Fungal Respiratory Infections (*Aspergillus, Histoplasma, Cryptococcus, Pneumocystis*)

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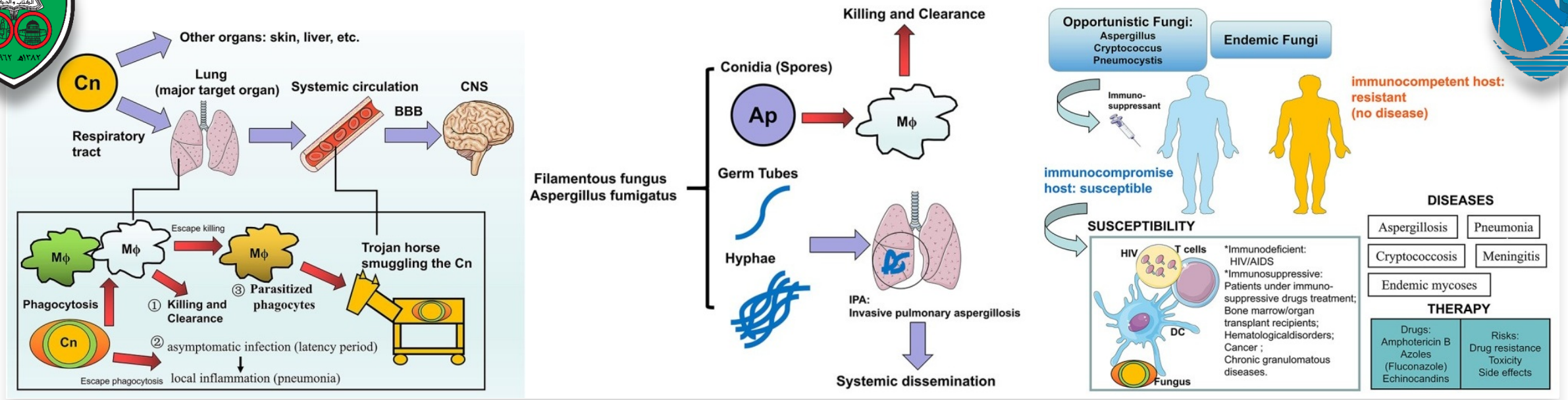


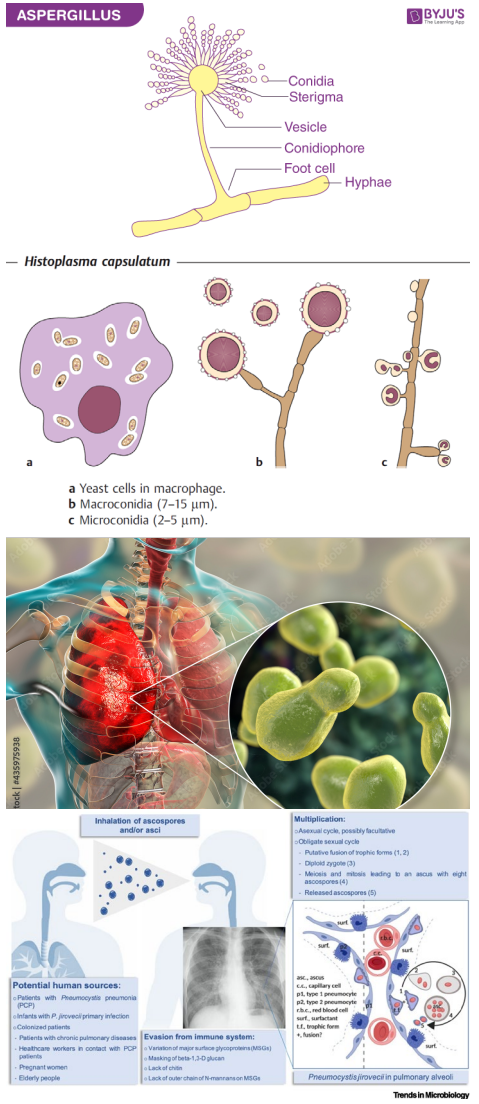
Source: Li, Zhi et al. “Pathogenic Fungal Infection in the Lung.” Frontiers in immunology vol. 10 1524. 3 Jul. 2019,

