Fungi in disease (mycoses)

Most fungi are dimorphic

- Mucorales
- Corneaflora
- Flabellulata
- Penicillium
- Scedosporia
Importance as disease agents

- 1.5 million species of fungi
  - Only ~200 species pathogenic
- Generally rare in WY
- Important geographically:
  - Coccidiodymoconis – SW US
  - Histoplasmosis – Mississippi-Ohio valleys
  - Cryptococcosis – NW US and western Canada
- Nosocomial infections
- Immune-suppressed people and animals:
  - Important due to HIV and chemical immunosuppression
  - Immunosuppressive diseases in animals (e.g., FeLV)
- Mistaken for bacterial infections, with fatal consequences
Situations where we see fungal infections

- **Common:**
  - Ringworm, dogs, cats, calves, horses and show lambs
  - Malassezia, dogs
  - Localized and disseminated infections in birds (esp. aspergillosis)

- **Uncommon:**
  - Cattle: mycotic placentitis, pneumonia, mycotic encephalitis, rumenitis, abomasitis.....
  - Mycotic dermatitis and guttural pouch mycosis, horses
  - Mycotic rhinitis, dogs and cats
  - Histoplasmosis-like agent, dogs and cats

General features of fungal diseases

- Infection not necessary for maintenance/dissemination of most fungi
- Generally chronic disease
  - Typically, granulomatous reactions
- Main categories of disease:
  - Opportunistic
  - Superficial (skin)
  - Internal organs ("deep mycoses")
- Rarely one single pathogenic factor
- Complicated taxonomy, based on how fungi reproduce
- Infection often respiratory tract via spores:
  - Upper and lower respiratory tract disease

(Simplified Map of the Distribution of Histoplasmosis in the United States)
Why fungal diseases are not more common

- High natural immunity is high
- Barriers: skin and mucus membranes
- Most fungi saprophytic
- Redox potential in vivo conditions too reducing for most:
  - Some pathogenic fungi exhibit thermal dimorphism
  - Mesophilic: fungi grow better below 37°C
Features of fungi

- Eukaryotic
- Heterotrophic ("other feeding"): require preformed organic material
- Cell walls: chitin, glucan, chitosan, mannan:
  - Induce foreign body reaction
- Reproduction by spores (conidia)
- Spread by wind
- Sexual (meiotic) and asexual (mitotic) spores produced, depending on species/conditions
- Typically not motile
- Like plants, stable haploid & diploid states
- Vegetative body may be
  - Unicellular (yeasts)
  - Multicellular (hyphae)

Characteristics of fungi and their diseases

- Fungal infections = mycoses
- Eukaryotes; most dimorphic
  - Multicellular filaments (hyphae) = molds
  - Single cells (some in chains) = yeast
- Major categories
  - Opportunistic - most
  - Pathogenic - few
  - Intermediate = mostly opportunistic, but some in apparently immunologically normal individuals
- Tendency to be geographically localized
- Granulomatous diseases (may look cancer-like)

Granulomatous inflammation common in mycoses
Determinants of disease

- Inoculum size
- Site of infection
- Pathogenicity of fungus: rarely one virulence factor
  - Adherence to host cells
  - Interference with inflammatory response
  - Resistance to phagocytosis – *Histoplasma capsulatum*
  - Ability to grow at host temperatures
  - Mycotoxin secretion
  - Enzyme secretion (esp. collagenase, elastase, keratinase)
  - Surface hydrophobicity
  - Phenotypic switching
  - Invasion of vessels
- Immunity of host
  - Immunoologically compromised
  - Cats: FeLV; humans: HBV; inherited immunodeficiencies

Immunity of host

- Most major fungal diseases opportunistic
- Many fungal infections asymptomatic:
  - High rates of seropositivity
- Susceptibility due to:
  - Compromised epithelial barriers
  - Systemic diseases
  - Neutrophil/macrophage disorders
  - Immune disorders (primary and acquired)
  - Drugs and therapeutic agents
  - Malignancy and hematologic disorders

