Antifungals
Topical Antifungals

- Polyenes
- Azoles
- Allylamines/Benzylamines
- Hydroxypyridone (Ciclopirox)
- Selenium Sulfide
Polyenes

- Nystatin
- Amphotericin B

- Macrolide ring of carbons with multiple conjugated double bonds and closed by internal ester or lactose (hence the name polyene)
Nystatin

- Produced by Strep. noursei and albidus
- Water insoluble and not absorbed from intact skin, GI tract, or vagina
- Structure and mode similar to Amphotericin but only used topically because of systemic toxicity.
Nystatin

- Mechanism of Action (MOA)
  - Irreversibly binds to sterol of susceptible candidal species
  - Thereby changing the membrane permeability
  - And allowing leakage of essential intracellular components

- Fungistatic AND Fungicidal (in vitro)
Nystatin

- Clinical Indications (CI)
  - Candida
  - Ineffective for dermatophytes

- Formulations Available (FA)
  - Cream, ointment, and powder (BID application)
  - Suspension or Troche (4-5 times daily)
Nystatin

- Adverse Effects (AE’s)
  - All uncommon
  - Burning, pruritus, rash, eczema, pain, and Hypersensitivity reaction (v. rare)
Azoles

- MOA
  - Inhibits **Lanosterol 14-alpha demethylase** (CYP450 enzyme)
  - The azole nitrogen links to the heme Fe of the cytochrome (the site where oxygen binds)
  - Blocks the CYP450 catalysis of **lanosterol to ergosterol**
The Target

Cholesterol

Ergosterol
Azoles

- Skin is relatively impermeable to these compounds
- <1% absorption occurs, may increase to 4% on inflamed or damaged skin
- Fungistatic
Miconazole (Monistat-Derm, Micatin)

- **Action**
  - Penetrates S. corneum well, detectable up to 4 d. following single application
- **Spectrum**
  - T. rubrum, mentagrophytes, and E. floccusum; C. albicans, M. furfur; Gram positive Bacteria
Miconazole (Monistat-Derm, Micatin)

- CI
  - Tinea pedis, corporis, cruris
  - Tinea versicolor
  - Cutaneous candidiasis
- FA
  - Cream; BID dosing
Clotrimazole (Lotrimin, Fungoid, Mycelex Troches)

- **Spectrum**
  - Trichophyton, Epidermophyton, and Microsporum; Gram pos. Bacteria; Candida

- **CI**
  - T. pedis, corporis, cruris; TV; Cutaneous Candidiasis

- **FA**
  - Cream, Lotion, Solution (BID dosing)
  - Intravaginal tab (TID), Troches (4-5 X Qday)
Ketoconazole (Nizoral)

- **Action**
  - No systemic absorption (hence safe to use in infants)

- **Spectrum**
  - Broadly covers dermatophytes; C. albicans, and M. furfur

- **CI**
  - All previous plus Seborrheic Dermatitis

- **FA**
  - 2% cream; 1%, 2% shampoo
Oxiconazole (Oxistat)

- **Action**
  - Rapidly absorbed!
  - Systemic Absorption negligible
- **CI**
  - T. pedis
- **FA**
  - 1% cream, lotion (choice for large or hairy areas)
Econazole (Spectazole)

- **Action**
  - Readily found in epidermis down to mid dermis; systemic absorption low

- **Spectrum**
  - Most strains of Trichophyton, Microsporum, Epidermophyton; C. albicans, and M. furfur; Gram pos. and neg. Bacteria

- **CI**
  - Same as previous

- **FA**
  - 1% cream
Sulconazole (Exelderm)

- **Action**
  - Most systemically absorbedazole (8-11%)

- **Spectrum**
  - As previous (modest Gram pos. coverage)

- **CI**
  - Same as previous. Offers little advantage over previous meds

- **FA**
  - 1% cream, solution; use QD-BID for 2-4 weeks
Sertaconazole (Ertaczo)

- **Action**
  - Most lipophilic azole leading to greater reservoir effect in S. corneum
  - Second MOA-direct membrane damage of susceptible microbes
- **CI**
  - T. pedis
- **FA**
  - 2% cream
Allylamines/Benzylamines

- Naftifine
- Terbinafine
- Butenafine (Benzylamine)
Allylamines/Benzylalamines

- Inhibit *Squalene Epoxidase*, an earlier step in ergosterol synthesis
- CYP450 independent
- Fungicidal AND Fungistatic
The Target

Cholesterol

Ergosterol
Naftifine (Naftin)

- **Action**
  - Highly lipophilic, therefore penetrates S. corneum and hair follicles well

- **Spectrum**
  - Dermatophytes, yeast, and saprophytes (*T. megnagrophytes*)

- **FA**
  - Cream and gel, QD-BID
Terbinafine (Lamisil)

