

ANTIFUNGAL DRUGS

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TREATMENTS OF FUNGAL INFECTIONS

Superficial Fungal Infections

Tinea versicolor

Dermatophytoses

Candidiasis

These fungal infections account for 15-20 % of skin diseases.

General Principles of Treatments

1. The anatomic area involved was a major factor in both diagnosis and therapy.

The character and quantity of the keratinized and cornified skin vary so greatly from one anatomic site to another.

2. A single species may produce very different signs and symptoms depending on the anatomic site infected.

In contrast, many different species produce similar changes in the same anatomic site.

3. The severity : Intensity of inflammation

 Degree of skin damage

The extent of the infection over the skin surface.

These are important variables that must be considered in therapy.

4. Duration of the fungal infection or the frequency of recurrence is influenced by

1) the character of the host response

2) the portion of the anatomy and integument infected

Host Response, Clinical Manifestations and Therapy in Dermatomycoses

Parameter	Cell-mediated immunity to the infecting fungi	
	Present and Intense	Absent or Compromised
Pathologic Presentation	Acute intense dermatitis Few fungi	Chronic dermatitis Abundant fungi
Symptoms and signs	Bright erythema, vesicles, pustules, oozing, weeping, tenderness	Mild erythema, scaling, hyperkeratosis, fissures, dryness, and pruritus
Typical response to therapy	Excellent	Poor, relapsing

5. Factors influencing selection of an antifungal drug

- 1) Antifungal sensitivity testing
- 2) Age, sex, habitus, occupation and general health
- 3) Compliance, cosmetic considerations, practicality for the particular individual
- 4) Concurrent therapy for other diseases, adverse effects the patient may have previously experienced from an antifungal drug
- 5) Cost of a course of therapy

Symptomatic Treatment

1. Nature of infection dictates what should be done

- 1) Acute, severely inflamed skin which is denuded and weeping responds to soothing compresses much more rapidly than to a specific antifungal agent
- 2) Keratolytic agents are of value in thick, chronic lesions

2. The anatomic location of the infected part

- 1) Strong, irritating topical medication should never be used on

Antifungal drugs and fungal infection for which they are primarily indicated

	Tinea versicolor	Dermato- phytes	Candida
Moderate potency			
Castellani's paint	+	+	+
Gentian violet	+	+	+
8-hydroxyquinoline		+	+
Selenium sulfide	+		
Sodium thiosulfate	+		
Thymol in chloroform		+	+
Fatty acids		+	
Whitfield's ointment	+	+	
Higher potency			
Amphotericin B			+
Clotrimazole	+	+	+
Haloprogin		+	
Miconazole	+	+	+
Nystatin			+
Tolnaftate		+	
Systemic agents			
Orally administered agents			
5-Fluorocytosine			+
Griseofulvin		+	
Ketoconazole	+	+	+
Intravenous agents			
Amphotericin B			+
Miconazole		+	+

delicate, sensitive skin such as the mouth, eyes, or eyelids

- 2) Formulation : An ointment is unacceptable on the scalp and a lotion is a poor choice for the foot
- 3) Lesions on the lower leg or foot almost always respond more slowly than lesions on the trunk or face

3. Evidence of bacterial infection necessitated local cleansing and possibly antibiotic coverage
4. Allergic manifestations, and its eruption, or a kerion celsi can usually be controlled with a short course of corticosteroids plus the appropriate antifungal agent

TINEA VERSICOLOR

General Recommendations

1. Use the topical agents for an adequate length of time
2. The topical treatment should be applied to the entire torso from the neck to the waist
3. The pigmentary changes resolve much more slowly (months)
4. In spite of seemingly adequate therapy, relapse or reinfection is common
5. Tinea versicolor does not respond to griseofulvin
6. Maintenance therapy : therapy is continued for 2 consecutive nights each month for 1 year.

Topical Treatment

1. Rx 20-25 % sodium thiosulfate solution

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salicylic acid 1 %

Alcohol 10 %

The agents should be applied to the lesion bid for several weeks.

