fungal infections are treated by using topical medications. They might be fungistatic or fungicidal. Fungistatic agents act by suppressing the growth of fungi; fungicidals kill fungi and spores. Some of these are nonprescription products and have been proven to be safe and effective.

Topical treatment is typically preferred because of the incidence of mild side effects, if any. Sometimes topical and systemic administrations are used concurrently. Ointments, creams or liquids can be applied over the infection site as well as the adjacent healthy area. The patient should continue the use of the medication as directed even if the symptoms become less intense. Relief is usually achieved within one week following application. A physician or a pharmacist must be consulted if improvement does not take place. Factors such as immunity status of the patient, nature of the causative fungus, site, magnitude of the infection and cost should be considered when determining the choice between topical and systemic meds. In case of chronicity, systemic administration may be required. Prompt initiation of treatment is essential, since infections in the early stages are likely to respond more positively and thoroughly than advanced conditions.

Antifungal medications are available in four primary classes: polyenes, azoles, allylamines and echinocandins.

POLYENE ANTIFUNGALS
The mechanism of action of this group involves binding with ergosterol that is present in the fungal cell membranes causing death of the cell. An example is amphotericin B, which is a systemic antibiotic. Nystatin, which has the same mechanism of action as amphotericin, may be used topically and systemically.

AZOLES
This group includes a large number of antifungals that belong to the derivatives of imidazole, triazole and thiazole.

The imidazoles include bifonazole, butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, ketoconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole and tioconazole. The ones that are clinically effective are clotrimazole, miconazole and ketoconazole. These three act by inhibiting the growth of fungi by blocking the enzyme lanosterol 14-demethylase, which is needed for the conversion of lanosterol to ergosterol. Once ergosterol ceases to be produced, fungal cells will be disrupted followed by inhibition of
fungal multiplication. The side effects of the imidazoles are usually mild and include irritation, burning, erythema and rash.

**Clotrimazole**
It is available as a 1% lotion, cream or solution. It is effective in treating superficial fungal infections as well as *Candida* and certain strains of gram-positive bacteria. Side effects are mild and are tolerated well.

**Ketoconazole**
It is available as a 2% topical cream or shampoo. It may be used orally to treat superficial and deep fungal infections. It is well-absorbed from the GI tract and is distributed widely in the body following oral administration. Optimal absorption occurs when the drug is taken on an empty stomach. Ketoconazole should not be given concurrently with drugs such as cimetidine, ranitidine, famotidine and antacids that reduce the acidity of the gastric fluid. An increase in pH of the stomach contents results in a decrease in absorption of ketoconazole. Nausea, vomiting, dizziness, abdominal pain, headache and insomnia have been reported following oral use.

**Miconazole**
It is available in the form of a 2% aerosol, aerosol powder, cream, vaginal cream as well as vaginal suppositories. Adverse effects of topical and intravaginal use include burning, stinging, headache, hives and pelvic cramps.

**Fluconazole**
Fluconazole may be administered orally or IV. It is well absorbed from the GI tract. It is used for systemic fungal infections and in patients with HIV infection who developed opportunistic fungal infections, or in individuals who are immunocompromised. The drug is considered to be safe. A minority of patients experience transient elevation of liver enzymes. Rare serious hepatotoxicity has been reported. Others reported nausea, vomiting, diarrhea, abdominal pain, rash and headache.

**Itraconazole**
This systemic antifungal has a broad spectrum of antifungal activity. It is used in the treatment of onychomycosis of the toenails and fingernails caused by dermatophytes. The drug is available in capsule form, each containing 100 mg; solution form in a concentration of 10 mg/ml; and in solution of 10 mg/ml for IV administration. The recommended oral dose for treating onychomycosis is 200 mg once daily for 12 consecutive weeks. Adverse effects of itraconazole include GI disturbances, skin rash, headache, dizziness, hypertension, and hepatic function abnormalities.

**Econazole**
Econazole acts as fungistatic agent at low concentrations and a fungicidal drug at higher blood levels. The nitrate salt is used in topical preparations. It is available as a 1% cream, lotion or solution. Its adverse effects are similar to other azoles.

**Oxiconazole**
Oxiconazole possesses antifungal as well as antibacterial properties against some Gram-positive bacteria. It is available as a 1% cream.

**Sulconazole**
Sulconazole acts as a fungistatic drug but at higher concentrations it is considered fungicidal due to its direct action on fungal cell membranes. It is available as a 1% cream or solution.
**Sertaconazole**

It is available as a cream or in vaginal tablets. Its action is unique in that it acts as a fungistatic, fungicidal, antibacterial, anti-inflammatory, antipruritic and antitrichomonal.

