Topical Anti Fungal Drugs
DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

- **Squalene Epoxidase Inhibitors**
  - These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane.
  - Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

![Mode Of Action of Squalene Epoxidase Inhibitors][1]

[1]: image.png
1. **Terbinafine**: Oral *terbinafine* [TER-bin-a-feen] *is the drug of choice* for treating dermatophyte onychomycoses (fungal infections of nails).

- It is better tolerated, requires a shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin*. Therapy is prolonged (usually *about 3 months*) but considerably shorter than that with *griseofulvin*.

- *Oral terbinafine may also* be used for tinea capitis (infection of the scalp). Topical antifungals are ineffective.

- Topical *terbinafine* (1% cream, gel or solution) *is used to treat* tinea pedis, tinea corporis (ringworm), and tinea cruris (infection of the groin).

- Duration of treatment is usually *1 week*. 
Naftifine: [NAF-ti-feen]

- is active against Trichophyton, Microsporum, and Epidermophyton.
- Naftifine 1% cream and gel are used for topical treatment of tinea corporis, tinea cruris, and tinea pedis.
- Duration of treatment is usually 2 weeks.

Butenafine: [byoo-TEN-a-feen]

- is active against Trichophyton rubrum, Epidermophyton, and Malassezia.
- Like naftifine, butenafine 1% cream is used for topical treatment of tinea infections.
**Nystatin**

- **Nystatin** [nye-STAT-in] is a polyene antifungal, and its structure, chemistry, mechanism of action, and resistance profile resemble those of amphotericin B.
- It is used for the treatment of cutaneous and oral Candida infections.
- The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (acute infusion-related adverse effects and nephrotoxicity).
- It is administered as an oral agent (“swish and swallow” or “swish and spit”) for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.
- Adverse effects are rare after oral administration, but nausea and vomiting occasionally occur.
- Topical and vaginal forms may cause skin irritation.
Azole Antifungals

• Azole antifungals are made up of two different classes of drugs imidazoles and triazoles.

• Although these drugs have similar mechanisms of action and spectra of activity, their pharmacokinetics and therapeutic uses vary significantly.

• In general, imidazoles are given *topically* for cutaneous infections, whereas triazoles are given systemically for the treatment or prophylaxis of cutaneous and systemic fungal infections.

• The triazole antifungals include *fluconazole*, *itraconazole*, *posaconazole*, and *voriconazole*. 
Imidazoles

- As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida, and Malassezia, depending on the agent.

- The topical imidazoles have a variety of uses, including tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvovaginal candidiasis.

- Topical use is associated with contact dermatitis, vulvar irritation, and edema.

- Clotrimazole is also available as a troche (lozenge), and miconazole is available as a buccal tablet for the treatment of thrush.

- Oral ketoconazole has historically been used for the treatment of systemic fungal infections but is rarely used today due to the risk for severe liver injury, adrenal insufficiency, and adverse drug interactions.

- azole derivatives, which currently include:
  - Butoconazole [byoo-toe-kon-a-zole].
  - Clotrimazole [kloe-trim-a-zole].
  - Econazole [e-kone-a-zole].
  - Ketoconazole [kee-toe-kon-a-zole].
  - Miconazole [my-kon-a-zole].
  - Oxiconazole [oks-i-kon-a-zole].
  - Sertaconazole [serta- koe-na-zole].
  - Sulconazole [sul-kon-a-zole].
  - Terconazole [ter-kona-zole].
  - Tioconazole [tye-oh-KONE-a-zole].
Ciclopirox

• **Ciclopirox** [sye-kloe-PEER-oks] inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins.

• Ciclopirox is active against Trichophyton, Epidermophyton, Microsporum, Candida, and Malassezia.

• It is available in a number of formulations.

• **Ciclopirox 1% shampoo** is used for treatment of seborrheic dermatitis.

• Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the **0.77% cream, gel, or suspension.**
Tolnaftate

• **Tolnaftate** [*tole-NAF-tate*] distorts the hyphae and stunts mycelial growth in susceptible fungi.

• **Tolnaftate is active against** Epidermophyton, Microsporum, and Malassezia furfur.

• **Tolnaftate is not effective** against Candida.

• **Tolnaftate is used to treat** tinea pedis, tinea cruris, and tinea corporis.

• It is available as a 1% solution, cream, and powder.
Topical Antiviral Drugs
Topical Antiviral Drugs

• Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections.

• The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.
**Acyclovir**

- Acyclovir [ay-SYE-kloe-veer] (acycloguanosine) is the **prototypic antiherpetic** therapeutic agent.
- Herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to acyclovir.
- It is the treatment of choice in HSV encephalitis.
- The most common use of acyclovir is in therapy for genital herpes infections.
- It is also given prophylactically to seropositive patients before bone marrow transplant and post–heart transplant to protect such individuals from herpetic infection.
• **Acyclovir**, a guanosine analog, is monophosphorylated in the cell by the herpesvirus-encoded enzyme thymidine kinase.

