



Secundum Artem

Current & Practical Compounding
Information for the Pharmacist.

COMPOUNDING FOR SUPERFICIAL FUNGAL INFECTIONS

GOALS AND OBJECTIVES

Goal: To provide information on the drugs and dosage forms used in the treatment of superficial fungal infections, including athlete's foot, jock itch, ringworm and nail infections.

Objectives: Objectives: After reading and studying the article, the reader will be able to:

1. Describe the characteristics of athlete's foot, ringworm (body and scalp), jock itch and nail infections.
2. List the antifungal agents used in the treatment of superficial fungal infections.
3. Explain the different dosage forms used in the treatment of superficial fungal infections.
4. Discuss various formulations used in the treatment of athlete's foot, jock itch, ringworm and nail infections.

INTRODUCTION

Compounding for superficial fungal infections may be required when multiple agents are needed for specific individuals, the patient is allergic or sensitive to ingredients in commercial preparations, the concentration of the commercial products is not appropriate, a product is in short supply or has been discontinued, or an alternative dosage form is needed. Compounding pharmacists have a great opportunity in working with family medicine physicians and dermatologists in the treatment and prevention of superficial fungal infections.

Fungal infections (dermatomycoses) are among the most common cutaneous disorders, affecting as many as 10 to 20% of the population of the United States. They are relatively minor infections that are a significant part of modern day society. Mycotic infections of the skin are generally categorized as either superficial or deep. Many skin and nail disorders have characteristic lesions that become evident upon a complete examination of the entire skin sur-

face, including the nails, scalp, palms, soles and mucous membranes in bright light. The most prevalent dermatomycosis is tinea pedis (athlete's foot), followed by tinea corporis (body ringworm), tinea cruris (jock itch), tinea capitis (scalp ringworm) and then other types of tinea, including onychomycosis (Tinea unguium or nail infections).

Fungal infections generally prefer environments of high temperature and high humidity; therefore, they generally occur most frequently in tropical and subtropical areas. Pathogens generally responsible for the various superficial fungal infections include *Trichophyton*, *Microsporum* and *Epidermophyton*, and occasionally, *Candida*.

SYMPTOMS AND DESCRIPTION

Athlete's foot may present as (1) macerated, boggy, whitened, odorous and itching skin between the toes, (2) an acute vesicular inflamed and fissuring condition also accompanied by odor and itching, or (3) a

fine scale over the bottom part of the foot (moccasin-type tinea pedis); each form may become more symptomatic during the summer months. Because of the emphasis on personal health and exercise, fungal infections of the feet have become quite common and are easily transmitted from person to person if proper precautions are not observed. Such precautions could include keeping the feet clean and dry, drying the feet thoroughly after bathing or showering, using thongs when using public showers (sports clubs, workout gyms, etc), not sharing footwear and treating the infection when it first appears. Some individuals appear to be more susceptible than others. The causative agent in most athlete's foot infections is the trichophyton species. Upon initial contact, patients commonly complain of, or present with, itching, burning or stinging symptoms involving the feet.

Body ringworm occurs over the body (excluding the scalp, hands, feet, groin, ears and face) and appears typically as an oval, scaly patch with an inflamed border. The skin in the center of the lesion actually appears normal. Ringworm lesions are most often on the exposed areas of the body, such as the face and arms. Generally, a history of exposure to an infected cat is often involved, usually indicating a microsporum infection. The most common pathogens include *Trichophyton rubrum*. Symptoms may include itching and a classic ring-shaped lesion that may have an advancing scaly border and central clearing, occasionally with hyperpigmentation. These rings spread peripherally and the borders may contain vesicles or pustules. Common methods of preventing body ringworm include washing and drying the body with different cloths/towels than those used for the feet, not playing with strange cats or dogs, avoiding contact with affected individuals, losing weight to minimize areas of intertriginous rubbing/chafing and drying thoroughly after bathing.

Jock itch affects the groin area with sharply defined lesions with inflamed borders and reddish-brown centers. The itching becomes very intense and can become painful, if sweating accumulates further macerating the skin. It can be irritated with tight-fitting undergarments. Preventive methods include losing weight to minimize intertriginous skin folds, avoiding sexual contact with one that has jock itch, wearing undergarments that minimize moisture accumulation, and washing and drying the groin area with different cloths/towels than those used on the feet.