Fungi as causes of RTI

- The primary route of entry is the inhalation of airborne spores.
- The fungal RTI severity depends more on host immunity than inoculum size. In immunocompetent often asymptomatic or self-limited while in immunocompromised severe, invasive, or disseminated disease
- Fungal RTIs often mimic bacterial or TB pneumonia and are subacute or chronic and fail to respond to antibacterial therapy

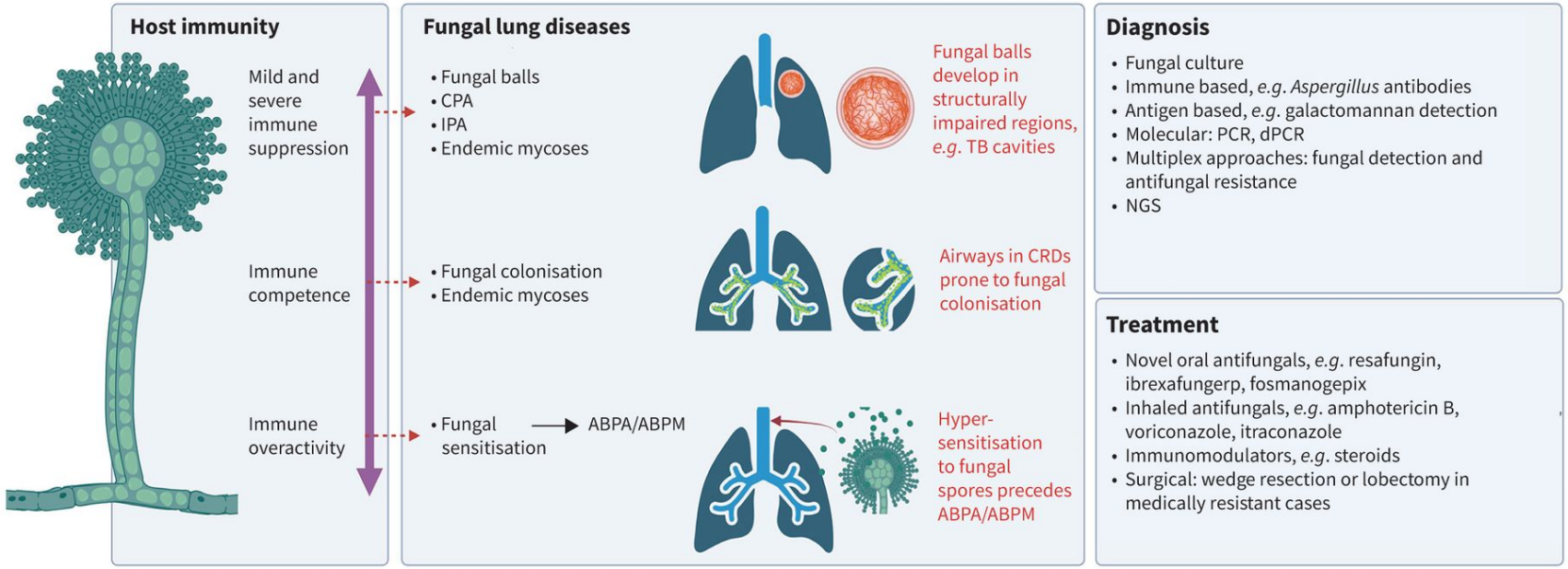
Why and when fungi are important causes of RTI?

- **The major respiratory fungal pathogens:**
- *Aspergillus*: Ubiquitous environmental mold causes opportunistic infections and allergic disease (e.g., aspergilloma and invasive aspergillosis)
- *Histoplasma capsulatum*: Dimorphic fungus associated with bird and bat droppings. Endemic exposure; pulmonary infection common. Also, other all endemic mycoses.
- *Cryptococcus neoformans*: Encapsulated yeast acquired by inhalation causing severe disease in immunosuppressed (especially CNS involvement)
- *Pneumocystis jirovecii*: Atypical fungus causes severe interstitial pneumonia classic in AIDS and advanced immunosuppression



