Presented by Dr. SMF Noorbakhsh

ANTIFUNGAL

GRISEOFULVIN

- Fungistatic antibiotic produced by *Penicillium griseofulvin*
- Preparations
  - Microsized: 25-70%
  - Ultramicrosized: 100% bioavailability
    - Ultramicrosized preparations are not used often in veterinary medicine due to the higher cost
    - If the ultramicrosized form is used, the dose must be decreased to account for differences in absorption

GRISEOFULVIN

- **MECHANISM OF ACTION**
  - Selective toxicity is based on an energy-dependent uptake into susceptible fungi
  - Mitotic arrest in metaphase
    - *Curling phenomenon*
  - May also interfere with cytoplasmic tubule formation, thereby inhibiting normal cellular traffi cking
- **SPECTRUM OF ACTIVITY**
  - *Microsporum*spp., *Trichophyton spp., and Epidermophyton.*
  - *Fungal*
  - Resistance to griseofulvin, caused by decreased energy dependent uptake into the fungal cell,

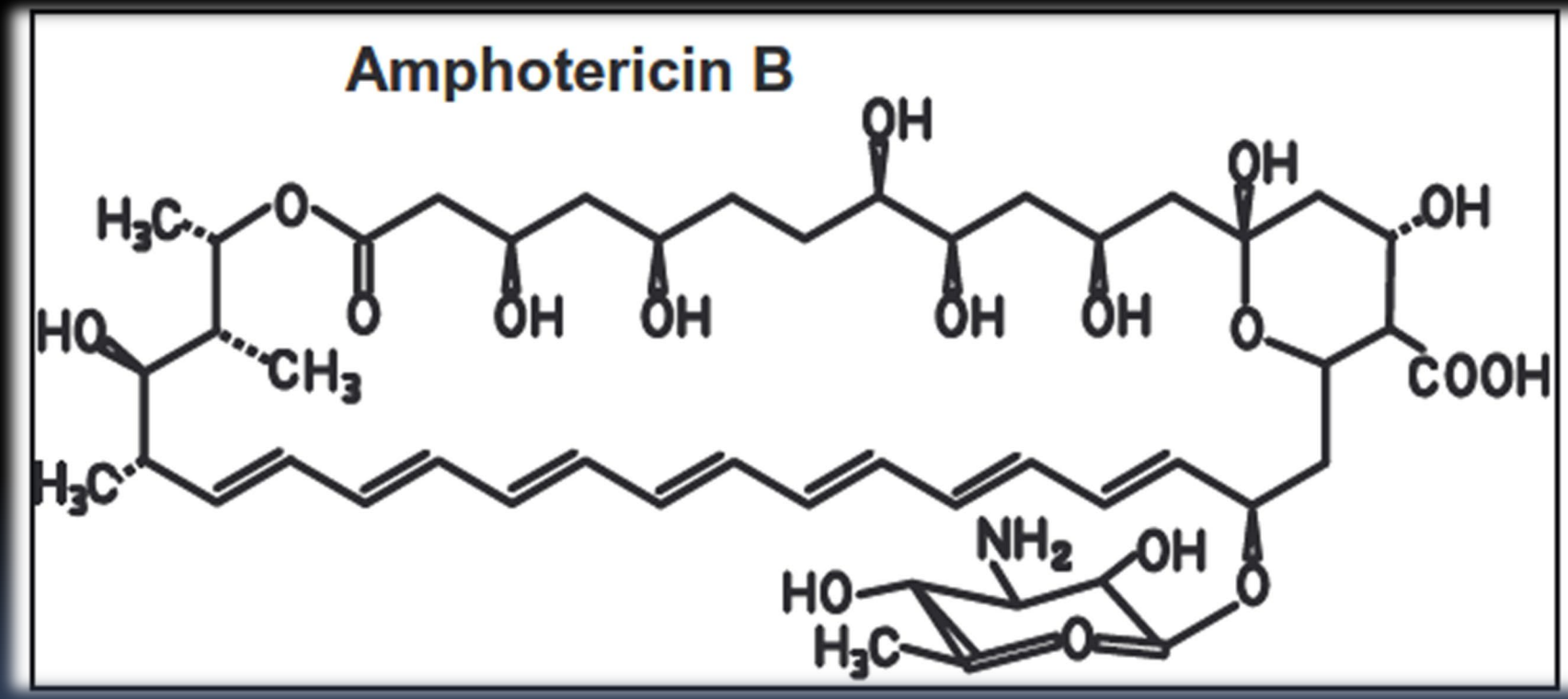
GRISEOFULVIN

- **PHARMACOKINETICS**
  - Absorption is enhanced when given with a meal with high fat content
  - The half-life at the site of action—the stratum corneum—is **prolonged** because the drug is bound tightly to keratinocytes and remains in the skin until these cells are shed.
  - New hair or nail growth is first to become free of disease
- **CLINICAL USE**
  - **Small Animals:** at least 4 weeks are needed for successful therapy, and some patients require 3 months (or more) of continuous therapy(onychomycosis)
  - **Avian**

