## 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 syncytium 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 *Sporothrix schenkii*

**Pseudohyphae:** linear syncytium 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 hematogenous or lymphatic spread.
  - *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidoides*
  - Typically dimorphic. Affect immunocompetent patients.

**Opportunistic:** Require immunocompromised host
  - *Cryptococcus neoformans, Penicillium marneffei, Candida albicans, Aspergillus, Pneumocystis jiroveci*

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

### MYCOTOXICOsis:
*Aspergillus* produces aflatoxin, a potent hepatic carcinogen. *Claviceps purpurea* produces ergot alkaloids, causing peripheral necrosis + gangrene

### HOST DEFENSE:
Primarily innate immunity and CMI. *Aspergillus* is typically cleared by neutrophils.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Classification Morphology</th>
<th>Human Pathology and Natural History</th>
<th>Specialized Virulence</th>
<th>Diagnosis and Notes</th>
<th>Treatment Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUPERFICIAL MYCOSES</strong></td>
<td></td>
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<td></td>
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</tbody>
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| *Malassezia furfur*     | Dimorphic                 | *Tinea versicolor*  
Dandruff + Seborrhoeic Dermatitis  
Seen in HIV+ve patients  
*Sepsis*  
Seen in infants on TPN with concentrated essential lipids. | Lipophilic  
Colonizes the sebaceous glands  
Hyphal form is pathogenic  
Yeast form is commensal |                     |                       |
| *Exophilia weneckii*    |                           | *Tinea Nigra*  
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**   |                           |                                                                                                       |                       |                     |                       |
| *Trichophyton*          |                           | *Tinea capitis, nabaee, manuun, pedis, unguium*  
Infection classified based on anatomic involvement | Keratinophilic  
Typically infects nonviable keratinized layers of the epidermis, but may extend to the dermis |                     |                       |
| *Microsporum*           |                           |                                                                                                       |                       |                     |                       |
| *Epidermophyton*        |                           |                                                                                                       |                       |                     |                       |
| **DEEP-TISSUE MYCOSES** |                           |                                                                                                       |                       |                     |                       |
| *Sporothrix Schenckii*  | Dimorphic                 | *Sporotrichosis* (Gardner’s Disease)  
Lymphocutaneous Disease |                       |                     |                       |
<table>
<thead>
<tr>
<th>Zygomyctota (Absidia, Condiobolus)</th>
<th>Rhinocerebral Zygomycosis</th>
<th>Transmission by inhalation (affects sinuses and lungs) OR direct implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinofacial Zygomycosis</td>
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<tr>
<td>Cutaneous, Mucocutaneous, and Disseminated Disease</td>
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<tr>
<td>Pseudallescheria boydii Madurella grisea</td>
<td>Mycetoma</td>
<td>Produce melanin Introduce via traumatic implantation</td>
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<tr>
<td>Dematiceous Fungi</td>
<td>Chromoblastomycosis</td>
<td>Produce melanin Introduce via traumatic implantation</td>
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<tr>
<td>Cryptococcus Neoformans</td>
<td>Uninucleate Budding Yeast</td>
<td>Ecology Ubiquitous in environment. Concentrated in guano from pigeons Distribution Worldwide Epidemiology Exposure is universal. Leasing cause of meningitis in AIDS patients and other immunocompromise</td>
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<tr>