Scalp ringworm usually presents as a circular patch of scaly skin accompanied by a limited area of alopecia. Patients may appear with (1) scaly, dry, noninflammatory dermatosis with other patchy areas of

involvement, (2) active, inflamed weeping lesions, or (3) cup-shaped crusts around several hairs that expand to involve the entire scalp. Household animals can transmit fungal infections to occupants in a house, as in the case of ringworm infections. Preventive steps can include avoiding touching the scalp if a tinea infection is present elsewhere on the body, avoiding contact with cats and dogs, not sharing headwear (caps, hats), observing proper scalp hygiene and not using the same cloth or towel on the head as that used in an area of the body with a tinea infection.

Onychomycosis (Tinea unguium, nail infections) changes the appearance of the nails from normal and shiny to that of being dull, opaque and yellowing; they also become thickened, brittle and crumble. Onychomycosis is a trichophyton infection of one or more (but rarely all) fingernails or toenails. Generally, the most commonly found microorganism is *Trichophyton rubrum*. The nails become lusterless, brittle and hypertrophic; the substance of the nail becomes friable. Patients may become embarrassed because the nails may become thick and unsightly due to a buildup of byproducts from fungal growth. Nail infections are very difficult to treat because access to the causative microorganism is limited, nail growth is slow and a long duration of therapy is usually required. Fingernail involvement generally responds more rapidly than toenail involvement. In many cases, avulsion of the nail is required either surgically or chemically. Urea 40% topical preparations are commonly used for this procedure. Onychomycosis can be avoided or minimized by following the same preventative steps as those outlined above in tinea pedis.

TREATMENT OF FUNGAL INFECTIONS

Outcomes of successful treatment can be aimed at symptomatic relief, eradicating the infection and preventing future infections.

Athlete's foot can be treated using either local or systemic measures. Local measures may include, during the macerated stage, treatment with aluminum subacetate solution, topical imidazoles or ciclopirox, terbinafine or butenafine; during the "dry and scaly stage", the addition of urea 10% preparations under an occlusive dressing may enhance the efficacy of the topical treatments. Table 1 lists usual concentrations of locally applied antifungal agents. Systemic measures may include itraconazole or terbinafine; griseofulvin should only be used in severe cases.

Ringworm (body and scalp, including jock itch)

treatment can include local and systemic measures. Locally, miconazole, clotrimazole, ketoconazole, econazole, sulconazole, oxiconazole, ciclopirox, and terbinafine have been used. Systemic measures have included orally administered griseofulvin, itraconazole and terbinafine.

Onychomycosis can be treated either locally or systemically, but local treatment has relatively low efficacy (10% or less). If the involvement is minimal and if the patient is motivated, local (topical) treatment may be effective. Another approach is to use a 40% urea topical preparation for nail avulsion, prior to beginning treatment with an antifungal agent. In some cases, the antifungal treatment may begin after a few weeks of urea 40% treatment. The 40% urea will soften the nail and enable it to be removed over a period of time. Also, surgical or mechanical removal of the nail can be used. Drugs commonly used include ciclopirox and naftifine. Systemic treatment may involve griseofulvin, itraconazole, terbinafine and ketoconazole. In some cases, local and systemic treatment have been combined. Table 2 lists some commonly prescribed oral antifungals used to treat superficial fungal infections.

DOSAGE FORMS USED AND THEIR APPLICATION

Numerous dosage forms are used in the topical treatment of these superficial fungal infections, including creams, liquids, gels, ointments, lacquers and others. The treatment of athlete's foot and ringworm can easily be accomplished with creams, liquids gels and ointments. Water-soluble ointment vehicles tend to be used because they will not necessarily induce sweating and contribute to maceration of the skin in the affected area. An example is Polyethylene Glycol Ointment USP. Also, this vehicle is easily removed with washing. After application, a dressing can be applied to prevent the applied medication from being mechanically removed. Occlusive dressings may also be applied. As a preventive in athlete's foot, an antifungal powder can be used. If required, an antifungal agent can be mixed, generally at about a 1% concentration, in an absorbent powder such as talc or cornstarch, or a blend of the two, and dusted in the shoes or socks.

Treatment of nail infections is somewhat more difficult. The causative agent is actually residing beneath the nail and access is limited. Nail softening agents, such as salicylic acid and urea, have been used to assist in chemical debridement of the hypertrophic nail, generally in a cream or a gel vehicle. In some

cases, the antifungal agent may be applied simultaneously with the softening agent, or it can be applied after the nail has been removed. Generally, occlusive dressings are employed in this method of treatment. This may be in the form of a plastic wrap, a bandage, or the tip of a latex glove that has been cut off to the proper size. It is common practice to protect the healthy tissue using a barrier of white petrolatum. In any case, nail infections require months of treatment (approximately up to about 6 months for fingernails and up to a year or more for toenails).