GRISEOFULVIN

- **ADVERSE EFFECTS**
  - Most serious adverse effects associated with griseofulvin in cats
    - Leukopenia, anemia, increased hepatic enzyme activity, and neurotoxicosis, Ataxia in a kitten and bone marrow hypoplasia in an 8-year-old cat
    - Griseofulvin toxicity may be idiosyncratic
    - FIV appear to be at increased risk for griseofulvin associated neutropenia
- Griseofulvin should never be administered to pregnant cats: cranial, skeletal, ocular, intestinal, and cardiac malformations

AMPHOTERICIN B



AMPHOTERICIN B

- **MECHANISM OF ACTION**
  - Major action of amphotericin B is to bind ergosterol in the fungal plasma cell membrane, making the membrane more permeable and resulting in leakage of cell electrolytes and cell death
  - At high concentrations is thought to cause oxidative damage to the fungal cell or disruption of fungal cell enzymes
  - The selective toxicity is based on its decreased binding to the major cell membrane sterol of mammalian cells as compared to that of fungal cells

AMPHOTERICIN B

- Concentration dependent fungicidal activity
- Postfungal effect
  - Allows for intermittent therapy
- **SPECTRUM OF ACTIVITY**
  - Sensitive fungi include *H. capsulatum, C. neoformansC. immitis, B. dermatitidis, Candida spp., and many strains*of *Aspergillus. Amphotericin B has been indicated for treatment*of mucormycosis, sporotrichosis, and phycomycosisMost
  - Strains of *Pseudallescheria boydii, as well as some agents causing chromoblastomycosis* and phaeohyphomycosis, are resistant to amphotericin.

AMPHOTERICIN B

- **PHARMACOKINETICS.**
  - Is poorly absorbed from the GI tract
  - Locally, intravenously, or intrathecally
  - Binds extensively (~95%) to serum proteins
  - The highest concentrations are found in liver, spleen, kidney, and lungs, with little accumulation in either muscle or adipose tissue.
  - Concentrations of amphotericin B in fluids from inflamed pleura, peritoneum, synovium, and aqueous humor are about two-thirds of those in serum
  - Readily crosses the human placenta
  - Penetration into normal or inflamed meninges, vitreous humor, and normal amniotic fluid is poor

AMPHOTERICIN B

CLINICAL USE

Species	Formulation	Disease Treated	Dosing Protocol	Reference
Canine	Fungizone	Unspecified	Pretreatment with 0.9% sodium chloride followed by infusion of 0.5 mg/kg in 5% dextrose over 4–6 hours IV q48h; a test dose of 0.25 mg/kg is sometimes recommended.	Rubin 1986
Canine	Abelcet	Blastomycosis	1 mg/kg IV EOD to a total cumulative dose of 8–12 mg/kg.	Krawiec et al. 1996
Canine	Abelcet	Unspecified	2–3 mg/kg IV 3 times per week diluted in 5% dextrose to a concentration of 1 mg/ml for a total of 9–12 treatments (cumulative dose of 24–27 mg/kg.)	Grooters and Taboada 2003
Canine	AmBisome	Leishmaniasis	3–3.3 mg/kg IV.	Oliva et al. 1995
Canine	Fungizone 40 ml sterile water and 10 ml 10% Intralipid	Leishmaniasis	Pretreatment with 50 ml/kg of 0.9% sodium chloride followed by 10 ml/kg 20% mannitol. Drug mixture infused over 30–60 minutes at incrementally increasing dosing from 1–2.5 mg/kg IV twice a week for a minimum of 8 injections.	Lamothe 2001
Canine/Feline	Fungizone in 0.45% saline with 2.5% dextrose	Cryptococcosis	0.5–0.8 mg/kg SC in 400 ml for cats or 500 ml in dogs given twice a week for a cumulative dose of 8–26 mg/kg.	Malik et al. 1996
Feline	Abelcet	Unspecified	1 mg/kg IV 3 times per week diluted in 5% dextrose to a concentration of 1 mg/ml for a total of 12 treatments (cumulative dose of 12 mg/kg).	Grooters and Taboada 2003