When to suspect a fungal RTI

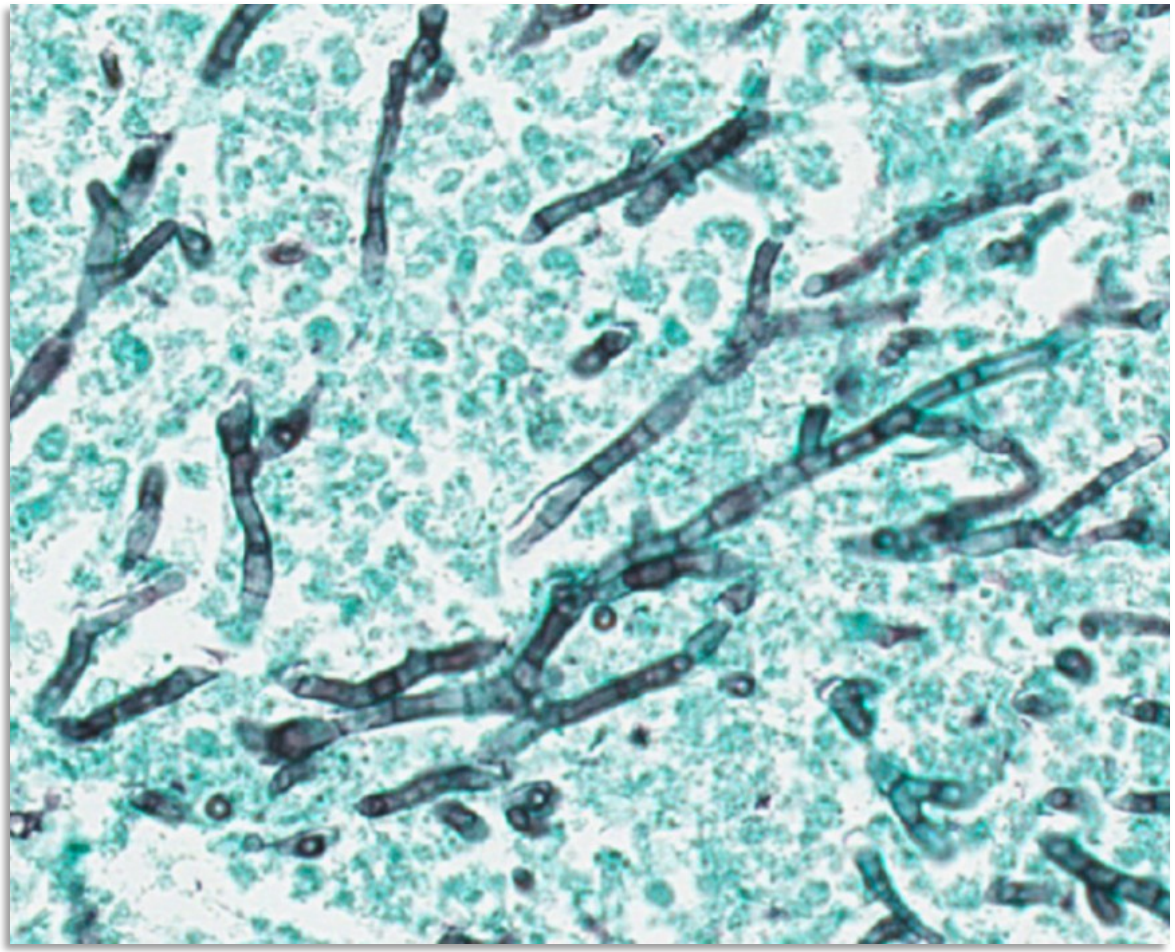
- Immunosuppression
  - HIV/AIDS
  - Transplant recipients
  - Prolonged corticosteroids or chemotherapy
- Structural lung disease
  - TB cavities
  - Bronchiectasis
  - COPD
- Environmental or occupational exposure
  - Bird or bat droppings
  - Construction, soil, caves
- Severe or atypical pneumonia
  - Hypoxia out of proportion to imaging
  - Diffuse interstitial patterns
- Poor response to antibiotics



Source: Jaggi, Tavleen Kaur et al. "Fungal lung disease." The European respiratory journal vol. 64,5 2400803. 28 Nov. 2024