2. Selenium sulfide suspension (Selsun)

It should be applied to the affected areas, allowed to dry, and then allowed to remain for 15 min for 7-14 consecutive days or alternate days for 2 weeks.

Irritating to the intertriginous skin.

3. Zinc Pyrithione

An antifungal and antibacterial agent incorporated into shampoos, is very effective against lipophilic yeasts such as *P. orbiculare*.

Shampoos containing this chemical could be applied 5 min nightly for 14 days.

4. Clotrimazole, miconazole, haloprogin, or tolnaftate

More expensive and not more effective than any of the foregoing.

5. Keratolytic creams, ointments, or lotions containing

3-6 % salicylic acid

3-6 % sulfur and salicylic acid ointment

3 % salicylic acid in 70 % alcohol,

applied overnight for 1-2 weeks.

6. Propylene glycol 50 % in water applied bid for 2 weeks

A slight burning sensation may occur.

7. Retinoic acid cream applied bid for 2 weeks.

It is more useful in those particularly embarrassed by the hyperpigmentation of infected skin.

Systemic Treatment

Ketoconazole 1 tablet (200 mg) before meal. once daily, for 3 weeks.

Maintenance therapy for recalcitrant infections : periodic monthly, one tablet 3 days per month.

DERMATOPHYTE INFECTIONS

(Dermatophytoses; Tinea; Ringworm)

General Principle

Humans may acquire dermatophyte infections from three sources :

1. Organisms that live in soil
2. Animal fungi
3. Pathogens that infect only humans and cannot survive elsewhere

All dermatophytes which are members of the genera *Microsporum*, *Epidermophyton* and *Trichophyton* grow only within the keratin layers of the epidermis, in nails and in hair.

Predisposing factors :

1. Poor nutrition and hygiene
2. A tropical climate
3. Debilitating diseases
4. Contact with infected animals, persons, or fomites

Clinical Types of Infection

1. Tinea capitis (Ringworm of the scalp)

Children upto puberty are more susceptible. Boys are infected more often than girls.

Patchy hair loss and broken hairs, inflammation and scaling are characteristic.

A kerion appears as a pustular folliculitis within an area of purulence and swelling. Scarring can result.

2. Tinea corporis (Infection of the nonhairy skin)

Children are most susceptible.

The typical lesions start as erythematous macules or papules that spread outward and develop into annular and arciform lesions with sharp, scaling or vesicular, advancing borders and healing centers.

3. Tinea cruris (Ringworm of the groin; jock itch)

Heat, friction, and maceration predispose to this infection.

The lesions affects both the groin and upper inner thigh symmetrically and often has a butterfly appearance with clearly defined, raised borders. Lesions often extend into the gluteal folds and onto the buttocks.

4. Tinea manuum (Tinea of the hands)

Mild erythema with hyperkeratosis and scaling, mainly over the palmar surfaces.

5. Tinea pedis (Tinea of the feet)

Tinea pedis may take several forms

- 1) Mild to severe interdigital scaling and maceration with fissures is the most common form
2. Widespread fine scaling in "moccasin-foot" distribution is very frequent. The scaling usually extends up onto the sides of the feet and lower heel, when it exhibits a characteristic clearly defined, fine polycyclic scaling border.
3. Vesicular or bullous erythema with large blisters.

6. Onychomycosis (Fungal infection of the nails)

Infection starts at the free margin or lateral borders of the nail as a white or yellow discoloration and progresses proximally.

The nail may become thickened, distorted, and crumbly, and may be lifted up by an accumulation of subungual keratin and debris.

Investigative Diagnosis

1. Microscopic identification of hyphae and spores in scales or hair.
2. Fungal culture
3. Examination of infected areas with long-wave ultraviolet light (Wood's lamp).

Prophylactic Measures

1. Intertriginous or interdigital areas should be dried thoroughly after bathing and a simple talcum powder or antifungal powder should be

applied then and each morning.

2. Footwears should fit well and be nonocclusive (leather shoes or sandals are best; avoid plastic footwear or sneakers).
3. Patients with hyperhidrosis should wear absorbent cotton socks and avoid synthetic fibers. Use antiperspirants.
4. Clothing and towels should be changed frequently and be well laundered in hot water.

