ANTIFUNGAL AGENTS
Fungal infections fall into two well-defined groups: the **superficial** and the **deep-seated** mycoses. The **superficial** mycoses are the **most common** and are caused for the most part, by a homogeneous group of fungi, the **dermatophytes**.
These include the various forms of tinea, or ringworm, which are infections of the hair or hair follicles, the superficial infections of flat areas of hairless skin, and infections of the nails.

As a rule, these lesions are mild, superficial, and restricted.
The causative microbes are specialised with the unusual ability to **digest** keratin.

They are frequently **transmitted** from one host to another (e.g., **athlete’s foot**).

A species of yeast, **Candida**, also produces a dermatophyte like disease.
Systemic Mycoses

The deep-seated, systemic mycoses are common in some parts of the world and unknown in other geographical areas. These diseases have a heterogeneous etiology.

Diseases caused by the systemic organisms include histoplasmosis, sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, and paracoccidioidomycosis.
The causative agents for these diseases have **ability to adapt to the internal environment of their host**.

These organisms share a common route of infection. Fungal spores are inhaled into the lung, and a **mild, coldlike condition** may result. This may be the only symptom.
In most cases, disease is inapparent asymptomatic disease.

**Diagnosis**
detected by a **skin test** or other **immunological procedure**. (The immune system deals with these infections producing the giant cells that are common in **type IV hypersensitivities**)

**X-ray examination**
Opportunistic Fungal Infections

Because of overuse of antibacterial antibiotics, immunosuppressive agents, cytotoxins, irradiation, and steroids, a new category of systemic mycoses has become prominent.

This allows organisms of normally low inherent virulence to exploit the host.
Such infections include *systemic candidiasis*, *aspergillosis*, and *mucormycosis*.

Bacterial infections, fungal infections and viral infections also attack such patients. *Multiple infections* with various microorganisms are common.
Oral candidiasis is common in poorly nourished persons, in patients on immunosuppressive drugs, and in persons with acquired immunodeficiency syndrome (AIDS). Opportunists can grow in nearly every circumstance in which a patient’s immune system is compromised.
Cutaneous Infections (Dermatophytoses)

The most common types of human fungal disease are among the dermatophytoses. These are superficial infections of the keratinized epidermis and keratinized epidermal appendages (i.e., the hair and nails). The severity of an infection depends largely on the location of the lesion and the species of the fungus involved.
Though certain other fungi, notable *Candida* spp., produce clinically similar diseases, the ability of these organisms to invade the **cornified tissues of hair, skin and nails** is closely associated with, and dependent on their **common physiological characteristic**—metabolic use of the highly insoluble keratin.
The biochemical use of keratin is rare and is shared by the dermatophyte species of the family Gymnoascaceae, with only a few species of the family Onygenaceae, and certain tineae. In humans, the genera *Trichophyton* (notably *T. rubrum* [nails, beard, smooth skin], *T. tonsurans* [scalp, beard, nails], *T. violaceum* [scalp, skin nails], *T. mentagrophytes* [nails, nails, nails], *T....
*T. mentagrophytes* [commonest cause of athlete’s foot], *T. verrucosum* [scalp, beard], and *T. rubrum* [psoriasis-like lesions of smooth skin, infections of nails]), *Microsporum* (*M. gypseum* [scalp], *M. fulvum* [scalp, hairless skin], and *M. canis* [scalp, hairless skin]), and *Epidermophyton* (eczema) contain the most common dermatophytes. These organisms cause the conditions known as tinea (ringworm).
# Locations of the Common Types of Tinea (Ringworm)

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
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<tbody>
<tr>
<td>Tinea manuum</td>
<td>Hand</td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>Groin</td>
</tr>
<tr>
<td>Tinea sycosis</td>
<td>Beard</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td>Scalp</td>
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<tr>
<td>Tinea unguium</td>
<td>Nails</td>
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</tbody>
</table>
### Clinical Types of Fungal Infection

