# FUNGI: AGENTS OF SUPERFICIAL, CUTANEOUS, and DEEP MYCOSES

**STRUCTURE**

The fungal membrane contains: phospholipids + ergosterol (instead of cholesterol)

The fungal cell wall contains: carbohydrate oligomers [chitin, α/β-glucan, α-mannan] + mannoproteins.

Chitin and β-glucan are specific to fungi. DOES NOT contain diamonopimelate (DAP), unlike bacteria.

Most fungi are **free-living** organisms.

*Candida albicans* and *Malassezia furfur* are NF in humans.

They are non-motile and saprophytic (usually)

**Yeast:** unicellular morphology, dividing via budding or fission.

The yeast morphotype of *Histoplasma capsulatum* is pathogenic. *Cryptococcus neoformans* is only found in the yeast form.

**Mold:** a synctitium that may grow via apical extension and form branched hyphal networks.

The mold morphotype of *Candida albicans* is invasive. *Aspergillus* is only found in the mold form.

Most pathogens involved in superficial, cutaneous, and deep tissue mycoses EXCEPT *Malassezia furfur* and *Sprothrix schenkii*

**Pseudohyphae**: linear synctitium formed by incomplete septation during budding or fission

**Dimorphic:** *Malassezia furfur*, *Histoplasma capsulatum*, *Coccidoides, Sporothrix schenkii*, *Candida albicans*

**TYPES OF INFECTION**

Superficial: confined to the stratum corneum or cuticle of hair shaft

Typically limited host immune response

*Malassezia furfur*, *Exophiala weneckii*, *Trichosporon beigelli*, *Piedraia hortai*

Cutaneous: involvement of all epidermal layers, nails, and cortex of hair shafts. Caused by **dermatophytes**.

*Trichophyton, Microsporum, Epidermophyton*

Subcutaneous: Dermis, subcutaneous adipose, fascia, bone

Sporotrichosis, zygomycosis, mycetoma

Systemic: inoculation via RT and metastasis via hematogensous or lymphatic spread.

*Histoplasma capsulatum, Blastomyces dermatitidis, Coccidoides*

Typically dimorphic. Affect immunocompetent patients.

Opportunistic: Require immunocompromised host

*Cryptococcus neoformas, Penicillium marneffei, Candida albicans*, *Aspergillus, Pneumocystis jiroveci*

**ALLERGIES:** *Alternaria, Cladosporum, Aspergillus, Penicillium* (cheese-washers lung)

**MYCOTOXICOSIS:** *Aspergillus* produces aflatoxin, a potent hepatic carcinogen. *Claviceps pupurea* produces ergot alkaloids, causing peripheral necrosis + gangrene

**HOST DEFENSE:** Primarily innate immunity and CMI. *Aspergillus* is typically cleared by neutrophils.

| Organism | Classification<br>Morphology | Human Pathology and Natural History | Specialized<br>Virulence | Diagnosis and<br>Notes | Treatment<br>Vaccination |
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| **SUPERFICIAL MYCOSES** | | | | | |
| *Malassezia furfur* | **Dimorphic**<br>Yeast form is NF<br>Hyphal form is pathogenic | **Tinea versicolor**<br>**Dandruff + Seborrheic Dermatitis**<br>Seen in HIV +ve patients<br>**Sepsis**<br>Seen in infants on TPN with concentrated essential lipids. | Lipophilic<br>Colonizes the sebaceous glands<br>Hyphal form is pathogenic<br>Yeast form is commensal | | |
| *Exophilia weneckii* | | **Tinea Nigra**<br>Causes brown lesions, typically on the extremities. Confused with carcinoma. | | | |
| *Trichosporon beigelli* | | **White piedra** | Cause infections of the hair cuticles (thus classified as superficial mycoses) | | |
| *Piedraia hortai* | | **Black piedra** | | | |
| **CUTANEOUS MYCOSES (DERMATOPHYTES, TINEAE, RINGWORMS)** | | | | | |
| *Trichophyton*<br>*Microsporum*<br>*Epidermophyton* | | **Tinea capitis, nabae, manuun, pedis, unguium**<br>Infection classified based on anatomic involvement | Keratinophilic<br>Typically infects nonviable keratinized layers of the epidermis, but may extend to the demris | | |
| **DEEP-TISSUE MYCOSES** | | | | | |
| Typically found in soil and decaying material<br>Inoculation via traumatic implantation. Lesions develop at site of entry.<br>Invasion of the dermis and subcutaneous tissue + extension though epidermis<br>Lymphatic dissemination<br>Surgical debridement or amputation is usually necessary<br>Can be confused with infection by actinomycetes, streptomycetes, abd mycobacteria | | | | | |
| *Sporothrix Schenckii* | Dimorphic<br>Environment: mold<br>Host: yeast (thermal control of morphology) | **Sporotrichosis** (Gardner's Disease)<br><br>**Lymphocutaneous Disease** | | | |