AMPHOTERICIN B

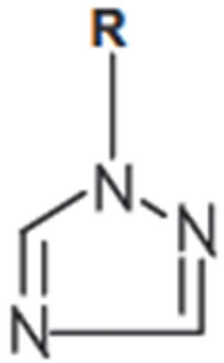
- **ADVERSE EFFECTS**
  - Nephrotoxicity
    - TDM
  - Phlebitis, fever, nausea, and vomiting, hypokalemia and anemia

FLUCYTOSINE

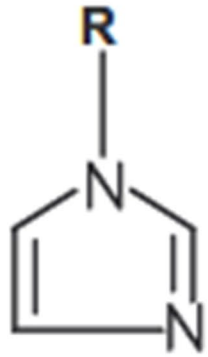
- Synthetic antifungal agent available as an oral preparation
- **MECHANISM OF ACTION**
  - Must be taken into the fungal cell by cytosine permeate and then converted to the active form, 5-fluorouracil (5-FU), by a fungal cytosine deaminase enzyme
  - Mammalian cells do not have cytosine deaminase
- *Candida or Cryptococcus neoformans*
- Fungal mutations leading to alterations in the permease or deaminase enzyme activity has led to the development of resistance
- **ADVERSE EFFECTS**
  - Anemia, leukopenia, and thrombocytopenia

AZOLE

Triazole



Imidazole



Triazoles

- Itraconazole
- Fluconazole
- Voriconazole
- Posaconazole

Imidazoles

- Ketoconazole
- Clotrimazole
- Enilconazole
- Miconazole

AZOLE

Drug	Solubility	pH Dependent	LogP	Protein Binding
Ketoconazole	pi	Yes	3.78	>90%
Fluconazole	ss	No	0.54	10–12%
Itraconazole	pi	Yes	5.66	>98%
Voriconazole	vss	No	1.81	32–58%

Drug	Activity		
	Yeasts	Aspergillus	Fusarium
Ketoconazole	+	±	–
Fluconazole	+	–	–
Itraconazole	+	±	–
Voriconazole	+	+	±

AZOLE

- MECHANISM OF ACTION

KETOCONAZOLE

- **Spectrum of Activity**
  - Is most effective against yeast and dimorphic fungi such as *Candida*, *Malassezia pachydermatis*, *C. immitis*, *H. capsulatum*, and *B. dermatitidis*, *as well as most dermatophytes* .
  - It is less effective against *C. neoformans, and Aspergillus spp.*
- **Pharmacokinetics**
  - Oral absorption
  - Is soluble only in acid aqueous environments (pH <3)
  - Is highly protein bound (>98%)
    - Does not penetrate into the cerebrospinal, seminal, or ocular fluid to a significant degree; although it is found in mother's milk.
  - Distributes throughout the skin and subcutaneous tissue, making it effective for treatment of superficial and systemic fungal skin infections.

KETOCONAZOLE

- **Clinical Use**
  - Dermatophytosis in cats
  - Canine blastomycosis, histoplasmosis, nasal cryptococcosis, and coccidioidomycosis, *Malassezia dermatitis*
  - Is not absorbed well orally in horses and no approved formulations for use in food animals
- **Adverse Effects**
  - Nausea, anorexia, and vomiting
  - Chronic therapy pruritus, alopecia, lightening and drying of the hair coat, and weight loss
  - Dos erelated inhibition of testosterone has resulted in gynecomastia, sexual impotence, and azoospermia.
  - Cats appear to be more sensitive to ketoconazole liver toxicity than are dogs but they are less sensitive to the hormonal suppressive side effects

KETOCONAZOLE

- Cataracts have been reported after long-term(15months) ketoconazole therapy in dogs
- It is therefore not recommended for use in pregnant or lactating animals.

ITRACONAZOLE

- **Spectrum of Activity**
  - Important fungi, including *Microsporum*, *Trichophyton*, *Candida*, *Malassezia* , *Sporothrix*, *Pythium*, *Histoplasma*, *Aspergillus*, *Blastomyces*, *Coccidioides*, *and Cryptococcu*
  - It has little activity against *Fusarium sp.*
- **Pharmacokinetics**
  - Oral absorption
  - Is highly protein bound (>99.8%)
  - Tissue to plasma concentration ratios range from 1 : 1 in brain to 8 : 1 in keratin to 25 : 1 in fat stores.
  - Highest tissue levels are seen in the liver and adrenal cortex

ITRACONAZOLE

- **Clinical Use**
  - *Small Animals*
    - ***Cats:*** dermatophytosis(week-on/week-off schedule), feline disseminated cryptococcosis
    - ***Dogs :*** blastomycosis, *Malassezia* dermatitis
  - Aspergillosis in caged birds
  - *Large Animals*
    - *Horse:* mycotic rhinitis, osteomyelitis, and guttural pouch mycosis
- **Adverse Effects**
  - Itraconazole is better tolerated than ketoconazole
  - Appears to be no need for dosage adjustments in patients with liver disease