Local Therapy

1. Acute, inflammatory lesions with blistering and oozing should be treated with intermittent (4-6 times a day) open wet compresses. Blisters should be decompressed but roofs left intact.
2. Most topical antifungal agents listed for dermatophytes have a high initial cure rate (80-90 %) but relapse or reinfection is very common. The solution or cream applied tid. will cause involution of most superficial scaling lesions within 1-3 weeks. Treatment should be continued for at least 4 weeks in order to decrease the relapse rate.
3. Overnight application of appropriate keratolytic agents, such as Keralyt gel (60 % propylene glycol in water, 6 % salicylic acid, 20 % ethyl alcohol) for 1-2 weeks, is effective for toe-web infection, presumably by removing the stratum corneum in which the fungi are growing.
4. Thick hyperkeratotic involvement, as on the palms or soles may require keratolytic agents which will cause softening and exfoliation of the skin.
 - 1) Apply Keralyt gel (or the like) under occlusion overnight or for 2-3 hours in the evening, and to use an antifungal agent at other times.
 - 2) 3 and 5 % sulfur and salicylic acid ointment, and half-or full-strength Whitfield's ointment may be applied bid. or alternated with an antifungal agent.
5. Interdigital tinea pedis in its more severe macerated form is associated with an enormous overgrowth of aerobic bacteria. 30 % aluminium chloride hexahydrate applied bid. for 7-10 days will:

- 1) produce resolution of odor, itching, and maceration
- 2) dry the web space and kill bacteria

6. Topical treatment of the nails will rarely, if ever, result in total cure of onychomycosis.

1) 40 % urea ointment may be employed as a painless technique for avulsing symptomatic dystrophic nails. The ointment facilitates treatment with antifungal solutions.

2) Surgical avulsion of the toenails, concomitant with systemic griseofulvin therapy, is often the only treatment that will clear toenail onychomycosis.

3) Local application of clotrimazole, miconazole, tolnaftate or haloprogin solutions may be helpful occasionally.

Griseofulvin

It is only effective against all dermatophyte fungi.

1. Tinea pedis

Microsized griseofulvin 1.0 gm every day for 3 months. Within the next 3 months the final cure rate should be about 70 %.

Clotrimazole used alone would yield a final "cure" rate of 18 % and there appears to be no advantage to using the two drugs simultaneously.

For *intertriginous tinea pedis* combined griseofulvin-clotrimazole treatment would be expected to yield about a 90 % 3-month "cure" with a final rate of 80 % after 3 subsequent months without treatment.

Griseofulvin alone or clotrimazole are less effective.

2. Infection of nonhairy skin

Usually responds to the use of griseofulvin, but it is needed only for *extensive, recalcitrant, or recurrent* lesions.

Use microsized griseofulvin 1 gm every day for 3-4 weeks.

Avoid terminating therapy until there is definite evidence of a cure, *complete clearing of lesions, negative fungal scrapings, and a negative culture.*

3. Tinea capitis

Use 0.5-1.0 gm microsized griseofulvin every day for a period of 6-8 weeks. Approximately 20 mg/kg of body weight for children.

Patients should be treated for 2 weeks beyond the time that Wood's light or KOH preparations are negative.

Trichophyton tonsurans infection require longer treatment than *M. canis* and *M. audouini* infections.

Local antifungal remedies add little to the results obtained from griseofulvin alone.

4. Onychomycosis

Relapse is common.

Fingernails respond more readily than toenails.

Infection of the first toenail responds hardly at all unless the nail is first removed.

The starting dose of microsized griseofulvin should be 1.5-3.0 gm every day for the first month, with gradual lessening of the dose to 1 gm every day.

Duration of therapy

- for fingernails 6-9 months
- for toenails 9-18 months

Local therapy adds little.

Side effects at these higher drug levels are most commonly headache, mild G.I. discomfort, and photosensitivity.