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| | | Traumatic implantation → punctuate and painless nodule → fixation → progressive enlargement to a fluctuant mass → ulceration<br>Does not disseminate beyond local lymphatics<br><br>**Pulmonary Disease**<br>Inhalation → primary disease and colonization of cavitary lesisons<br>**Cutaneous, Mucocutaenous, and Disseminated Disease** | | |
| *Zygomycota* (*Absidia, Condiobolus)* | | **Rhinocerebral Zygomycosis**<br>An emergent and fulminant infection<br>RF: DKA, neutropenia<br>**Rhinofacial Zygomycosis**<br>Progressive disfigurement due to direct extension from nasal sinuses<br>**Cutaneous, Mucocutenaous, and Subcutaneous Disease** | Transmission by inhalation (affects sinuses and lungs) OR direct implantation | |
| *Pseudallescheria boydii*<br>*Madurella grisea* | | **Mycetoma**<br>Chronic supperative infection<br>Involves subcutaneous tissue + subjacent deep fascia and bone<br>Typically affect the extremities<br>Granular prurulent drainage | | |
| Dematiceous Fungi | | **Chromoblastomycosis**<br>Crusted verrucous lesions with granulomatous inflammation<br>LM shows sclerotic bodies with brown pigmenetaiton<br>**Phaeohyhomycosis**<br>Brown septate hyphae in tissue sections<br>No sclerotic bodies | Produce melanin<br>Introduced via traumatic implantation | |
| **OPPOTUNISTIC FUNGAL PATHOGENS** | | | | |
| *Cryptococcus Neoformans* | Uninucleate Budding Yeast | **Ecology**<br>Ubiquitous in environment. Concentrated in guano from pigeons<br>**Distribution**<br>Worldwide<br>**Epidemiology**<br>Exposure is universal.<br>Leasing cause of meningitis in AIDS patients and other immunocompromise | **Capsule**<br>GXM + GalXM + mannoprotein<br>Exhibits structural and antigenic variation<br>Bases for serotyping<br>The capsule is shed and may be detected in the CSF and serum<br>Antiphagocytic (anionic, massive volume, protection of cell wall antigens)<br>Depletion of complement | Severe infection:<br>Amphotericin B and 5-flucytosine → fluconazole<br><br>Limited Infection and prophylaxis:<br>Fluconazole |

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| | | var. grubii (Serotype A) is the major cause of human disease<br><br>**Pulmonary Disease**<br>Focal infiltrates, diffuse interstitial pneumona, pleural effusion, ARFD<br>**Disseminated Disease**<br>Meningitis, encephalitis, cutaneous infection<br>The prostate is a reservoir site | Suppression of CMI, chemotaxis, NO synthesis<br>The capsule size is regulated by iron and CO2<br>**Phenoloxidase**<br>Result in conversion of phenols to quinines and melanin.<br>Resistance to ROSs<br>Resistance to antifungal agents, phagocytosis, pH, and UV<br>**Complex Signal Tranduction** | |
| *Penecullium Marneffei* | Dimorphic<br>Environment: mold<br>Host: yeast (replicates via fission)<br><br>Intracellular organism | **Distribution**<br>Restricted to Thailand<br><br>**Systemic Disease**<br>Affects HIV +ve patients with travel history or residence in endemic areas | | |
| *Candida Albicans* | Dimorphic<br>Yeast are NF<br>Hyphal forms are invasive<br>Psuedohyphae common<br>Germ tubes (associated with yeasts)<br><br>Pathogenic forms are: hyphae, germ tubes, and pseuudohyphae<br><br>Yeasts can be seen in disseminated disease | **Cutaneous**<br>Dermatitis, par/onychomycosis, otitis externa<br>**Mucosa**<br>Vaginitis, oropharyngeal cadidiasis (thrush), esophagitis, perianal infection<br>**Chronic Mucocutaenous Candidiasis**<br>Defect in CMI. Infection of skin, nais, and oropharynx without invasion.<br>**Invasive and Disseminated Diseas**<br>Pulmonary involvement, fugemia, endocaridtis, meningitis, endopthalmitis, dissemination thoughout skin (hematogenous), UTI<br><br>**Epidemiology**<br>Leading pathogen in AIDS patients (nearly universal infection)<br>BUT disseminated disease is | **Dimorphism**<br>**Adhesins**<br>Molecular similarity to mammalian integrin complement receptors (CR3, CR4)<br>**Hydrolytic Enzymes**<br>**Antigen Variation** | Limited infection:<br>topical antifungals, oral azoles<br><br>Intermediate infections:<br>IV azoles or echinocandins<br><br>Severe infection:<br>IV amphotericin B or echinocandins<br><br>Most serovars are susceptible to antifungal agents<br>*C. glabrata* and C. krusei are resistant to fluconazole |

