# Antifungal Drugs

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**Fungal Zoonosis?**

- There are a number of fungal pathogens presented in this lecture that can infect humans, including Aspergillosis, blastomycosis, coccidiomycosis, Cryptococcus, histoplasmosis, dermatophytosis and sporotrichosis
- Biosecurity and strict hygiene are essential when working with animals that are infected with a particular fungal pathogen; it is important to keep in mind that most pathogens are not infrequently to rarely considered zoonotic (dermatophytosis an important exception).
    - Immune suppressed individuals are at increased risk for zoonotic transmission

**Fungal Taxonomy (this is by far an exhaustive list)**

- Yeasts
    - Candidiasis
    - *Cryptococcus neoformans*
- Molds
    - *Pseudogymnaoscus spp.*
    - Aspergillosis
    - Dermatophytosis (primarily *Trichophyton spp.* and *Microsporum spp.)*
- Dimorphic Fungi
    - Histoplasmosis
    - Blastomycosis
    - Coccidiomycosis

**Fungal Pathogenesis**

- Many fungi are present commonly in the environment and are considered opportunistic, i.e. a host must be otherwise compromised or come into contact with an overwhelming burden of fungal spores in order to become infected
- *Candida spp.* are generally present within the gastrointestinal tract of most organisms; infection is considered opportunistic in animals that cannot mount an immune response or who suffer from dysbiosis such that the fungi can take hold
- There are a number of dimorphic fungi that are dangerous fungal pathogens to certain animal hosts; the majority of these pathogens have a certain geographic prevalence (none regularly encountered in the state of Florida); visit the CDC website to learn more about Coccidiomycosis, Blastomycosis and Histomycosis

**Predisposing Factors for Fungal Infection**

- High environmental fungal burden
- Poor quality food (i.e. contamination with fungal spores; don't forget to think about storage)
- Concurrent disease / illness

- Concurrent medications (i.e. antibiotics, steroids)
- Insufficient management conditions
    - Poor ventilation / air flow
    - Poor sanitation / hygiene (i.e. allowing mold growth on food or in enclosure)
    - Stress
    - High stocking density

**Preventive Actions**

- Improve husbandry
    - Better ventilation
    - Better sanitation
- Improve food quality
- Treat the whole animal (i.e. address all sources of potential injury or disease)
- Critically evaluate medication use
    - Are antibiotics necessary?
    - What effect do medications have on immune function?
- Reduce stress whenever possible
    - Limit handling / contact / visualization
    - Conspecifics when appropriate

**Antimycotic Targets**

- Most of the medications used for antifungal treatment in wildlife affect the fungal cell membrane and alter its permeability
- Other medications (less commonly used in wildlife medicine) affect nucleic acid synthesis, disrupt microtubule functions and block beta-glucan synthesis

**Meet the Drugs – refer to the NWRA Wildlife Formulary for additional information including drug dosages**

- When thinking about antimycotic therapy, it is important to consider that treatment is often required for a prolonged period of time, i.e. months
- Throughout the time of antimycotic therapy, patient monitoring is required depending on the drug selected to monitor for side effects (i.e. liver or kidney damage)
- In addition to using antimycotic therapies to directly treat fungal pathogens, antimycotic therapy is routinely used in wildlife medicine for fungal prophylaxis (i.e. to prevent fungal infections).
    - Two primary indications for antifungal prophylaxis
        - Susceptible species that require indoor housing or intensive care
        - Susceptible species that require therapy with an antibiotic
    - Common species for prophylaxis
        - Seabirds, including sea ducks
        - Falcons

**Polyenes**

- Nystatin
    - Used for the treatment of Candidiasis
    - Must come into contact with the fungus in order to be effective (common to paint medication onto fungal plaques/lesions within the oral cavity, esophagus and crop
    - Large volumes often required for successful treatment (may lead to selection of another antifungal drug due to difficulty of large volume administration)
    - Few side effects as drug is excreted unchanged in the feces
- Amphotericin B
    - Two formulations available – use the lipid-complex formulation whenever possible (slightly lower side effects)
    - Considered nephrotoxic (i.e. toxic to the kidneys) – monitoring required
    - Must be administered by intravenous (IV) route – no oral dosing
    - Effective against systemic fungal pathogens

**Squalene Epoxidase Inhibitors**

- Terbinafine
    - Available in oral and topical formulations (topical as spray or cream)
    - Spray formulation can be nebulized (for birds) or used in baths (for amphibians)
    - Thoughts to have fewer side effects than Azole drugs due to limited use of cytochrome P450 enzymes
    - Can cause gastrointestinal side effects
    - More research is needed to determine clinical effectiveness of use for WNS in bats, for chytridiomycosis and amphibians and for ophidiomycosis in reptiles (snakes)

**Azoles**

- Imidazoles
    - Clotrimazole
        - Solution (available through compounding pharmacies) can be nebulized (nebulization therapy generally replaced by newer, more effective medications)
        - Common ingredient in otic preparations
        - Can be used for local dermatophytosis (in cream formulation)
    - Miconazole
        - Topical antifungal generally used for fungal dermatitis and chytridomycosis
    - Ketoconazole
        - Generally avoided due to severe systemic side effects including gastrointestinal effects, liver toxicity, and suppression of gonadal and adrenal steroid synthesis
        - Has been replaced by newer, safer medications, i.e. triazoles
- Triazoles
    - First generation
        - Fluconazole
            - Can cause gastrointestinal side effects and liver toxicity
            - Not thought to be effective against Aspergillosis
            - May be useful for treatment of central nervous system fungal infections?
        - Itraconazole

- Has been the mainstay of antifungal prophylaxis against Aspergillosis (fungistatic, not fungicidal)
- Commonly used for systemic mycoses
- Anorexia reported as side effect
- Do not use compounded formulations due to inconsistent absorption
- Tissue distribution varies between species
- Can cause liver toxicity, i.e. monitor liver values
- Sponorox has been brand name available for years (both liquid and capsule formulations; within past 3 months, Itrafungol has become available
    - Large volumes often required for treatment (not very concentrated at 10mg/mL)

- Second generation
    - Voriconazole and Posaconazole
    - Both considered front-line antifungal medications for Aspergillosis in humans
    - Both currently quite expensive (posaconazole cost-prohibitive, although will be off patent in 2019 so hopefully generic formulations will become available)
    - Both medications available for PO and IV use
    - Posaconazole has the lowest mean inhibitory concentration (MIC) of any antifungal medication currently on the market
    - In human medicine, posaconazole is useful against both itraconazole and voriconazole resistant strains of *Candida spp*.
    - Adverse effects of both medications similar to itraconazole, although anorexia less commonly reported (include liver dysfunction)

**Deciding on an Antimycotic Drug**

- Spectrum
    - Drug needs to be effective against particular pathogen
- Route of administration
    - Needs to work for both patient and for pathogen type/location
- Concurrent disease
- Monitoring ability
    - Many antifungal medciations require routine blood monitoring for liver/kidney values
- Drug interactions
- Cost