

Fungal Infections

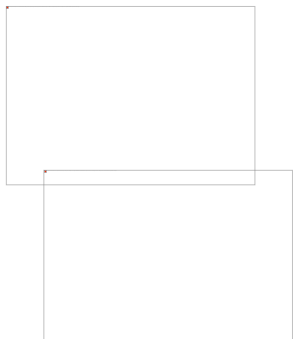
- Once exotic and rare; now increasingly common
- Fungi are not "virulent"
- But they are good at taking advantage
- "Opportunistic" in many senses

Fungal biology

- Eukaryotic (organized nucleus and cell structure)
- Non-motile
- Aerobic
- Saphrophytic or parasitic
- Cell wall contains glucan and chitin
- Cell membrane contains ergosterol

Fungal cell structure

- Yeasts (unicellular, budding)
- Molds (hyphae, mycelia, spores)
- Dimorphs (both)



Pathogenesis

Toxins: produced, but not relevant to human infections

Disease from:

- Bulk of organisms
- Immune response to them or their byproducts

Overview of fungal infections

- Superficial or cutaneous (skin, hair, nails)
- Subcutaneous
- Systemic
 - "true pathogens" may cause disease in normal hosts although worse with immunocompromise
 - "opportunists" cause disease almost exclusively in immunocompromised hosts

Superficial fungal infections

Dermatophytes: molds producing keratinase

Pathogenesis: grow as saprophytes on skin/nails; cause inflammation below

Clinical:

- Tinea corporis Tinea cruris
- Tinea pedis Tinea unguum
- Tinea capitis

Superficial fungal infections

Malassezia furfur: lipophilic yeast (derives nourishment from skin lipids)

Pathogenesis: lives on skin, causes pigment changes and itch underneath

Diseases:

- Tinea versicolor
- Occasionally fungemia with lipid infusion

Subcutaneous fungal infections

- Pathogenesis: introduced through skin by foreign body, grow in subcutaneous tissues, spread via lymphatics
- Disease; usual local; may disseminate to adjacent bones, joints.
- Most common in nonindustrialized world (mycetoma of feet)

Subcutaneous fungal infection: Sporotrichosis

- Organism: Sporothrix schenckii
 - Dimorphic soil fungus (mold in environment, yeast in body)
- Habitat: soil, worldwide
- Pathogenesis: splinters or thorns inoculate organism into subcutaneous tissues

Sporotrichosis

Pathophysiology:

- Spore inoculated by foreign body
- Yeasts travel along lymphatics
- Elicit mixed pyogenic-granulomatous reaction

Clinical:

- Gardeners and outdoorspersons
- Ulcerating nodules along hard cord
- Bone and joint destruction
- Dissemination rare

Systemic fungal infections: the “true pathogens”

Histoplasmosis, Coccidioidomycosis, Blastomycosis

- Dimorphic
- Respiratory acquisition
- Restricted geographic distribution
- Infect normal hosts
- Disease reminiscent of TB

Histoplasmosis

Organism: Histoplasma capsulatum

– Soil dimorph (yeast in body, mold in environment)

Habitat: soils with high N content

– Ohio-Mississippi valley; Caribbean; Central and S. America

– Guano of bats, birds, poultry (chicken coops and caves)

Pathogenesis: inhalation of spores

Histoplasmosis

Pathophysiology:

- Mold spores transform into yeast in lung, elicit cellular immunity as per TB
- Hematogenous dissemination
- Skin test reactivity
- Walled off granulomata

Clinical:

- Mimics TB. Usually latent disease, but
 - may cause acute/chronic cavitory lung disease
 - may disseminate after infection (infancy, immunocompromise)
 - may reactivate years later

Coccidioidomycosis

Organism: *Coccidioides immitis*

- Dimorph: mold in soil, spherules and endospores in host

Habitat: lower Sonoral life zone (arid): Southwest US, Mexico, Central and South America

Pathogenesis: inhalation of spores

Cocci

Pathophysiology:

- Spores transform into spherules in lung, elicit cellular immunity as per TB
- Hematogenous dissemination
- Skin test reactivity
- Walled off granulomas

Clinical:

- Acute self-limited flu-like seroconversion syndrome (“Valley fever”)
- Acute or chronic lung disease
- Dissemination (pregnancy, dark skin, immunocompromise)
 - Skin
 - Bone
 - CNS