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| | | uncommon<br>4th leading cause of nosocomial bloodsteam infection (overall)<br><br>Immunocompetent: susceptible to superficial cutaneous + mucosal infections<br><br>**Epidemiology**<br>Nearly universal in patients with AIDS. Occurs early in HIV viremia. | | |
| *Aspergillus* spp. | Mold only<br>Demonstrates hyphal forms and **condia** | **Hypersensitivity Pneumonitis**<br>**Allergic Bronchopulmonary Aspergillosis**<br>**Mycotoxicosis**<br>Due to aflatoxins (raw or processed seeds + nuts). Cause hepatitis and hepatic carcinoma.<br>**Colonization of preexisting lesions**<br>e.g. aspergilloma development in bullous emphysema<br>Mass effect may cause bronchial obstruction<br>RF: anatomic anaomlies (e.g. cavitary lung lesions, smoking)<br>**Invasive Pulmonary Aspergillosis (IPA)**<br>Results in necrotizing granulomatous inflammation. May cause massive hemoptysis.<br>**Dissemination**<br><br>**Host Defense**<br>Neutrophils clear hyphal forms<br>Macrophages clear conidia<br><br>Neutropenia is a RF for disseminated disease and locally invasive apsergillosis. | **Allergens**<br>Does not require inncoualtion with viable organism<br>**Toxins**<br>**Hydrolytic Enzymes** | DOC:<br>voriconazole<br><br>Transplant:<br>voriconazole + echinocandin<br><br>Prophylaxis: Posaconazole<br><br>High dose amphotericin B may be used, bhut is not the preferred therapy |
| *Pneumocystis jiroveci* | **Trophozoites**<br>The major morphology in the host.<br>**Cysts**<br>Larger form. Generation by fusion of trophozoites | **Diffuse Interstitial Pneumonia (DIP) or Pneumocystis Pneumonia (PCP)**<br>Direct damage of Type I pneumocytes by Trophozoites. Formation of cysts within the lung parenchyma. Alveolar airspaces filled with eosinophilic infiltrate (resembles ARDS). | **Major Surface Glycoporotein (MSG)**<br>Demonstrates significant antigenic variation<br><br>**Atypical Features** | Treatment and prophylaxis:<br>TMP-Sulfa<br>Dapsone, pyrimethamine<br><br>Acute Illness (e.g. ARDS):<br>Prednisone |

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| | (haploid) and subsequent meiosis | **Disseminated disease**<br><br>**Unknown reservoir and mode of transmission**<br>**Presumed:** environmental exposure and transmission via respiratory tract<br><br>PCP occurs in most AIDS patients (70 – 80%)<br>Causes 15 – 20% of mortality in AIDS patients | Resistance to amphotericin B<br>No ergosterol in cell membrane (has cholesterol).<br>Susceptibility to TMP-Sulfa and antiparasitic agens<br>Conversion between cyst forms (nonmotile) and trophozoites (mobile)<br>Fragile cell wall<br>Cannot be cultured in media<br><br>**Diagnosis**<br>Cannot be cultured<br>Almost all individuals are seropositive<br>Gold standard: lung Bx or LAB | |

## DIMORPHIC SYSTEMIC FUNGAL INFECTION

**Transmission**
Occurs though the respiratory tract. Infectious mold particles are inhaled and enter the small airways.
May occur via direct inoculation
No horizontal transmission.

**Morphology**
Thermally regulated dimorphism (conversion to pathogenic form in host)
Exist as **molds** in the environment
- Hc, Bd, Pb: convert to budding yeast
- *Coccidioides*: converns to endosporulating spherule (collection of spores)

**Diagnosis**
Gold standard is culture
Typically: Bx with clinical Hx and non-response to antibacterial Abx

*Histoplasma*: specific Ag-detection assay for acute disseminated disease (esp. in AIDS patients). Samples may be obtained from urine (renal elimination), serum, and CSF. High specificicity and sensitivity in target populations.
*Blastomycosis*: specific Ag=detection assay (similar to Hc), but significant x-reactivity with Hc, Pb, and *Penicillium marneffei*

Serology: Histoplasmosis, Coccidioidomycosis, Blastomycosis
- Specificity: limited by antigen selection and cross-reactivity
- Sensitivity: limited by host AMI response (cannot use with acute disease or in immunocompromise)

Skin test: Histoplasmosis. Based on DTH. Detects latent disease but is not used to Dx acute infection.