Aspergillus

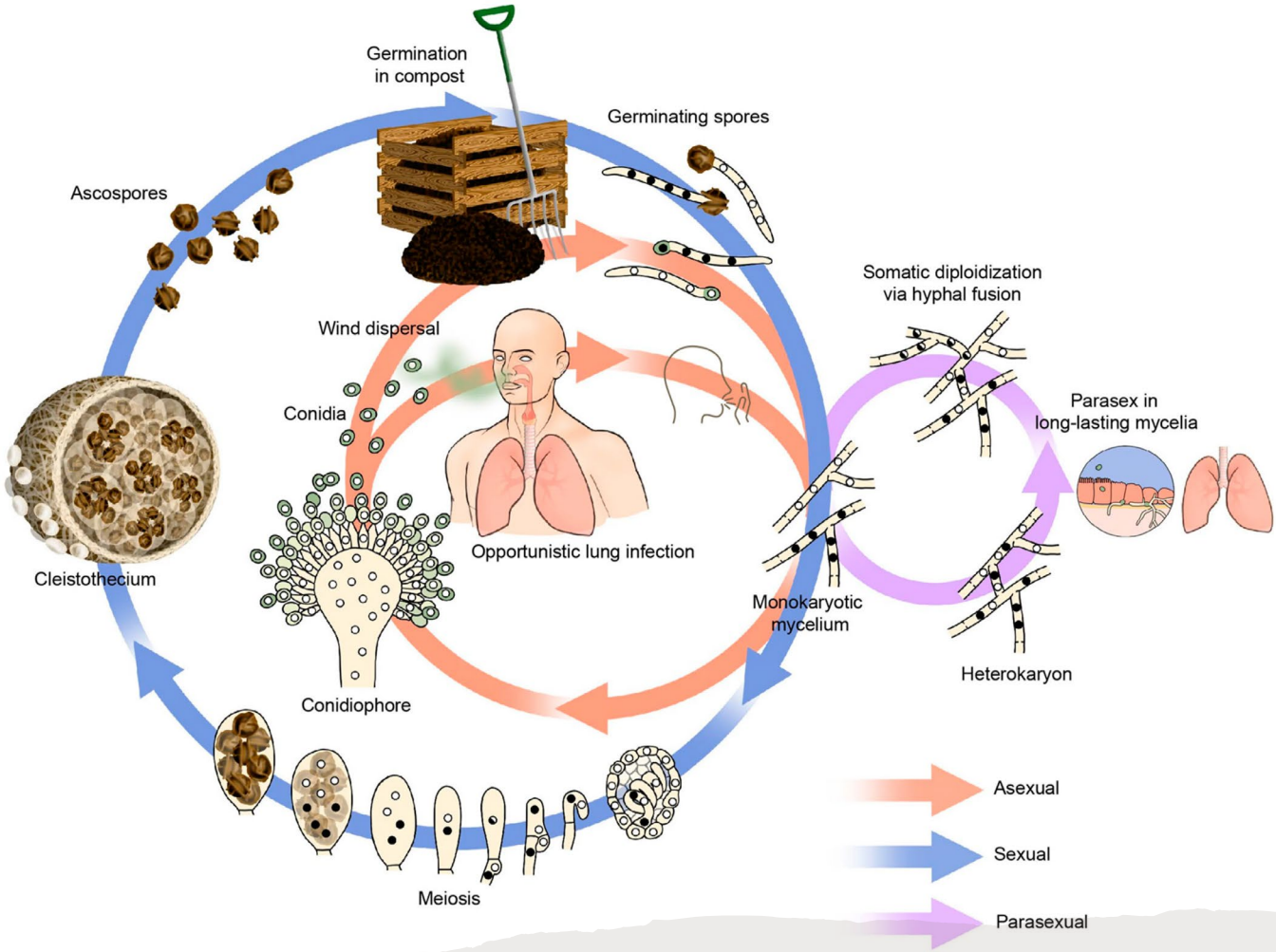
- **Morphology**
- Filamentous mold with septate hyphae
- Acute-angle (45°) branching and classic V-shaped appearance on histology
- Reproduces by conidia (airborne asexual spores)
- **Medically important species:**
- *Aspergillus fumigatus*: the most common and most pathogenic
- *Aspergillus flavus*: aflatoxin producer; invasive disease
- *Aspergillus niger*: colonization, otomycosis



Source: Larkin, P.M.K.; Multani, A.; Beaird, O.E.; Dayo, A.J.; Fishbein, G.A.; Yang, S. A Collaborative Tale of Diagnosing and Treating Chronic Pulmonary Aspergillosis, from the Perspectives of Clinical Microbiologists, Surgical Pathologists, and Infectious Disease Clinicians. J. Fungi 2020, 6, 106.