FLUCONAZOLE

- **Spectrum of Activity**
  - Effective in animal models of *Blastomyces, Candida, Coccidioides, Cryptococcus, and Histoplasma infections.*
  - It is not particularly active against *Aspergillus*
- **Pharmacokinetics**
  - **Oral absorption**
  - **Plasma protein binding(10-12%)**
  - Concentrations in saliva, sputum, skin, nails, blister fluid, and vaginal tissue and secretions were found to be similar to plasma concentrations
  - Higher CSF concentrations than ketoconazole or itraconazole: mycotic meningitis
  - **Renal excretion:**
    - Fungal cystitis
    - Extended dosing intervals in renal insufficiency
  - **Needs loading dose**

FLUCONAZOLE

- **Clinical Use**
  - *Small Animals*
    - Dermatophytosis
    - Canine nasal aspergillosis and penicilliosis
  - *Exotic Animals*
  - *Large Animals*
    - Nasal conidiobolomycosis lesions in mares
    - Disseminated candidiasis in foals
- **Adverse Effects**
  - Its use in pregnant patients is not recommended

VORICONAZOLE

- **Spectrum of Activity**
  - *Aspergillus and Fusarium spp.*
- **Pharmacokinetics**
- **Clinical Use**
  - Dogs and Cats
  - Horses
  - Birds
- **Adverse Effects**
  - GI side effects in cat, and the polyuria observed in birds
  - In people, increased liver enzymes and hepatotoxicity have been observed
  - In experimental animals and people, visual disturbances have been reported

POSACONAZOLE

- It is used for invasive fungal infections, including those caused by *Aspergillus and Candida*
- Its advantage over other azole drugs is the activity against Zygomycetes
- It should not be used during pregnancy because of inhibition of steroidogenesis

OTHER AZOLE ANTIFUNGAL DRUGS

- Isavuconazole, ravuconazole, and albaconazole.

TERBINAFINE

- MECHANISM OF ACTION
  - Inhibits squalene epoxidase to decrease synthesis of ergosterol
  - Fungal cell death results from disruption of cell membrane
- Clinical Use
  - Treatment of dermatophytosis in dogs and cats
    - Average treatment length lasted approximately 60 days
  - *Malassezia* dermatitis in dogs
- **Adverse Effects**
  - In dogs ALT and ALP was increased
  - In cats facial dermatitis and pruritus has also been reported
  - No teratogenic effects of the drug have been noted in people

LUFENURON

- Is commonly used in dogs and cats for control of flea infestations
- Although there are reports of successful treatment of dermatophytosis in dogs and cats, the success of this treatment has been controversial.
  - Topical or local use of lufenuron may be more efficacious
- May also be used in water baths for the treatment of aquatic species and amphibians

SODIUM OR POTASSIUM IODIDE

- Treat sporotrichosis in dogs, cats, and donkeys as well as nasal fungal granulomas caused by *Basidiobolus Conidiobolus*
- These drugs are seldom used as a sole therapy
- Treatment is recommended to extend 30 days beyond the resolution of clinical signs
- Iodoject IV is labeled for use in cattle for the treatment of actinomycosis and actinobacillosis
- Adverse Effect
  - Iodism: lacrimation, salivation, coughing, anorexia, dry scaly skin, and tachycardia
  - Abortion and infertility may also be observed, therefore Care should be taken when administering this drug to breeding animals

CLOTRIMAZOLE

- Nasal aspergillosis in dogs
- Dogs and cats with fungal candiduria
- Otomax®: otitis externa caused by *Malassezia pachydermatitis* or susceptible bacteria in dogs.

ENILCONAZOLE

- Topical treatment of dermatophyte infections in dogs, cats and horses
- Nasal aspergillosis in dogs
- Guttural pouch mycosis
- Poultry hatcheries to control *Aspergillus*

MICONAZOLE

- 1% solution for topical treatment of keratomycosis.
- 2% cream or 1% spray or lotion for the treatment of dermatophytosis in dogs and cats
- combined with chlorhexidine as a shampoo for the adjunct treatment of dermathophytosis in animals

NATAMYCIN

- Humans as a 5% ophthalmic suspension
- Choice for *Fusarium keratomycosis* in the horse
- Topical therapy for nasal aspergillosis as well as guttural pouch mycosis and dermatophytosis

NYSTATIN

- Candidiasis, particularly in exotic animal species
- Panalog®: antibiotics (neomycin, thiostrepton) and anti inflammatory(triamcinolone)

THE END