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| *Histoplasma capsulatum* (Hc) | Environment: multinucleated hyphal forms with tuberculate macroconidia and microconidia<br><br>Host: uninucleate budding yeast. Intracellular (infection of macrophages) and extracellular | **Pumonary Lesions**<br>Can present as a wide variety of lesion types (focal, cavitary)<br>RF: emphysema<br>**Mucocutaneous**<br>**Disseminated**<br>Requires extracellular population of organisms. Lymphatic and hematogenous spread OR via motile macrophages if intracellular<br>**Ocular**<br>Results in calcifications; frequenctly seen in addition to chronic pulomary disease and disseminated infection<br><br>**Transmission** via inhalation of microconidia and hyphal fragments → rapid conversion to yeast → intracellular replication in macrophage phagolysosomes<br><br>Immunocompetent: Infection nearly universal, BUT most disease is subclinical and benign (primary pulmonary infection presents an non-specific flu-like syndrome)<br>Causes persistent latent infection and reactivation<br><br>**Host defence** is CMI: activated macrophages are fungistatic; require therapy for fungicidal activity<br><br>**Epidemiology**<br>Leading fungal RTI worldwide<br>Leading systemic mycosis in the US<br>Leading non-opportunistic endemic mycosis in AIDS patients<br>**Ecology**<br>Favors nitrogenous soil and droppings from birds | **Intracellular residence in macrophage phagolysosomes**<br><br>**Binding to phagocyte glycoprotein receptors (CD18, CD11a)**<br>Avoids activation of oxidative burst<br><br>**Resistance to acidification of phagolysosome**<br><br>**Dx**<br>Serology<br>Direct Ag detection (in acute disseminated disease affecting AIDS patients)<br>Skin test for latent or endemic disease | DOC for severe infection:<br>IV amphotericin B<br><br>Mild disease, resolution, or prophylaxis in immonocompromised background:<br>Itraconazole solution |

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| | | **Distribution**<br>Worldwide<br>Mississippi and Ohio River valleys | | |
| *Blastomyces dermatitidis* (Bd) | Environment: Hypae with uninucleate microconidea<br><br>Host: multinucleate budding yeast | **Acute Pulmonary Disease**<br>**Chronic Pulmonary Disease**<br>**Diffuse Dissemination**<br>Cutaneous mycoses, UG infection, osseous infection<br><br>Primary pulmonary infection is typically asymptomatic; patients present with chronic cutaneous and osseous manifestations<br>Prominent in dogs<br><br>**Ecology**<br>Found in acidic soil<br>**Distribution**<br>Equivalent geographical distribution to Hc in US.<br>**Epidemiology**<br>Weakly associated with HIV co-infection | **Bad1**<br>Secreted and rebinds to chitin in fungal cell wall<br>Homology to *Yersinia* invasion protein<br>Expressed by yeast form only<br>Adhesin: binding to host macrophages via integrins (similar to Hc)<br>Depresses host TNF-α release (TGF-β dependent *and* independent)<br><br>**Dx**<br>Direct Ag-detection (x-reactivity with Hc, Pb, *Penicillium marneffei*)<br>Serology | DOC: amphotericin B<br><br>Mild disease in immunocompromised background:<br>Itraconazole solution<br><br>AIDS patients are not treated prophylactically since the disease has a low prevalence |
| *Coccidioides immitis*<br>*Coccidioides posadasii* | Environment: septate hyphae + alternating arthroconidia and inviable vacuolated cells<br><br>Host: endosporulating spherule. | **Primary pulmonary disease** is typically asymptomatic, but may result in severe fungal pneumonia<br>**Disseminated** diseasehas a a high mortality<br><br>Common presentations: meningitis, bone infection, cutnaeous mycoses<br>Seen in early HIV viremia<br><br>**Ecology**<br>Favors soil with calcium sulfate, borates, and semiarid climates<br><br>**Geographic distribution**<br>Southwestern US<br><br>**Epidemiology**<br>Highest incidence in late summer and early | **Secreted Hydrolases**<br><br>**Dx**<br>Serology | Resistant to amphotericin B and azoles<br><br>Typically employ multidrug therapy: amptecerin B, fluconazole, itraconazole |

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| | | autumn + after soil disruptions<br>Highest virulence: only small inoculum (<10 organisms) required | | |
| *Paracaoccidioides basiliense*s (Pb) | Envrironment: hyphae with variable sporulation<br><br>Host: yeast with mutiple attached buds | **Primary Pulmonary Infection**<br>Typically asymptomatic<br>**Chronic Pulmonary Infection**<br>**Disseminated Disease**<br>Ulcerative granulomatous lesions in mucous membranes (oral and nasal mucosa, GI tract)<br>Constitutional symptoms<br><br>**Geography**<br>Central and South America<br><br>**Ecology**<br>Moist soil in humid environments<br><br>**Epidemiology**<br>Disease presents predominately in males. | | |