Ketoconazole (Nizoral)

A new broad-spectrum oral imidazole antifungal agent, is an effective and safe treatment for recalcitrant and chronic dermatophytosis as well as other cutaneous and systemic fungal infections.

The cure rate for ketoconazole was 83 % with a relatively low relapse rate.

One 200-mg tablet is taken once daily at the beginning of a meal. Initial improvement takes place in one week.

CANDIDIASIS

The yeastlike fungus *Candida albicans* can normally be found on mucous membranes, skin, in the gastrointestinal tract, and in the vaginal vault.

Factors that predispose to infection include

1. A local environment of moisture, warmth, maceration, and/or occlusion.
2. The systemic administration of antibiotics, corticosteroids, or birth control pills.
3. Pregnancy
4. Diabetes
5. Cushing's disease
6. Debilitated states
7. Reduction of immune reactivity to *Candida*
 - in infants upto 6 months of age
 - in patients with certain neoplastic diseases of the blood and reticuloendothelial systems
 - in patients on immunosuppressive therapy

Clinical pattern

1. Paronychia and onychia

Rounding and lifting of the posterior nail fold and erythema and swelling of the distal digit (usually without overt purulence).

The nail becomes ridged and may have a green or brown discolouration.

C. albicans can activate complement and induce epidermal neutrophilic microabscesses in acute infections.

2. Intertrigo

Intertriginous lesions (inframammary, axillary, groin, perianal, interdigital) are moist and red, with occasional scaling, and are often macerated in the folds.

Well-defined, peeling borders surrounded by satellite erythematous papules or pustules are characteristic of *Candida* infections.

3. Thrush

White plaques loosely attached to oral or vaginal mucous membranes. The underlying mucosa is bright red and moist.

Lesions start as pinpoint spots and may extend to the corners of the mouth or into the esophagus.

4. Perleche

A cracked and fissured erythematous and moist area in the corners of mouth.

5. Vulvovaginitis

Vulvar erythema and edema, vaginal discharge, and white plaque.

Therapy

1. Paronychia

1) All wet work must be stopped. Gloves and cotton liners must be worn to protect the hands.

2) Apply imidazole compounds cream or solution, or nystatin cream to nail folds frequently.

If there is associated pain or edema, a steroid-imidazole or steroid-nystatin cream or ointment are used.

If paronychia is severe, oral nystatin 500,000 units PO 3-4 times a day, and imidazole compounds under occlusion, is often helpful.

3) Amphotericin B lotion or cream or 1 % alcoholic solution of gentian violet may also be of value.

Do not use amphotericin B along with imidazole agents as their effects may counteract each other.

4) The use of 2-4 % thymol in chloroform (or absolute alcohol) applied 2-3 times a day, often works in those who cannot stop wet work.

2. Intertrigo

1) Conditions leading to moisture and maceration must be eliminated or countered.

2) If lesions are inflammatory, compress 3-4 times a day with water

or Burow's solution to cool and soothe as well as to remove the irritant endotoxin substance.

3) After compresses and thorough drying, apply one of the topical antifungal agents given for paronychia to affected areas.

4) Gentian violet 1-2 % or Castellani's paint (fuchsin, phenol, resorcinol).

3. Thrush

1) Nystatin oral suspension 4-6 ml (400,000-600,000 units) qid. should be held in the mouth for several minutes before swallowing (2 ml for infants).

2) Gentian violet solution 1-2 %.

4. Vulvovaginitis

1) Cotrimazole or miconazole vaginal tablet or cream should be inserted intravaginally once daily for 7 days.

2) Nystatin vaginal suppositories (100,000 units) twice daily for 7-14 days, then nightly for an additional 2-3 weeks.

3) In severe Candida vulvitis, addition of a topical corticosteroid for the first 3-4 days will speed resolution.

ANTIFUNGAL DRUGS

Griseofulvin

It was first isolated in the 1930s from *Penicillium griseofulvum* and later from *P. jancezewskii*.

It was first introduced to medicine in 1958.

The compound is practically insoluble in water.

The absorption of the drug is poor, and only low blood levels are achieved. Absorption may be increased :

1. with the use of the microsized and ultramicrosized forms. The latter has been found to almost double the bioavailability.