Aspergillus life cycle

- Inhalation of conidia which reach alveoli
- Immunocompetent host: Alveolar macrophages and neutrophils kill conidia and no disease
- Immunocompromised host (e.g., neutropenia, steroids): Conidia germinate leading to hyphal invasion of the lungs
- Angioinvasion resulting in thrombosis, infarction, hemorrhage and dissemination to brain, kidneys, heart



Source: Zhang, J.; Debets, A.J.M.; Verweij, P.E.; Snelders, E. Azole-Resistance Development; How the Aspergillus fumigatus Lifecycle Defines the Potential for Adaptation. J. Fungi 2021, 7, 599.

Aspergillus causes allergic disease in immunocompetent hosts, colonization in abnormal lungs, and invasive disease in immunocompromised patients

1. Allergic Bronchopulmonary Aspergillosis (ABPA)

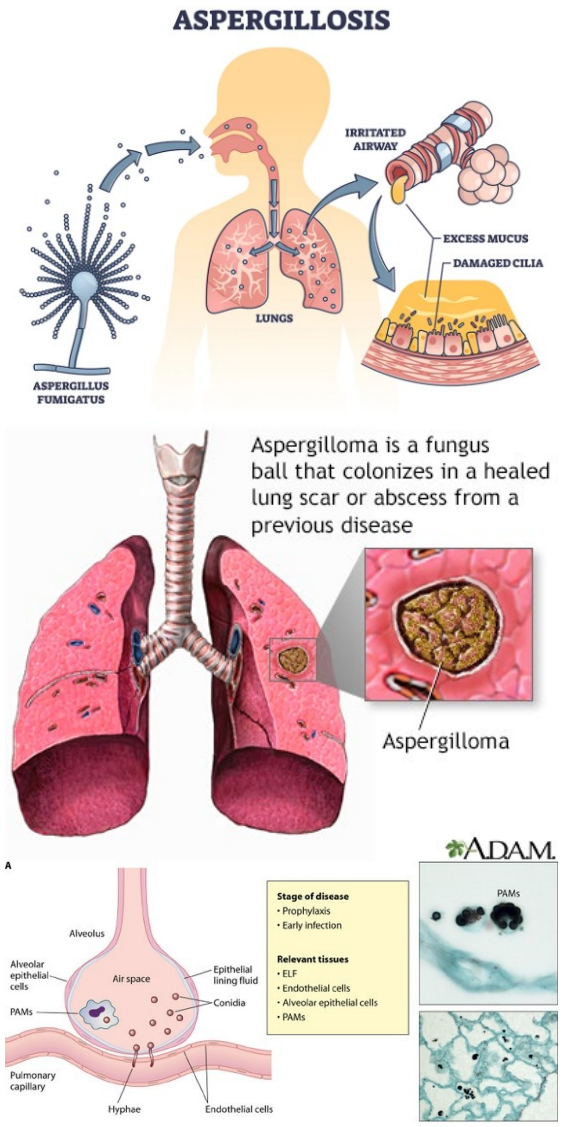
- Type I hypersensitivity reaction to *Aspergillus* antigens and it occurs in asthma and cystic fibrosis. Characterized by markedly elevated IgE and eosinophilia. Recurrent wheezing, mucus plugging, lung damage if untreated.

2. Aspergilloma (Fungus Ball)

- Colonization of a pre-existing lung cavity. Common predisposing conditions: Prior TB, sarcoidosis, old lung abscesses. Characterized by hemoptysis without tissue invasion

3. Invasive Pulmonary Aspergillosis (IPA)

- Occurs in neutropenia, hematologic malignancy, transplant recipients, prolonged corticosteroid use. Pathogenesis: Angioinvasion of blood vessels causing tissue necrosis, hemorrhage, thrombosis. High mortality without rapid diagnosis and treatment



Source: Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014 Jan;27(1):68-88.