<table>
<thead>
<tr>
<th>Type</th>
<th>Disease State</th>
<th>Causative Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial infections</td>
<td>Tinea versicolor</td>
<td><em>Pityrosporum orbiculare</em></td>
</tr>
<tr>
<td></td>
<td>Piedra</td>
<td><em>Trichosporon cutaneum</em> <em>(white)</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Piedraea hortae</em> <em>(black)</em></td>
</tr>
<tr>
<td>Cutaneous infections</td>
<td>Ringworm of scalp, hairless skin, nails</td>
<td><em>Dermatophytes, Microsporum, Trichophyton, Epidermophyton</em></td>
</tr>
<tr>
<td></td>
<td>Candidosis of skin, mucous membranes, nails; sometimes generalized</td>
<td><em>Candida albicans and related forms</em></td>
</tr>
<tr>
<td>Subcutaneous infections</td>
<td>Chromomycosis</td>
<td><em>Fonsecaea and related forms</em></td>
</tr>
<tr>
<td></td>
<td>Mycotic mycetoma</td>
<td><em>Allescheria boydii, Madurella mycetoma, etc.</em></td>
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<tr>
<td></td>
<td>Entomophthoromycosis</td>
<td><em>Basidiobolus haptosporus, Conidiobolus coronatus</em></td>
</tr>
<tr>
<td>Systemic infections</td>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em></td>
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<tr>
<td></td>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em></td>
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<tr>
<td></td>
<td>Paracoccidioidomycosis</td>
<td><em>Paracoccidioides brasiiliensis</em></td>
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<tr>
<td></td>
<td>Coccidioidomycosis</td>
<td><em>Coccidioides immitis</em></td>
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<tr>
<td></td>
<td>Cryptococcosis</td>
<td><em>Cryptococcus neoformans</em></td>
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<tr>
<td></td>
<td>Sporotrichosis</td>
<td><em>Sporothrix schenckii</em></td>
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<tr>
<td></td>
<td>Aspergillosis</td>
<td><em>Aspergillus fumigates</em></td>
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<tr>
<td></td>
<td>Mucormycosis</td>
<td><em>Mucor spp., Absidia spp., Rhizopus spp.</em></td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis duboisii</td>
<td><em>Histoplasma capsulatum var. duboisii</em></td>
</tr>
</tbody>
</table>
Subcutaneous Fungal Infections

*Subcutaneous mycosis* refers to a group of fungal diseases in which both the skin and subcutaneous tissue are involved. They are primarily soil saprophytes of very low-grade virulence and invasive ability and in most human and animal infections, they gain access as a result of a trauma to the tissue.
Tissue Reactions of Fungal Disease

The tissue response of the host to the infecting fungus depends somewhat on various invasive organisms.

In dermatophyte infections, erythema is generally produced and is a result of the irritation of the tissues by the organism.
Sometimes, severe inflammation, followed by scar tissue and keloid formation, occurs.

This results from an exaggerated inflammatory response and an allergic reaction to the organism and its products.
Topical Agents for Dermatophytoses

The skin is a barrier to drug penetration, and many of the topical agents work best if an adjuvant is added that opens the barrier function of the skin.

Keratolytic agents such as salicylic acid or other hydroxy compounds perform this function.
Adults have an **acidic, fatty substance** in and on the skin called **sebum**. Sebum functions as a **natural antifungal agent**, part of the **innate immune system**.
Fatty acids have been used for years with the idea that if a **substance similar to sebum** could be applied to the infected area, the effect of the sebum would be augmented and fungi could be eradicated. The application of fatty acids or their salts does in fact have an antifungal effect, albeit a feeble one.
Propionic Acid

Propionic acid is an antifungal agent that is nonirritating and nontoxic. After application, it is present in perspiration in low concentration (0.01%). Salt forms with sodium, potassium, calcium, and ammonium are also fungicidal.
Propionic has a **characteristic odour**. It is soluble in water and alcohol. The salts are usually used because they are **nonvolatile and odourless**.
Zinc Propionate

Zinc propionate occurs as an **anhydrous form** and as a **monohydrate**. It is very soluble in **water** but only sparingly soluble in **alcohol**.
The salt is unstable to moisture, forming zinc hydroxide and propionic acid. Zinc propionate is used as a fungicide, particularly on adhesive tape.
Sodium Caprylate

Sodium caprylate is prepared from caprylic acid, which is a component of coconut and palm oils. The salt precipitates as cream-colored granules that are soluble in water and sparingly soluble in alcohol.
Sodium caprylate is used **topically** to treat **superficial dermatomycoses** caused by *C. albicans* and *Trichophyton, Microsporum*, and *Epidermophyton* spp. The sodium salt can be purchased in solution, powder and ointment forms.
Undecylenic Acid

10-Undecenoic acid (Desenex, Cruex) obtained from the destructive distillation of castor oil. It is almost completely insoluble in water but is soluble in alcohol and most organic solvents.