<td><strong>Penicillium Marneffei</strong></td>
<td><strong>Distribution</strong></td>
<td><strong>Systemic Disease</strong></td>
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<tr>
<td>Dimorphic</td>
<td>Restricted to Thailand</td>
<td>Affects HIV +ve patients with travel history or residence in endemic areas</td>
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<td>Environment: mold</td>
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<td>Host: yeast (replicates via fission)</td>
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<td>Intracellular organism</td>
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<tr>
<th><strong>Candida Albicans</strong></th>
<th><strong>Cutaneous</strong></th>
<th><strong>Dimorphism</strong></th>
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<tbody>
<tr>
<td>Dimorphic</td>
<td>Dermatitis, par/onychomycosis, otitis externa</td>
<td>Adhesins</td>
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<td>Yeast are NF</td>
<td>Mucosa</td>
<td>Molecular similarity to mammalian integrin complement receptors (CR3, CR4)</td>
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<td>Hyphal forms are</td>
<td>Vaginitis, oropharyngeal candidiasis (thrush), esophagitis, perianal infection</td>
<td>Hydrolytic Enzymes</td>
</tr>
<tr>
<td>invasive</td>
<td>Chronic Mucocutaenous Candidiasis</td>
<td>Antigen Variation</td>
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<td>Psuedohyphae common</td>
<td>Defect in CMI. Infection of skin, nails, and oropharynx without invasion.</td>
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<td>Germ tubes (associated with yeasts)</td>
<td>Invasive and Disseminated Diseases</td>
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<td>Yeasts can be seen in disseminated disease</td>
<td>Pulmonary involvement, fungemia, endocarditis, meningitis, endophthalmitis, dissemination throughout skin (hematogenous), UTI</td>
<td>Limited infection: topical antifungals, oral azoles</td>
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<tr>
<td>Pathogenic forms are: hyphae, germ tubes, and pseudohyphae</td>
<td>Epidemiology</td>
<td>Intermediate infections: IV azoles or echinocandins</td>
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<td>Leading pathogen in AIDS patients (nearly universal infection)</td>
<td>Severe infection: IV amphotericin B or echinocandins</td>
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<td>BUT disseminated disease is</td>
<td>Most serovars are susceptible to antifungal agents</td>
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<td>C. glabrata and C. krusei are resistant to fluconazole</td>
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| **Aspergillus spp.** | Mold only | **Hypersensitivity Pneumonitis**  
**Allergic Bronchopulmonary Aspergillosis**  
**Mycotoxicosis**  
Due to aflatoxins (raw or processed seeds + nuts). Cause hepatitis and hepatic carcinoma.  
**Colonization of preexisting lesions**  
e.g. aspergilloma development in bullous emphysema  
Mass effect may cause bronchial obstruction  
RF: anatomic anomalies (e.g. cavitary lung lesions, smoking)  
**Invasive Pulmonary Aspergillosis (IPA)**  
Results in necrotizing granulomatous inflammation. May cause massive hemoptysis.  
**Dissemination**  
**Host Defense**  
Neutrophils clear hyphal forms  
Macrophages clear conidia  
Neutropenia is a RF for disseminated disease and locally invasive aspergillosis. | **Allergens**  
Does not require inoculation with viable organism  
**Toxins**  
**Hydrolytic Enzymes** | **DOC:** voriconazole  
**Transplant:** voriconazole + echinocandin  
**Prophylaxis:** Posaconazole  
High dose amphotericin B may be used, but is not the preferred therapy |
| **Pneumocystis jiroveci** | Trophozoites  
The major morphology in the host.  
**Cysts**  
Larger form. Generation by fusion of trophozoites | **Diffuse Interstitial Pneumonia (DIP) or Pneumocystis Pneumonia (PCP)**  
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 Glycoprotein (MSG)**  
Demonstrates significant antigenic variation  
**Atypical Features**  
**Treatment and prophylaxis:** TMP-Sulfa  
Dapsone, pyrimethamine  
**Acute Illness (e.g. ARDS):** Prednisone |
### 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: converts 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 specificity 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. |