• Therefore, virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cell kinases.

• Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA chain termination.
Penciclovir

- **Penciclovir** [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV.
- Penciclovir is only administered *topically*.
- It is monophosphorylated by viral *thymidine kinase*, and cellular enzymes form the nucleoside triphosphate, which *inhibits* HSV DNA polymerase.
Trifluridine

- Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog that is structurally similar to thymidine.

- Once converted to the triphosphate, the agent is believed to inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, lead to the synthesis of defective DNA that renders the virus unable to replicate.

- Trifluridine is active against HSV-1, HSV-2, and vaccinia virus.

- It is indicated for treatment of HSV kerato-conjunctivitis and recurrent epithelial keratitis.
Trifluridine

• Because the triphosphate form of trifluridine can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use.

• Therefore, the use of trifluridine is restricted to a topical ophthalmic preparation. A short half-life necessitates that the drug be applied frequently.

• Adverse effects include a transient irritation of the eye and palpebral (eyelid) edema.
Agents For Pigmentation Disorders
AGENTS FOR PIGMENTATION DISORDERS

Agents for pigmentation disorders include:

• **Hydroquinone**, which are used for the treatment of hyperpigmented skin conditions.
• **Methoxsalen** for the treatment of vitiligo.
A. Hydroquinone

**Hydroquinone** [HYE-droe-KWIN-one] is:

- Topical *skin* whitening agent that reduces hyperpigmentation associated with freckles and melasma.
- It is often used in combination with topical retinoids to treat the signs of photoaging.
- The mechanism of action of *hydroquinone* is inhibition of the *tyrosinase* enzyme required for melanin synthesis.
- Hydroquinone lightens the skin temporarily and is commonly used as a **4% preparation**.
- It should not be used in higher concentrations, or in excessive quantities for an extended duration, as it is associated with possible *carcinogenicity*.
- Local skin irritation is the most common adverse effect.
Monobenzone

- Monobenzone [mon-oh-BEN-zone], the benzyl ether of hydroquinone, is sometimes used to even out the skin discoloration associated with vitiligo (depigmentation disorder of the skin).

- The drug may cause permanent depigmentation and is no longer available in many markets.
Methoxsalen

- Methoxsalen \([\text{meth-OX-ah-len}]\) is a photoactive substance (psoralen) that stimulates melanocytes and is used as a repigmentation agent or patients with vitiligo.
- It must be photoactivated by UV radiation to form a DNA adduct inhibiting DNA replication by a method called PUVA (psoralen plus UVA radiation).
- Methoxsalen inhibits cell proliferation and promotes cell differentiation of epithelial cells.
- Topical methoxsalen may be used for small patches of vitiligo, and oral therapy is used for more widespread disease.
- Because of the possibilities for aging of the skin and possible carcinogenicity, it is used with caution.
Psoriasis

- Psoriasis is a skin disease that presents with erythematous scaling plaques.
- It manifests with increased epidermal cell proliferation.
- Psoriasis appears to have both genetic factors and T-cell–mediated immune components.
- The majority of patients have mild to moderate psoriasis, and this can be managed with topical treatments including retinoids, vitamin D analogues, keratolytic agents and corticosteroids.
- More severe cases require systemic therapy with phototherapy (methoxsalen followed by UVA or UVB alone), methotrexate, cyclosporine, or biologic response modifiers (for example, etanercept, adalimumab)
A. Retinoids

- **Tazarotene** is a *topical retinoid* used for the treatment of plaque psoriasis.
- Adverse effects are similar to other retinoids.
- **Acitretin** [*a-si-TRE-tin*] is a second-generation retinoid used orally in the treatment of pustular forms of psoriasis.
  - It is a metabolite of **etretinate** (no longer available), which has a half-life of 120 days.
  - Since ingestion of ethanol can increase transesterification of **acitretin to etretinate**, ethanol is contraindicated with this agent.
  - Like other retinoids, **acitretin** is *teratogenic* and women must avoid pregnancy for at least 3 years after the use of this drug (due to the long duration of teratogenic potential).
- Cheilitis, pruritus, peeling skin, and hyperlipidemia are common adverse effects.
B. Vitamin D analogues

- Calcipotriene \([\text{cal-sih-poh-TRY-een}]\) and calcitriol \([\text{kal-si-TRYE-ol}]\) are synthetic vitamin D3 derivatives used topically to treat plaque psoriasis.

- They inhibit keratinocyte proliferation and increase keratinocyte differentiation.

- Their therapeutic effectiveness does not appear to decrease upon continued use.

- Transient elevations in calcium levels have been reported in some patients.

- Adverse effects include itching, dryness, burning irritation, and erythema.
C. Keratolytic agents

- Keratolytic agents such as coal tar and salicylic acid are effective in localized psoriasis, especially on the scalp.
- They improve corticosteroid penetration.
- Coal tar inhibits excessive skin cell proliferation and may also have anti-inflammatory effects.
- Because it is cosmetically unappealing, coal tar may have a low acceptance rate among patients and, consequently, its use has been largely supplanted by the newer topical agents.
TOPICAL CORTICOSTEROIDS
TOPICAL CORTICOSTEROIDS

• Corticosteroids (glucocorticoids) have immunosuppressive and antiinflammatory properties.