Undecylenic acid is one of the better fatty acids for use as a fungicide, although cure rates are low.
It can be used in concentrations up to 10% in solutions, ointments, powders and emulsions for topical administration.

The preparation should never be applied to mucous membranes because it is a severe irritant. Undecylenic acid has been one of the agents traditionally used for athlete’s foot (*tinea pedis*).
Triacetin

Glyceryl triacetate (Enzactin, Fungacetin) is a colorless, oily liquid with a slight odor and a bitter taste. The compound is soluble in water and miscible with alcohol and most organic solvents.
The activity of triacetin is a result of the *acetic acid* released by *hydrolysis* of the compound by *esterases* present in the skin. Acid release is a self-limiting process because the *esterases* are inhibited below pH 4.
Salicylic Acid

Salicylic acid is a strong aromatic acid (pKa 2.5) with both antiseptic and keratolytic properties. Salicylic acid is only slightly soluble in water but is soluble in most organic solvents.
The **greater acidity** of salicylic acid and its **lower solubility** in water compared with \( p \)-hydroxybenzoic acid are the consequence of **intramolecular hydrogen bonding**.

Salicylic acid is used externally in ointments and solutions for its **antifungal** and **keratolytic** properties. By itself, salicylic acid is a poor antifungal agent.
Resorcinol

*m*-Hydroxyphenol (resorcinol) possesses **antiseptic** and **keratolytic** activity. It occurs as white, needlelike crystals and has a slightly sweet taste. Resorcinol is **soluble in water, alcohols** and **organic solvents**.
Benzoic Acid

Benzoic acid possesses antifungal effects, but it cannot penetrate the outer layer of the skin in infected areas.

Therefore, benzoic acid when used as an antifungal agent must be admixed with a keratolytic agent. Suitable mixtures are benzoic acid and salicylic acid and benzoic acid and resorcinol.
An old preparation that is still in use is Whitfield’s Ointment, *USP*. This ointment contains benzoic acid, 6%, and salicylic acid, 6%, in a petrolatum base. The cure rates from preparations like these are low.
Several phenols and their derivatives possess topical antifungal properties for the treatment of tinea infections. Two phenolic compounds, **clioquinol** and **haloprogin**, are still official. A third agent, **ciclopirox olamine**, is not a phenol but has properties like those of phenols. All of these agents appear to **interfere with cell membrane integrity** and **function** in susceptible fungi.
Haloprogin (Halotex)

Is sparingly soluble in water and very soluble in ethanol. It is an ethereal derivative of a phenol. Haloprogin is used as a 1% cream for the treatment of superficial tinea infections.

Formulations of haloprogin should be protected from light because the compound is photosensitive. Haloprogin is available as a solution and a cream.
Haloprogin is probably not the first topical agent that should be recommended. Although the cure rates for topical fungal infections are relatively high, they come at a high price. The lesion typically worsens before it improves. **Inflammation** and **painful irritation** are common.
**Clioquinol** (Vioform)

Occurs as a spongy, light-sensitive, yellowish white powder that is insoluble in water. Vioform was initially used as a substitute for iodoform in the belief that it released iodine in the tissues.

It has been used as a powder for many skin conditions, such as atopic dermatitis, eczema, psoriasis, and impetigo.
A 3% ointment or cream has been used vaginally as a treatment for *Trichomonas vaginalis* vaginitis. The best use for Vioform is in the topical treatment of fungal infections such as **athlete’s foot** and **jock itch**. A combination with **hydrocortisone** (Vioform HC) is also available.
Ciclopirox Olamine (Loprox)

Is a broad-spectrum antifungal agent intended only for topical use. It is active against dermatophytes as well as pathogenic yeasts (\textit{C. albicans}).

Ciclopirox is considered an \textbf{agent of choice} in the treatment of \textit{cutaneous candidiasis, tinea corporis, tinea cruris, tinea pedis, and tinea versicolor}. 
Loprox is formulated as a cream and a lotion, each containing 1% of the water-soluble ethanolamine salt. Ciclopirox is believed to act on cell membranes of susceptible fungi at low concentrations to block the transport of amino acids into the cells. At higher concentrations, membrane integrity is lost, and cellular constituents leak out.
thank you!