Superficial or cutaneous mycoses

- Ringworm - skin
- Malassezia – skin
- Dermatophilosis - skin
- White-nose syndrome (geomycosis) - skin
- Candidiasis – mucosal surfaces
- Sporotrichosis – submucosa
- Other opportunistic fungal infections
**Malassezia**

- Non-mycelial yeast
- Lipophilic
- Multiple species in people
- In dogs (rarely cats and children):
  - *Malassezia pachydermatis*
- Normal inhabitant on skin – low numbers
- Predisposing factors:
  - Moisture + excessive sebum + host immunity
  - Hypersensitivity to yeast components
  - Primary seborrhea
  - Atopic dermatitis

**Ringworm**

- Dermatophytosis = "skin plant" disease
- Typical keratinized tissues:
  - Hair, feathers, stratum corneum, nails, claws, horn
  - Nutritional source for fungus
- Classically regarded as:
  - Geophilic = soil-associated
  - Zoophilic = non-human animals
  - Anthrophilic = humans
- Esp. *Trichophyton* and *Microsporum* spp.
  - Some species specificity
  - Some zoonotic
- Often asymptomatic (esp. cats)
- Predisposing factors: heat/humidity; poor nutrition; trauma; crowding

**Ringworm - dermatophytosis**

- Image of ringworm on dog skin
Pathogenesis

- Generally younger animals:
  - Innate immunity – cutaneous lipids
- Infect hair shafts
- Secondary damage to hair follicle:
  - Typically, folliculitis-furunculosis
  - Alepecia secondary to brittle hair shafts
  - Persistence of inflammation due to hair shafts and keratin released into dermis
  - Keratinases (nutritional source)
- Occasionally, infections elsewhere (e.g., otitis in cats)
- Generally, resolution due to immune response in 1 – 4 months

Malassezia dermatitis

- Lipophilic yeasts:
  - Esp. Malassezia pachydermatis
- Normal flora of skin, lips, anus-anal sacs
- Host-related factors, esp. skin microclimate
  - External ear canal: humidity; excessive wax; conformation
  - Altered sebum production
  - Excessive keratin production (“seborrhea”)
  - Allergic dermatitis
- Marked increase in numbers on skin required to induced disease:
  - >100- to 10,000-fold

Pathogenesis of Malassezia

- Adherence to stratum corneum
- Lytic enzymes:
  - Lipases, phospholipases, aspartyl proteases, sphingomyelinases
- Dogs and people
- Hypersensitivity to yeast components
- Self-trauma exacerbates infection
  - Hyperpigmentation, lichenification, malodor
Candidiasis

- Most common: *Candida albicans*
- Commensal (skin, mouth, GIT, vagina)
- Phenotypic switching in response to temperature, antibiotics, altered host physiology
- Typically oral or vaginal
- Rarely, fungemia (candidemia), esp in HIV
- Pathogenicity factors
  - Adhesins: binding to fibrinogen, fibronectin, laminin
  - Biofilm
  - Blocking oxidative burst (catalases)
  - Proteinases (esp. of extracellular matrix)

'Thrush' due to Candida sp.
Esophagitis due to Candida

Dermatophytic fungal infections

Systemic mycoses

- Major:
  - Coccidioidomycosis – *Coccidiodes immitis*
  - Blastomycosis – *Blastomyces dermatitidis*
  - Histoplasmosis – *Histoplasma capsulatum*
  - Cryptococcosis – *Cryptococcus neoformans*
- There are others, not covered here
Systemic mycoses

- Generally, entry via lung
  - Secondary spread depends on agent
- Tendency for geographically localization (US):
  - Predisposing factors often poorly understood:
    - Blastomycosis: shallow lakes and woods in NE
    - Coccidioidomycosis: SW US
    - Histoplasmosis: Ohio-Mississippi valleys
- Immune status determines outcome

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Veterinary Blastomycosis Cases in Minnesota by Probable County of Exposure, 1999-2009 (n=281)