MECHANISMS OF ACTION OF THE ANTI-FUNGAL AGENTS

Butenafine presumably exerts its activity by altering cellular membranes, resulting in increased membrane permeability and growth inhibition. Clotrimazole apparently binds to phospholipids in the fungal cell membrane altering cell wall permeability, resulting in loss of essential intracellular elements. Ciclopirox acts by inhibiting transport of essential elements in the fungal cell, causing problems in RNA, DNA and protein synthesis. Econazole alters fungal cell wall membrane permeability and may interfere with RNA and protein synthesis as well as lipid metabolism. Ketoconazole alters the cell wall permeability, inhibits biosynthesis of triglycerides and phospholipids and inhibits several fungal enzymes. Miconazole inhibits biosynthesis of ergosterol, damaging the fungal cell wall membrane; this increases membrane permeability resulting in leakage of the nutrients from the cell. Naftifine selectively inhibits the enzyme squalene epoxidase in a dose-dependent manner, resulting in the primary sterol, ergosterol, with the fungal membrane not being synthesized. Oxiconazole destroys the cytoplasmic membrane integrity by inhibition of ergosterol synthesis. Sulconazole interferes with microbial folic acid synthesis and growth by inhibiting para-aminobenzoic acid metabolism. Terbinafine inhibits squalene epoxidase, which is a key enzyme in sterol biosynthesis in fungi, resulting in an ergosterol deficiency and cell death. Tolnaftate distorts the hyphae and stunts mycelial growth in fungi that are susceptible to its effects.

PENETRATION ENHANCING VEHICLES FOR TRANSPORTING THE ANTI-FUNGAL AGENTS

Antifungals are commonly incorporated in various dosage forms containing different solvent systems for delivery vehicles. Penetration enhancers that may be a part of a dosage form include propylene glycol, glycerin, isopropyl myristate, dimethyl sulfoxide, polyethylene glycol 300, alcohol (ethyl and isopropyl)

and others. Flexible collodion can assist in enhancing efficacy by prolonging contact time of the antifungal agent with the affected area. Upon evaporation of the solvent system in flexible collodion, the active agent is kept in direct and prolonged contact with the skin within the "plastic" film.

COMPOUNDED FORMULAS FOR FUNGAL INFECTIONS

RX BENZOIC ACID AND SALICYLIC ACID OINTMENT (WHITFIELDS OINTMENT)

Benzoic acid	6 g
Salicylic acid	3 g
Polyethylene glycol ointment	91 g

Pulverize the benzoic acid and salicylic acid powders to a fine, uniform particle size. Melt the polyethylene glycol ointment using low heat. Remove the ointment from heat and incorporate the finely divided powder and mix well.

RX BENZOIC ACID AND SALICYLIC ACID OINTMENT, DOUBLE STRENGTH (WHITFIELDS OINTMENT, DOUBLE STRENGTH)

Benzoic acid	12 g
Salicylic acid	6 g
Polyethylene glycol ointment	82 g

Pulverize the benzoic acid and salicylic acid powders to a fine, uniform particle size. Melt the polyethylene glycol ointment using low heat. Remove the ointment from heat and incorporate the finely divided powder and mix well.

RX CICLOPIROX 8% TOPICAL GEL

Ciclopirox olamine	10.4 g
Sodium laureth sulfate	0.5 g
Hydroxypropyl cellulose 1% Gel	qs 100 g

To about 85 g of hydroxypropyl cellulose 1% gel, dissolve the ciclopirox olamine followed by the sodium laureth sulfate and mix well. Add sufficient hydroxypropyl cellulose 1% gel to volume and mix well.

RX FLUCONAZOLE IN DMSO TOPICAL LIQUID

Fluconazole	150 mg
Dimethyl sulfoxide	qs 15 mL

Dissolve the fluconazole in the dimethyl sulfoxide and mix well.

RX FLUCONAZOLE 10% TOPICAL CREAM

Fluconazole	10 g
Glycerin	15 mL
Dermabase™	qs 100 g

Mix the fluconazole with the glycerin to form a smooth paste. Incorporate into the Dermabase and mix well.

RX ITRACONAZOLE IN DMSO NAIL LIQUID

Itraconazole	100 mg
Dimethyl sulfoxide	qs 100 mL

Dissolve the itraconazole in the dimethyl sulfoxide and mix well.

RX IODOCHLORHYDROXYQUIN 3% OINTMENT

Iodochlorhydroxyquin	3 g
Castor oil	0.5 mL
White petrolatum	qs 100 mL

Make a smooth paste with the iodochlorhydroxyquin and a small amount of the white petrolatum that has been warmed. Add sufficient white petrolatum to total weight and mix well.