**ALLYLAMINES**

Allylamine antifungals such as naftifine, terbinafine, butenafine, and amorolfine act by inhibiting squalene epoxidase, an enzyme, that is required for ergosterol synthesis. The side effects of this group include itching, burning, rash, local irritation and swelling.

**Naftidrine**

It acts as a fungicide against dermatophytes, and is fungistatic against *Candida*. In addition to its activity as an antifungal, it possesses anti-inflammatory properties. When applied in concentrations of 3-6%, naftidrine may be absorbed systemically, and sufficiently active amounts remain in the upper layer of the skin up to 24 hours after application. The drug is well tolerated and has low toxicity. It is available as a 1% cream or gel and should be applied once daily for 2-6 weeks, depending on the type of dermatophyte and severity of the infection.

**Terbinafine**

Terbinafine is more effective than the imidazoles against dermatophytes, but less effective against *Candida*. It also has a more rapid action against fungi than the imidazoles. It is available as a 1% cream.

**Butenafine**

This drug is used mainly to treat fungal infections of the finger and toe nails. It is available as a 5% nail lacquer. It should be applied once or twice weekly for 3 to 6 months. Nail varnish or artificial nails should not be worn during treatment.

**Amorolfine**

Fluconazole may be administered orally or IV. It is well absorbed from the GI tract. It is used for systemic fungal infections and in patients with HIV infection who developed opportunistic fungal infections, or in individuals who are immunocompromised. The drug is considered to be safe. A minority of patients experience transient elevation of liver enzymes. Rare serious hepatotoxicity has been reported. Others reported nausea, vomiting, diarrhea, abdominal pain, rash and headache.

**ECHINOCANDINS**

This group of antifungals acts by inhibiting the synthesis of glucan in the cell wall. They possess a broad range of activity and are effective against azoles-resistant fungi. Some compounds of this group have been withdrawn due to toxicity.

**Caspofungin**

This echinocandin is administered via the IV route for systemic fungal infections.

**MISCELLANEOUS ANTIFUNGALS**

**Tolnaftate**

Tolnaftate belongs to the thiocarbamate group and exerts its activity by blocking sterol biosynthesis in fungal cells via inhibition of squalene epoxidase. It is available in a 1% cream, powder, aerosol powder, solution or aerosol. It is a broad spectrum antifungal and should be applied twice daily for 2 to 6 weeks. The main adverse effect is mild irritation.
Haloprogin
This antifungal is a halogenated phenolic ether that possesses broad-spectrum fungicidal activity as well as antibacterial action against certain gram-positive bacteria. It is available as a 1% solution or cream. Adverse effects are mild and include burning, irritation and scaling.

Undecylenic Acid and Its Salts
Antifungal activity is enhanced at acidic environment. Undecylenic acid (5%) is usually used in combination with zinc undecylenate (20%) to impact astringent activity.

Ciclopirox
This antifungal possesses antibacterial activity against many gram-positive and gram negative bacteria. It is available in a 1% cream and a 0.1% solution.

Selenium Sulfide
This agent is employed as a 2.5% lotion to treat T. versicolor. In addition, it possesses cytostatic antiseborrheic activity and, thus, is used to treat dandruff and seborrhea dermatitis. It may cause skin irritation. In order to minimize this, the medication should be rinsed thoroughly after remaining in contact with the skin for 10 minutes.

COMMON SUPERFICIAL FUNGAL INFECTIONS

Tinea pedis (Athlete’s foot)
Athlete’s foot is the most common superficial fungal infection. About 25% of the population in the U.S. experiences this condition annually. It is caused by T. Mentagrophytes and T. rubrum. The infection is characterized by maceration, soggy, scaly periphery and itching. A moist and warm environment facilitates its spread. Fissures and blisters may be conducive to pyogenic secondary bacterial infection. Keeping the feet well ventilated, such as remaining barefooted, may reduce the risk of infection. Since the fungus requires moisture, the feet should be dried thoroughly after showering and swimming. Shoes and socks must be kept clean and dry. Tolnaftate is effective in treating athlete’s foot.

Tinea cruris
This is an acute, subacute or chronic fungal infection that can affect the groin, perineum, and perianal areas of males and females. It is sometimes considered to be a sexually transmitted disease. The causative organisms are E. floccosum, T. rubrum, and T. mentagrophyte. The infection appears 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. Antifungals used for treating athlete’s foot are also used in treating jock itch.

Tinea corporis (Ringworm of the body)
Tinea corporis is caused by several species of Microsporum and Trichophyton. The lesions appear as single or multiple, scaly, circular, and erythematous patches. Antifungals used for treating athlete’s foot are effective in combating this infection.