2. possibly when oral dosages are accompanied by a fatty meal.

The majority of the drug is excreted unchanged in the feces.

The drug is delivered to the skin

1. by disposition in the keratin-producing epidermal cells of the skin, hair and nails.

2. via sweat. Sweat evaporation concentrates the drug in the stratum corneum. With excessive sweating in hot, humid climates, the amount of griseofulvin in skin is likely to be reduced, and more of the drug should be taken.

Mode of Action

Griseofulvin resembles colchicine structurally.

It is taken up by the dermatophytes and bound to cellular lipids. It causes metaphase arrest in rapidly dividing cells by interfering with nuclear mitotic division through interaction with the microtubule spindle apparatus.

Clinical Uses

Griseofulvin, a fungistatic and fungicidal antibiotic, is effective against all dermatophyte fungi, but is of no value against bacteria, *Malassezia furfur* and *Candida albicans*.

Resistant and relatively resistant strains of dermatophytes have been found.

Griseofulvin has the following cure rates :

- Tinea capitis 93.1 %
- Tinea of the glabrous skin 64.8 %
- Tinea of the palms and soles 53.3 %
- Tinea of the fingernails 56.9 %
- Tinea of the toenails 16.7 %

Dosage and administration

Up to 2 gm microsized griseofulvin per day.

Length of treatment varies with the site, magnitude, and chronicity of the infection.

Failure of treatment may occur because of

1. inadequate dosage
2. poor compliance
3. inadequate absorption
4. microsomal enzyme inactivation
5. drug interaction
6. failure of griseofulvin to enter the site of infection or diminished activity within that site
7. infection with an organism not sensitive to griseofulvin (such as *T. rubrum*)

Contraindication

1. Acute intermittent porphyria
2. Hepatocellular failure

Adverse reactions

Headache, peripheral neuritis, lethargy, mental confusion, vertigo, blurred vision

Fatigue, syncope

Oral thrush, nausea, vomiting, epigastric distress, thirst, diarrhea, heartburn

Leukopenia, neutropenia

Albuminuria, cylindruria

Skin rashes, photosensitivity eruptions

Drug Interaction

1. Anticoagulation with sodium warfarin (Coumadin) is reduced with griseofulvin therapy, apparently because of induced microsomal enzymes (drug-metabolizing liver enzymes), that accelerate break down of warfarin-type anticoagulants.
2. Patients taking barbiturates absorb griseofulvin poorly. The poor absorption is an intraluminal effect of the two drugs interacting.

Ketoconazole

Ketoconazole is a dibasic water-soluble imidazole compound.

Its solubility is dependent on dissolution of the tablet in an acid stomach. Absorption is increased when the agent is taken just prior to a meal.

Ketoconazole does not appear to induce hepatic microsomal enzymes.

Mode of Action

Similar to the other imidazole compounds, the drug affects fungi by mechanisms involving increased membrane permeability, inhibition of uptake of precursors of RNA and DNA, and synthesis of oxidative and peroxidative enzymes.

Clinical uses

The drug is supplied as 200 mg tablet

The first truly broad-spectrum oral antifungal, against

- pityrosporum orbiculare (tinea versicolor)

- Dermatophytes

- Candida

- Systemically invasive fungi : Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis

The drug should be reserved for

1. extensive lesions
2. recalcitrant cases
3. resistant to other treatments
4. frequent relapses
5. questionable compliance

Dosage and administration

Ketoconazole, 200 mg tablet, is administered orally once daily (or twice daily in some exceptional cases), at a beginning of meal

The dose need not be modified for renal failure.

It penetrates poorly into the cerebrospinal fluid.

Adverse effects

Mild nausea and occasional vomiting

Rare reports of :

- rash, pruritus - gynecomastia
- hypoesthesia - photophobia

Abnormal liver function tests, hepatitis, and several cases of hepatic necrosis. Liver function tests should be monitored in patients on ketoconazole therapy.

Contraindications

- Hepatic failure
- History of viral hepatitis

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