Endemic mycoses in RTI

- Acquired by inhalation of spores (primary lung infection).
- Dimorphic fungi: Mold in environment, yeast (or spherule) in host.
- Disease severity depends on inoculum size, host immunity. Can cause asymptomatic infection, acute pneumonia, chronic pulmonary disease, and disseminated disease (immunocompromised)

Table 1

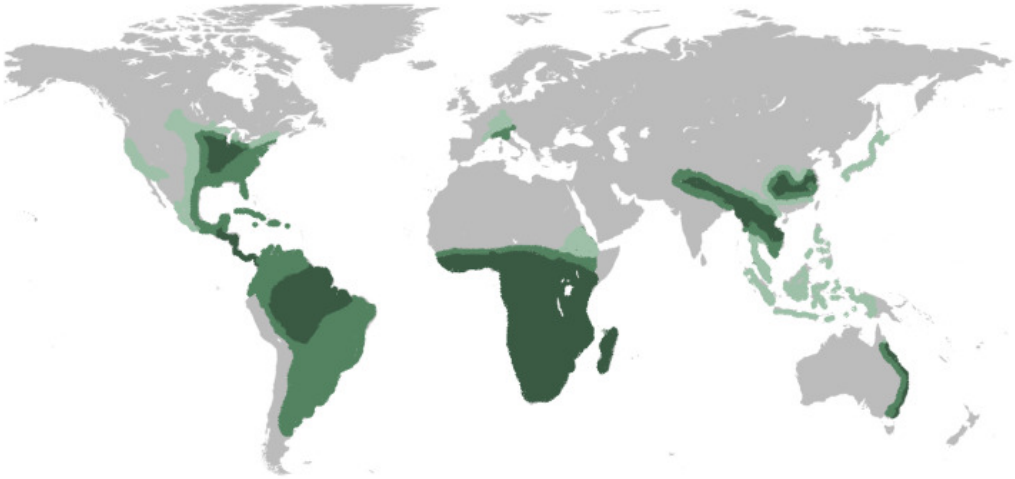
Imaging – an overview of possible chest imaging appearances in endemic mycoses.

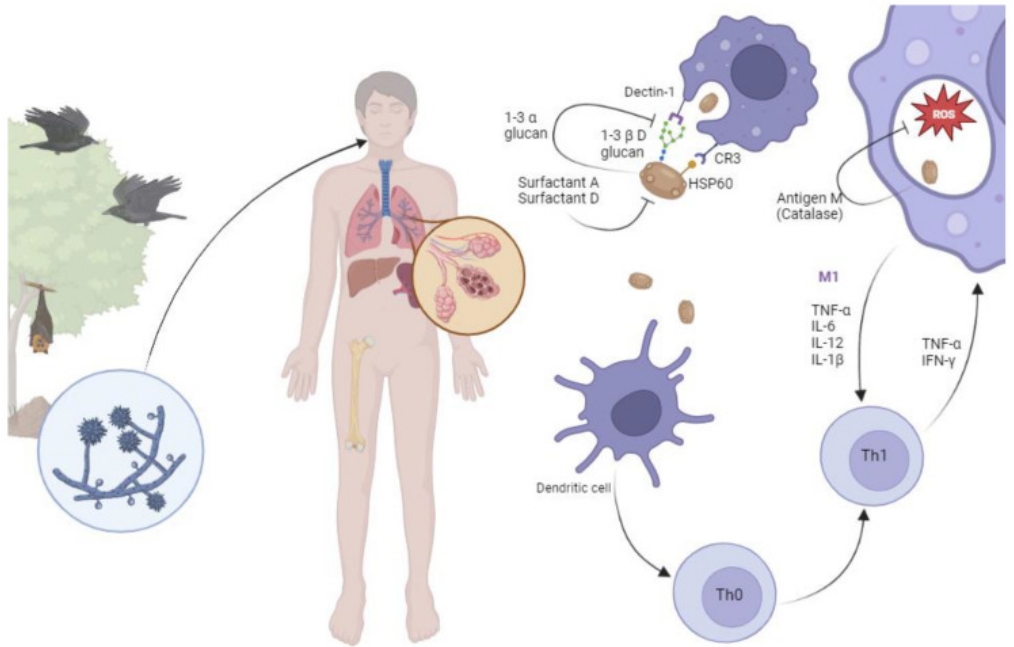
Radiological characteristics	Histoplasmosis	Coccidioidomycosis	Blastomycosis	Paracoccidioidomycosis	Talaromycosis
Consolidation (single or multiple lobes)		✓	✓	✓	
Pulmonary infiltrates	✓	✓	✓		✓
Nodules	✓	✓	✓	✓	✓
Miliary pattern	✓	✓	✓		✓
Cavities	✓	✓	✓	✓	✓
Mediastinal lymphadenopathy	✓	✓		✓	✓
Pleural effusions	✓	✓	✓	✓ (rare)	✓