Tinea capitis (Ringworm of the scalp)
This fungal infection mainly affects school age children and occasionally adults. The fungi live on hair and keratin of the scalp. Circular, erythematous, scaly or pustular patches are apparent, and the hair becomes loose and breaks off leaving behind a hairless lesion. The
causative fungi are M. andouini, M. canis, and T. tonsurans. The infection usually disappears at puberty, presumably due to the increased acidic sebaceous secretions that arise at this time. Treatment includes the use of griseofulvin, terbinafine, and fluconazole.

**Tinea unguium (Ringworm of nails)**

Also known as onychomycosis, ringworm of the nails is a chronic fungal infection characterized by inflammation of the skin folds surrounding the nail. The nail becomes thick, grooved, pitted and discolored. Toenails are usually the most common site. It is caused by *T. rubrum, E. floccosum, T. mentagrophytea and T. unguium*. The infection is very resistant to topicals. Systemic treatment with antifungals such as clotrimazole and terbinafine may be more effective.

**Tinea versicolor (Pityriasis versicolor)**

Tinea versicolor is a chronic fungal infection that causes mild to minimal symptoms. It is mainly a cosmetic concern. It appears as whitish to yellowish circular sots, especially in summertime when the skin becomes tanned. It mainly affects the upper trunk, chest, and shoulders. The causative organism is *Malassezia furfur*. Selenium sulfide, microconazole and clotrimazole are used in treating this infection.

**Summary**

Superficial cutaneous fungal infections are common worldwide. The upper layer of the skin is normally affected by these conditions which are caused mostly by *Trichophyton, Epidermatophytes and Microsporum*. These fungi live on dead body tissue such as keratin of the nails, skin and hair, as well as animal remains. The most commonly encountered cutaneous fungal diseases include athlete’s foot, ringworm of the body, ringworm of the scalp, ringworm of the nails and tinea versicolor. These are treated by a variety of effective and safe antifungals such as the polyenes, azoles, and allylamines, along with miscellaneous products that include tolnaftate, haloprogin, ciclopirox, and undecylenic acid and its salts. Many of these medications are available without prescriptions. In severe cases, systemic administration of antifungals may be required. This entire treatment area is important because it provides endless important information that we as pharmacists can share with patients.

**References**

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Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. **Does the program meet the learning objectives?**
   Differentiate between the parts of the skin  
   YES  NO
   List the most common superficial fungal infections  
   YES  NO
   Describe the signs & symptoms of these conditions  
   YES  NO
   State the three stages in which fungal infections occur  
   YES  NO
   List the types of antifungal medications & their adverse effects  
   YES  NO

2. **Was the program independent & non-commercial**
   YES  NO

3. **Relevance of topic**
   Low Relevance 2 3 4 5 6 7

4. **What did you like most about this lesson?**
   ___________________________________________

5. **What did you like least about this lesson?**
   ___________________________________________

**Please Mark the Correct Answer(s)**

1. **Infection of the nails is which stage of superficial fungal infections.**
   A. Acute  
   B. Peripheral  
   C. Subacute  
   D. Chronic

2. **Stratified squamous epithelium makes up the:**
   A. Dermis  
   B. Subcutaneous tissue  
   C. Peridermis  
   D. Epidermis

3. **Factors that assist in choosing a topical or systemic antifungal include:**
   A. Immunity status  
   B. Causative fungus  
   C. Magnitude of the infection  
   D. All of these

4. **Naftidine acts as a fungistatic against dermatophytes, and as a fungicide against Candida.**
   A. True  
   B. False

5. **Clinically effective azoles include:**
   A. Ketoconazole  
   B. Nystatin  
   C. Signazole  
   D. Tolnaftate

6. **Why should ketoconazole NOT be given with cimetidine?**
   A. Increase in pH  
   B. Decreased absorption of ketoconazole  
   C. Reduced acidity of gastric fluid  
   D. All of these

7. **Which of these polyenes may be used topically & systemically?**
   A. Nystatin  
   B. Ketoconazole  
   C. Naftidine  
   D. Cremalene

8. **Which of these is used mainly for treating fungal infections of the finger nails & toe nails?**
   A. Amphotericin  
   B. Amoxicillin  
   C. Amorolfine  
   D. Perdaniazole

9. **Echinocandins inhibit synthesis of:**
   A. Lanaberase  
   B. Keratase  
   C. Cellulite  
   D. Glucan

10. **Antifungal effectiveness is increased in a basic medium.**
    A. True  
    B. False
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