*27 cases were likely exposed in Wisconsin and 10 in Canada*

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Coccidioidomycosis

- Environmental sources
- Animal and human
- SW US
- Dust-associated
- Chronic pneumonia with dissemination
- In people:
  - 60% asymptomatic
  - 40% mild to severe disease – esp. HIV
  - Lung: recovery (most)
  - Systemic: poor prognosis
Some opportunistic fungal infections

- Candidiasis
- Aspergillosis
- Cryptococcosis
- Zygomycosis
- *Pneumocystis jirovecii* (carinii)

Opportunistic infections

Cancer (fatal mycoses)
- Candidiasis 44-80%
- Aspergillosis 20-30%
  - Zygomycosis Rare
  - Cryptococcosis Rare
  - Histoplasmosis Rare
  - Coccioidiomycosis Rare
  - Hyalohyphomycosis Rare

In HIV:
- Oral candidiasis 40-90%
- Esophageal candidiasis 50%
- Dermatophytosis 20-90%
- Cryptococcosis 3-33%
- Histoplasmosis 5-30%
- Pulmonary aspergillosis 5%
  - Coccioidiomycosis Rare
  - Cerebral sporotrichosis Rare
  - Hyalohyphomycosis Rare
  - Phaeohyphomycosis Rare
Features of opportunistic fungal infections

- No disease in healthy people or animals
- Disease in immunocompromised states:
  - Inherited immunodeficiencies,
  - Immunosuppressive drugs
    - Chemotherapy, corticosteroids, organ transplant rejection drugs
  - Radiation therapy
  - Infections (e.g., HIV)
  - Neoplasia
  - Diabetes mellitus
  - Advanced age
  - Malnutrition

Pneumocystis

- Recognized >100 years
- *Pneumocystis jirovecii*
- Originally considered protozoan
- Virtually all mammalian species
- Adherence to pneumocytes
- Pneumonia, esp. HIV
- Illness and death due to florid (inappropriate) response
- Not cultured
Aspergillosis

- Most common fatal infection in chronic granulomatous disease of childhood
  - Unable to form toxic oxygen radicals after phagocytosis.
- Progressive disseminated disease neoplastic diseases:
  - Acute leukemia, bone marrow and organ transplantation (not necessarily AIDS)
- Important in avian species:
  - Parrots; waterfowl
- Angioinvasive

Cryptococcosis

- Cryptococcus neoformans or C. gattii
- Yeast form in nature and host
  - Mycelial only in laboratory conditions
- Primarily immunocompromised individuals
  - Typically, T-cell deficiencies for C. neoformans
- Some immunocompetent individuals
  - Ex. cats and people with C. gattii
- Most infections asymptomatic
- Association with soil containing bird droppings:
  - Typically inhalation – small particles (2.5-10 µm)
  - Propensity for CNS-disease
- Other sources, including eucalyptus trees
- Characteristically, scant inflammatory reaction in affected tissues
Spread of Cryptococcus gattii in Pacific Northwest

Virulence factors for Cryptococcus

- Polysaccharide capsule:
  - Resist phagocytosis – essential for virulence
  - Reduce pro-inflammatory cytokine secretion (TNF, IL-1β, and IL-6)
- Shed products:
  - Cryptococcal antigens in blood = CMI
  - Inhibited migration of leukocytes
- Melanin
  - Oxidative damage by scavenging free radicals
- Mannitol
- Superoxide dismutase
- Proteases
- Phospholipases

Cryptococcosis
Two other ways fungi cause disease

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>Mycotoxins</th>
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<tbody>
<tr>
<td>Often upper or lower respiratory tract</td>
<td>Multiple:</td>
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<tr>
<td></td>
<td>- Acute disease</td>
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<td></td>
<td>- Chronic disease</td>
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<td>- Neoplasia</td>
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Fungi and pathology

- Three classes of fungal infections:
  - Superficial
  - Deep (pulmonary or systemic)
  - Opportunistic
- Also: allergic diseases and mycotoxicoses
- For many: infection common; severe disease rare
- Generally, no single virulence factor
- Granulomatous response:
  - May be confused with neoplasia grossly
- Importance of immunity as determinant of outcome:
  - HIV (humans); FeLV (cats)