- **Action**
  - Highly lipophilic...reducing probability of reinfection
  - 10-100X more potent than naftifine in vitro
  - 3-5% systemically absorbed, peaks at 3-5 days

- **Spectrum**
  - Dermatophytes, molds, dimorphic fungi, and C. albicans

- **FA**
  - 1% cream, spray
Butenafine (Mentax)

- **Action**
  - Allylamine group replaced by a butylbenzene group
  - Interacts and fixes to cutaneous lipids—a great depot effect
  - Also acts by squalene epoxidase inhibition

- **Spectrum**
  - Dermatophytes, aspergillus, and dimorphic fungi
Ciclopirox Olamine (Loprox, Penlac) (Hydroxypyridone)

- **MOA**
  - Does **NOT** affect sterol synthesis
  - Blocks transport of macromolecular precursors disrupting cell membrane integrity and
  - **inhibits enzymes essential for the respiratory process** (think of the “OX” in Loprox)

- **Spectrum**
  - Dermatophytes, M. furfur, C. albicans, Pityrosporum; Gram pos. and neg bacteria
  - **Anti-Inflammatory** by inhibiting PGL’s and Leukotriene production by PMN’s
Ciclopirox Olamine (Loprox, Penlac) (Hydroxypyridone)

- **FA**
  - Cream, gel, shampoo, lotion, and nail lacquer

- **Penlac**
  - Penetrates nail plate
  - 40% cure rate
  - Requires prolonged daily use
  - $$$$$
Selenium Sulfide

- Cytostatic effect of cells of the epidermis and follicular epithelium.
- Results in decreased corneocyte adhesion and allows shedding of the fungus
- Pregnancy Class C (not studied)
The Big Picture

- Overall, allylamines are more potent that azoles.
- Butenafine=terbinafine>ciclopirox>naftifine>azoles
- Higher efficacy
  - Fungicidal activity
- Lower relapse rates
  - Lipophilicity
    - retained in the epidermis
Candidiasis

- Covered by azoles, allylamines, and hydroxypyridone
- Efficacy is not equal
- Ciclopinox > azoles >> butenafine > naftifine = terbinafine
Anti-Inflammatory Properties

- **Azoles**
  - Inhibits PMN chemotaxis
  - Inhibits calmodulin, integral in synthesis of PGL’s and release of histamine

- **Ketoconazole (and bifonazole)**
  - Inhibits 5-lipoxygenase...dec. 5-HETE and Leukotriene B₄
Anti-Inflammatory Properties

- **Naftifine**
  - Interferes with leukocyte pseudopod formation and therefore inhibits PMN chemotaxis
  - Impedes PMN production of Reactive Oxygen Species
  - Inhibits 5-lipoxygenase
Anti-Inflammatory Properties

- Ciclopirox
  - Inhibits 5-lipoxygenase and cyclooxygenase
Antibacterial Properties

- Serve as adjuvant where a dermatophytosis complex is present

- Never agents of choice for primary bacterial infections

- **Ciclopirox for Interdigital T. pedis**
Pregnancy

- Topical vulvar and IV multidose treatments with azoles for Vulvovaginal Candida

- Reduces risk of Preterm Labor
Propylene Glycol

- “Two edged sword”
- Enhances percutaneous penetration of medicine but can be an irritant
- With antifungal failure, consider ICD

- Nizoral, Oxistat, Lamisil, Nystatin
Systemic Antifungals
Systemic Antifungals

- Griseofulvin
- Ketoconazole (imidazole)
- Itraconazole (triazole)
- Fluconazole (triazole)
- Terbinafine (allylamine)
Griseofulvin (Gris-PEG...)

- Produced by Penicillium griseofulvum
- MOA: Interferes with microtubule function, causing arrest at metaphase
- *Fungistatic* for Dermatophytes only
Griseofulvin (Gris-PEG...)

- Ultramicrosized
  - Gris-PEG (125,150 mg tabs; 125 mg/ml susp)
  - Fulvicin P/G (125, 165, 250, 330 mg tabs)

- Microsized
  - Fulvicin U/F (125, 250 mg tabs)
  - Grifulvin V (500 mg tabs; 125mg/ml susp)
Griseofulvin (Gris-PEG...)

- Bioavailability: 24%
- Increase in drug bioavailability occurs with:
  - food-induced increase in drug solubility
  - secretion of bile in response to food intake
- So, give with fatty foods!
Griseofulvin (Gris-PEG...)

- **AE’s**
  - GI irritation, photosensitivity, granulocytopenia, hepatotoxicity, teratogenic
- **CI**
  - Porphyria or Hepatocellular Failure
- **Pregnancy Class C**
Griseofulvin (Gris-PEG...)