• Topical corticosteroids are used for the treatment of psoriasis, eczema, contact dermatitis, and other skin conditions manifested by itching and inflammation.

• They are administered locally and via topical and intralesional routes.
- Corticosteroids work via intracellular receptors and initiate several transcriptions and translations leading to their multiple effects.
- The actions include inhibitory effects on the arachidonic acid cascade, depression of production of many cytokines, and effects on inflammatory cells.
- In psoriasis, they inhibit epidermal cell mitosis.
- Numerous topical corticosteroids are available, with varying potencies and multiple vehicles of delivery.
- Tachyphylaxis (decrease in response after repetitive use, tolerance) can occur with continuous use.
• Substitution of a different corticosteroid or less frequent use can minimize tolerance.

• Adverse effects include skin atrophy (thinning of the skin), striae, purpura, acneiform eruptions, dermatitis, local infections, and hypopigmentation.

• In children, potent agents applied to a large surface area can cause systemic toxicity, including depression of the hypothalamic–pituitary–adrenal axis and growth retardation.
# Potency of various topical corticosteroids

<table>
<thead>
<tr>
<th>LOW STRENGTH</th>
<th>INTERMEDIATE STRENGTH</th>
<th>HIGH STRENGTH</th>
<th>VERY HIGH STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alclometasone dipropionate 0.05% (c, o)</td>
<td>Betamethasone dipropionate 0.05% (c)</td>
<td>Acmicinonide 0.1% (c, l, o)</td>
<td>Betamethasone dipropionate 0.05% (o, g)</td>
</tr>
<tr>
<td>Clocortolone pivalate 0.1% (c)</td>
<td>Desonide 0.05% (c, l, o)</td>
<td>Betamethasone dipropionate, augmented 0.05% (c, l)</td>
<td>Clobetasol propionate 0.05% (c, g, o)</td>
</tr>
<tr>
<td>Fluocinolone acetonide 0.01% solution (s)</td>
<td>Desoximetasone 0.05% (c)</td>
<td>Desoximetasone 0.05% (o)</td>
<td>Diflorasone diacetate 0.05% (o)</td>
</tr>
<tr>
<td>Hydrocortisone base or acetate 0.25% to 2.5% (o, c)</td>
<td>Fluocinolone acetonide 0.025% (c, o)</td>
<td>Diflorasone diacetate 0.05% (o, c)</td>
<td>Fluocinonide 0.1% (c)</td>
</tr>
<tr>
<td>Triamcinolone acetonide 0.025% (c, l, o)</td>
<td>Flurandrenolide 0.025 to 0.5% (c, o)</td>
<td>Fluocinonide 0.05% (c, g, o, s)</td>
<td>Fluorandrenolide 0.05% (l)</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.005% to 0.05% (o, c)</td>
<td>Halcinonide 0.1% (c, o)</td>
<td>Halobetasol 0.05% (c, o)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone butyrate 0.1% (c, o, s)</td>
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<tr>
<td></td>
<td>Hydrocortisone valerate 0.2% (c, o)</td>
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<tr>
<td></td>
<td>Mometasone furoate 0.1% (c, o, l)</td>
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</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide 0.1% to 0.2% (c, o)</td>
<td></td>
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</tbody>
</table>
Trichogenic Agents

- **Minoxidil** [min-OX-i-dil] and **finasteride** [fih-NAH-steh-ride] are trichogenic agents that are indicated for the treatment of androgenic alopecia ("male pattern baldness").

- **Minoxidil**, *originally used as a systemic antihypertensive*, was noted to have the adverse effect of increased hair growth.

- This adverse effect was turned into a therapeutic application in the treatment of alopecia.

- For hair loss, the drug is available as a *nonprescription topical foam or solution*.

- As a *topical therapy*, it does not cause systemic hypotension.
• **Minoxidil** is effective at halting hair loss in both men and women and may produce hair growth in some patients.

• Although the mechanism of action is not fully known, it is believed to act, at least in part, by shortening the rest phase of the hair cycle.

• The drug must be used continuously to maintain effects on hair growth.
Finasteride

- **Finasteride** is an oral 5-α reductase inhibitor that blocks conversion of testosterone to the potent androgen 5-α dihydrotestosterone (DHT).
- High levels of DHT can cause the hair follicle to miniaturize and atrophy.
- Finasteride decreases scalp and serum DHT concentrations, thus inhibiting a key factor in the etiology of androgenic alopecia.
- Finasteride is used in higher doses for the treatment of benign prostatic hyperplasia.
- Adverse effects include decreased libido, decreased ejaculation, and erectile dysfunction.
- The drug should not be used or handled in pregnancy, as it can cause hypospadias in a male fetus.
- Like minoxidil, use must be continued to maintain therapeutic benefits.