Blastomycosis

Organism: *Blastomyces dermatitidis*

dimorph: mold to yeast

Habitat: humid woodlands

- MidAtlantic zone
- Beaver dams, peanut farms
- Organic debris rather than soil

Pathogenesis: inhalation of spores

Blastomycosis

Pathophysiology:

- Spores transform into yeast in lung, disseminate
- No good antigen test to define exposed population

Clinical:

- Acute or chronic lung disease (nodular/cavitory)
- Disseminated disease:
 - Skin
 - Bone
 - Urinary tract in men

Systemic fungal infections:

B. “the opportunists”

Histo. Blasto. Cocci

- Geographic distribution
- Dimorphic
- Infection by inhalation
- Pyogenic/granulomatous host response
- Similar to TB
- Infection ≈ immunity

Opportunists

- Omnipresent
- Yeasts or molds
- Various routes of infection
- Host response varies
- Clinical syndromes vary
- No lasting immunity

Cryptococcosis

Organism: *Cryptococcus neoformans*
yeast with a thick polysaccharide capsule

Habitat: bioterrorists (of a sort), worldwide

Pathogenesis: inhalation of yeasts

Cryptococcosis

Pathophysiology:

- Inhalation leads to
- Transient colonization OR
- Acute/chronic lung disease OR
- CNS invasion

Clinical

- Pneumonia OR
- Meningoencephalitis
- Acute or chronic
- Fever, headache, stiff neck, fever, delirium
- Hydrocephalus

Cryptococcal meningitis

- India ink preparation of CSF may show organisms
- Serum or CSF antigen assay diagnostic in >95% cases of CNS disease

Candidiasis

- Organism: *Candida albicans* et al (yeasts with hyphal forms)
- Habitat: normal human flora
- Pathogenesis:
 - Colonized areas: change in environment leads to overgrowth
 - Noncolonized areas: change in immunity leads to invasion

Pathogenesis of Candida infections

- Primary host defenses:
 - Intact skin
 - Intact mucosa with normal pH and normal flora
 - Functioning lymphocytes
 - Functioning neutrophils

Pathogenesis of local Candida infections

- Environmental changes
 - Wet skin
 - Changes in local flora
 - Hormones, foreign bodies
- Lymphocyte dysfunction
 - Immaturity
 - Destruction (HIV)

Pathogenesis of invasive Candida infections

- Breach in anatomic integrity (often biofilm on catheter)
- Defective PML function (first line of defense)
 - Myeloperoxidase, complement necessary but not sufficient defense
 - Cytokines also essential for recruiting phagocytes in disseminated disease
 - Antibody may or may not be present; may or may not be protective

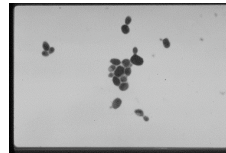
Invasive candidiasis

- Usually in critically ill patients with multiple risks (hospitalized, neutropenic, on antibiotics, many catheters)
- Fever, leukocytosis, organ dysfunction
- Microabscesses in kidney, liver, skin, eye, lung, heart
- Candida endocarditis

“Virulence” of Candida?

- Inherent “virulence”
 - environmental tolerance
 - Secrete hydrolases, beta proteases, phospholipases
 - Can adhere to plastic
 - Can invade GI, renal epithelium
- Additional hyphal virulence
 - Protects against phagocytosis
 - Knockout strains

Additional comments on candidiasis



- Gram stain may help identify
- Infection and colonization are difficult to distinguish
- Best treatment restores missing defense

Aspergillosis

- Organism: *Aspergillus fumigatus* and others
 - Mold without a yeast phase
- Habitat: everywhere, worldwide
- Pathogenesis: inhalation of spores

Summary: Fungal “opportunism”

- Metabolic (dermatophytes, *M. furfur*, *mucor*)
- Dimorphism (sporo, histo, blasto, cocci)
- Capsule (cryptococcus)
- Adherence (candida)

Summary: antifungal defenses

- Intact skin (dermatophytes, Candida)
- Lymphocyte function (dimorphs, cryptococcus, candida)
- Neutrophil function (candida, aspergillus, mucor)
- Body milieu (candida, mucor)