- **Drug Interactions**
  - A **CYP3A4 inducer** (you can see loss of efficacy in other drugs)
    - Statins, immunosuppressants, hormonal contraceptives, oral hypoglycemics, chemo, coumadin, anticonvulsants, antiarrhythmics, HIV meds (Protease Inhibitors)
  - May augment photosensitivity potential of other drugs
  - With EtOH, may give a disulfuram-like reaction
Ketoconazole (Nizoral)

- Fungistatic against:
  - Dermatophytes, Candida species, tinea versicolor, many dimorphic fungi

- AE’s
  - Fulminant hepatitis
  - Gynecomastia and Impotence
  - Dysregulation of the HPA axis
Ketoconazole (Nizoral)

- **Drug Interactions**
  - Potent inhibitor of CYP3A4
  - Antacids, H2 Blockers, Long acting H1 Blockers (terfenadine/astemizole), Systemic Steroids, Rifampin, Phenytoin, Warfarin, Sulfonylureas
Itraconazole (Sporanox)

- **Triazole**: Azole ring containing 3 nitrogen atoms (fluc, itra, and vori)
- **Bioavailability increased**
  - Postprandially
  - Acidic environment
- **Clinical Uses:**
  - Blastomycosis, histo, aspergillosis, candidiasis, cryptococcosis, coccidioidomycosis, sporotrichosis, dermatophyte infections, onychomycosis
Itraconazole (Sporanox)

- Potent Inhibitor of \text{CYP}_3\text{A}_4\ also
- Adverse Effects (more common with pulse therapy)
  - Headache, GI upset, Cutaneous (angioedema, EM, SJS)
- Drug Interactions
  - Cisapride, pimozide, quinidine, dofetilide, levomethadyl, digoxin, cyclosporine
- Contraindications
  - Any ventricular dysfunction-CHF, proarrythmic condition as itraconazole prolongs the QT interval
Fluconazole (Diflucan)

- Also a triazole
- Clinical Uses: Candidiasis, crypto meningitis, candidal prophylaxis, dermatophyte infections, histo, sporo, tinea versicolor
- Similar AE’s as itraconazole, but less frequent
  - N/V/elev. LFT’s
  - Alopecia (prolonged use)
Fluconazole (Diflucan)

- Potent inhibitor of CYP2C9
- Drug Interactions (elevates levels)
  - *Coumadin, nortryptiline, midazolam, triazolam, FK506*
Terbinafine (Lamisil)

- **MOA**
  - Inhibits Squalene Epoxidase

- **AE’s**
  - Hepatocellular injury, delayed gastric emptying, dysgeusia, reversible agranulocytosis, *lupus erythematosus, GI disturbance, other rashes*

- **Contraindications**
  - Chronic/acute Liver disease; CrCl <50ml/min
Terbinafine (Lamisil)

- Drug Interactions
  - Inhibits CYP2D6 (doxepin and amitryptiline)

- Pregnancy Category B
Terbinafine (Lamisil)

- Available in 250 mg tabs
  - 6 weeks therapy for fingernails, 12 week therapy for toenails
- No generic
- Bioavailability 80% to 40% (due to 1st pass hepatic metabolism)
Monitoring

- **Terbinafine**
  - Baseline AST, ALT
  - If symptoms of liver dysfunction, discontinue and do hepatic profile
  - CBC if patient is immunocompromised and is on med > 6 weeks

- **Intraconazol**e
  - LFT monitoring for all patients
Monitoring

- Griseofulvin
  - With prolonged therapy, check renal, hepatic and CBC
- Ketoconazole
  - Never use over 7-10 days
  - No monitoring needed for short therapy
Special Considerations

- Check **CsA levels** with *Itraconazole* or *Fluconazole*

- **Blood Glucose** with concomitant use of *oral hypoglycemics* and *fluconazole*

- Check **INR** frequently with *coumadin* and *fluconazole* combo therapy
FDA Approved Uses

- **Griseofulvin**
  - Tinea of skin, hair, and nails
- **Itraconazole**
  - Onychomycosis
  - Systemic mycoses (Blasto, Histo, Aspergillus)
- **Fluconazole**
  - Candidiasis (Oral, esophageal, vaginal)
- **Terbinafine**
  - Onychomycosis
Other Systemics

- Caspofungin (echinocandin)
  - Inhibits glucan synthesis (essential polysaccharide of fungal cell wall)
  - Covers Candida, Aspergillus

- Voriconazole
  - Covers Aspergillus, resistant fusarium and scedosporium
Other Systemics

- Posaconazole
  - Oropharyngeal Candidiasis assoc. with HIV; resistant systemic fungi
- Ravuconazole
  - Similar to fluconazole
  - Oropharyngeal and esophageal candidiasis
  - ? Future treatment of Onychomycosis