| Disseminated Disease | Unknown reservoir and mode of transmission. Presumed: environmental exposure and transmission via respiratory tract. PCP occurs in most AIDS patients (70 – 80%). Causes 15 – 20% of mortality in AIDS patients. |

| Resistance to amphotericin B | No ergosterol in cell membrane (has cholesterol). Sensitivity to TMP-Sulfa and antiparasitic agents. Conversion between cyst forms (nonmotile) and trophozoites (mobile). Fragile cell wall. Cannot be cultured in media. Diagnosis: Cannot be cultured. Almost all individuals are seropositive. Gold standard: lung Bx or LAB. |
| **Histoplasma capsulatum (Hc)** | **Environment:** multinucleated hyphal forms with tuberculate macroconidia and microconidia  
**Host:** uninucleate budding yeast. Intracellular (infection of macrophages) and extracellular  
**Pulmonary Lesions**  
Can present as a wide variety of lesion types (focal, cavitary)  
**RF:** emphysema  
**Mucocutaneous Disseminated**  
Requires extracellular population of organisms. Lymphatic and hematogenous spread OR via motile macrophages if intracellular  
**Ocular**  
Results in calcifications; frequently seen in addition to chronic pulmonary disease and disseminated infection  
**Transmission** via inhalation of microconidia and hyphal fragments → rapid conversion to yeast → intracellular replication in macrophage phagolysosomes  
Immunocompetent: Infection nearly universal, BUT most disease is subclinical and benign (primary pulmonary infection presents an non-specific flu-like syndrome)  
Causes persistent latent infection and reactivation  
**Host defence** is CMI: activated macrophages are fungistatic; require therapy for fungicidal activity  
**Epidemiology**  
Leading fungal RTI worldwide  
Leading systemic mycosis in the US  
Leading non-opportunistic endemic mycosis in AIDS patients  
**Ecology**  
Favors nitrogenous soil and droppings from birds | **Intracellular residence in macrophage phagolysosomes**  
**Binding to phagocyte glycoprotein receptors (CD18, CD11a)**  
Avoids activation of oxidative burst  
**Resistance to acidification of phagolysosome**  
**Dx**  
**Serology**  
Direct Ag detection (in acute disseminated disease affecting AIDS patients)  
Skin test for latent or endemic disease  
**DOC for severe infection:**  
IV amphotericin B  
Mild disease, resolution, or prophylaxis in immunocompromised background: Itraconazole solution
<table>
<thead>
<tr>
<th>Distribution Worldwide Mississippi and Ohio River valleys</th>
<th><strong>Blastomyces dermatitidis</strong> <em>(Bd)</em> Environment: Hypae with uninucleate microconidea Host: multinucleate budding yeast</th>
<th><strong>Acute Pulmonary Disease</strong> <strong>Chronic Pulmonary Disease</strong> <strong>Diffuse Dissemination</strong> Cutaneous mycoses, UG infection, osseous infection Primary pulmonary infection is typically asymptomatic; patients present with chronic cutaneous and osseous manifestations Prominent in dogs</th>
<th><strong>Bad1</strong> Secreted and rebinds to chitin in fungal cell wall Homology to <em>Yersinia</em> invasion protein Expressed by yeast form only Adhesin: binding to host macrophages via integrins (similar to Hc) Depresses host TNF-α release (TGF-β dependent and independent) <strong>Dx</strong> Direct Ag-detection (x-reactivity with Hc, Pb, <em>Penicillium marneffei</em>) Serology</th>
<th><strong>DOC:</strong> amphotericin B Mild disease in immunocompromised background: Itraconazole solution AIDS patients are not treated prophylactically since the disease has a low prevalence</th>
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<tr>
<td><strong>Coccidioides immitis</strong> <em>Coccidioides posadasii</em> Environment: septate hyphae + alternating arthroconidia and inviable vacuolated cells Host: endosporulating spherule.</td>
<td><strong>Primary pulmonary disease</strong> is typically asymptomatic, but may revert to severe fungal pneumonia <strong>Disseminated</strong> disease has a high mortality Common presentations: meningitis, bone infection, cutaneous mycoses Seen in early HIV viremia</td>
<td><strong>Secreted Hydrolases</strong></td>
<td><strong>Resistant to amphotericin B and azoles</strong> Typically employ multidrug therapy: amphotericin B, fluconazole, itraconazole</td>
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<td><strong>Ecology</strong> Favors soil with calcium sulfate, borates, and semiarid climates <strong>Geographic distribution</strong> Southwestern US <strong>Epidemiology</strong> Highest incidence in late summer and early</td>
<td><strong>Dx</strong> Serology</td>
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| **Paracoccidioides brasiliensis (Pb)** | autumn + after soil disruptions  
Highest virulence: only small inoculum (<10 organisms) required |  |

**Environment:** hyphae with variable sporulation  
**Host:** yeast with multiple attached buds

| **Primary Pulmonary Infection**  
Typically asymptomatic  
**Chronic Pulmonary Infection**  
**Disseminated Disease**  
Ulcerative granulomatous lesions in mucous membranes (oral and nasal mucosa, GI tract)  
Constitutional symptoms |

**Geography**  
Central and South America

**Ecology**  
Moist soil in humid environments

**Epidemiology**  
Disease presents predominately in males.