RX IODOCHLORHYDROXYQUIN 3% CREAM

Iodochlorhydroxyquin	3 g
Propylene glycol	1 mL
Dermabase™	qs 100 g

Make a smooth paste of the iodochlorhydroxyquin and the propylene glycol. Geometrically, incorporate the paste into the Dermabase and mix until uniform.

RX KETOCONAZOLE 1% TOPICAL SOLUTION

Ketoconazole	1 g
Dimethyl sulfoxide	5 mL
Polyethylene glycol 300	qs 100 mL

Mix the ketoconazole with the dimethyl sulfoxide and about 50 mL of the polyethylene glycol 300. Add sufficient polyethylene glycol 300 to volume and mix well.

RX KETOCONAZOLE 1% AND SALICYLIC ACID 10% IN FLEXIBLE COLLODION

Ketoconazole	1 g
Salicylic acid	10 g
Flexible collodion	qs 100 g

Mix the ketoconazole and salicylic acid with sufficient flexible collodion to total weight and mix well.

RX MICONAZOLE 2% TOPICAL CREAM

Miconazole	2 g
Dermabase™	qs 100 g

Mix the miconazole with the glycerin to form a smooth paste. Add sufficient Dermabase to weight and mix well.

RX MICONAZOLE 2% AND TOLNAFTATE 1% TOPICAL LIQUID

Miconazole	2 g
Tolnaftate	1 g
Polyethylene glycol 300	qs 100 mL

Mix the miconazole and tolnaftate powders together. Add sufficient polyethylene glycol 300 to volume and mix well.

RX TOLNAFTATE 1% CREAM

Tolnaftate	1 g
Glycerin	5 ml
Dermabase™	qs 100 g

Mix the tolnaftate with the glycerin to form a smooth paste. Geometrically, incorporate the Dermabase and mix well.

RX TRIACETIN 25% OINTMENT

Triacetin	25 g
Polyethylene glycol 3300	25 g
Polyethylene glycol 300	50 mL

Using gentle heat, mix the polyethylene glycol 3300 and polyethylene glycol 300 together. Remove from heat, add the triacetin and mix well until congealed.

RX TRIACETIN 25% TOPICAL LIQUID

Triacetin	25 mL
Propylene glycol	10 mL
Acetone	5 mL
Chloroxylenol	2.5 g
Benzyl alcohol	2 mL
Acetic acid, glacial	1 mL
Cetylpyridinium chloride	500 mg
Isopropyl alcohol 99%	qs 100 mL

Dissolve the chloroxylenol in the acetone. Mix the triacetin, propylene glycol and acetic acid in about 50 mL of the isopropyl alcohol. Mix the two solutions together. Add sufficient isopropyl alcohol to volume and mix well.

RX UNDECYLENIC ACID TOPICAL LIQUID

Undecylenic acid	10 g
Alcohol 95%	qs 100 mL

Dissolve the undecylenic acid in sufficient alcohol to volume and mix well.

RX COMPOUND UNDECYLENIC ACID OINTMENT

Undecylenic acid	5 g
Zinc undecylenate	20 g
Polyethylene glycol ointment	75 g

Melt the polyethylene glycol ointment using low heat. Incorporate the undecylenic acid and zinc undecylenate and mix well while cooling.

TABLE 1. ANTIFUNGALS AND THEIR USUAL CONCENTRATIONS

Antifungal Agent	Usual Concentration	Chemical Class
Benzoic and Salicylic acid	6%/3%	Acid
Bifonazole	1%	Azole
Butenafine	1%	Benzylamine
Ciclopirox	0.77%-1%	Pyridinone derivative
Clotrimazole	1%	Azole
Econazole	1%	Azole
Isoconazole nitrate	1%	Azole
Ketoconazole	2%	Azole
Miconazole	2%	Azole
Naftifine	1%	Allylamine
Oxiconazole	1%	Azole
Sodium propionate	5%	Acid salt
Sulconazole	1%	Azole
Terbinafine	1%	Allylamine
Tioconazole	1%	Azole
Tolnaftate	1%	Thiocarbamate
Triacetin	25%	Acid-former
Undecylenic acid	1 to 10%	Acid

TABLE 2. COMMON ORALLY ADMINISTERED ANTIFUNGAL AGENTS FOR TREATING SUPERFICIAL SKIN INFECTIONS

Drug	Dosage
Griseofulvin, Ultramicrosized	250-500 mg twice daily
Itraconazole	200 mg daily
Terbinafine	250 mg daily