Source: Wilson MJ, Harding I, Borman AM, Johnson E, Miller R. Pulmonary endemic mycoses. Clin Med (Lond). 2024 Jan;24(1):100014. doi: 10.1016/j.clinme.2024.100014. Epub 2024 Jan 23. PMID: 38382182; PMCID: PMC11024832.

Histoplasma capsulatum

- Intracellular survival similar to TB with granuloma formation turning into calcified nodules. The disease depends on exposure load and host immunity.
- The clinical forms include asymptomatic or mild flu-like illness (most cases). Acute pulmonary histoplasmosis (high inoculum). Chronic cavitary pulmonary histoplasmosis (e.g., COPD).

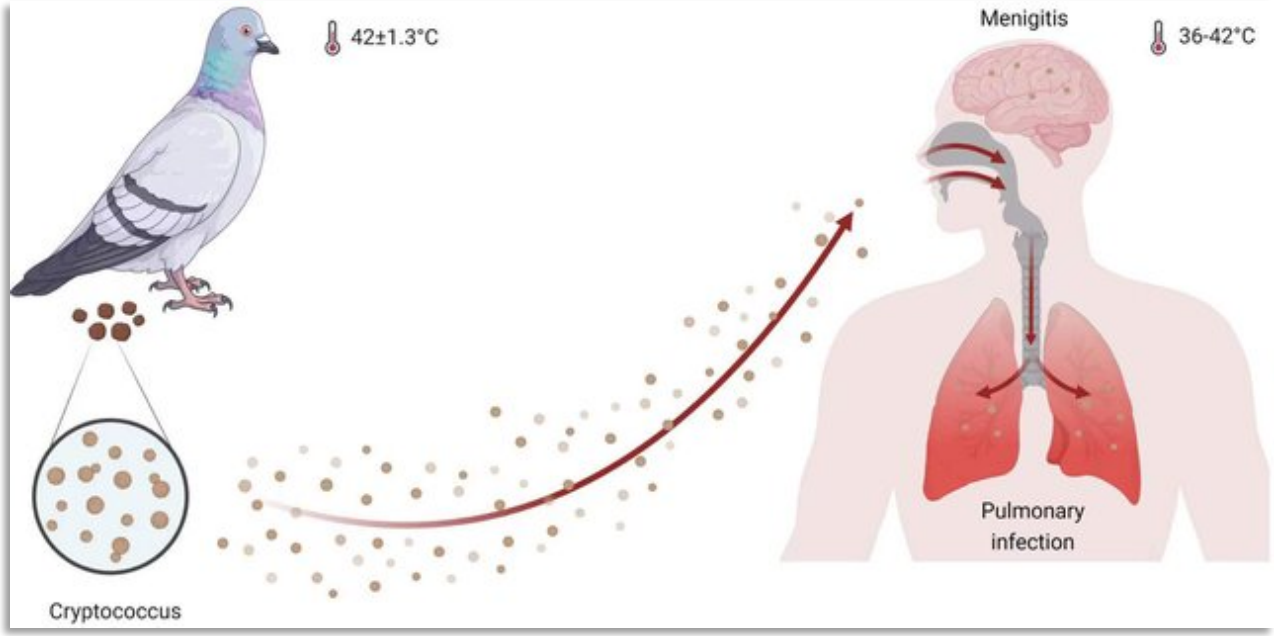




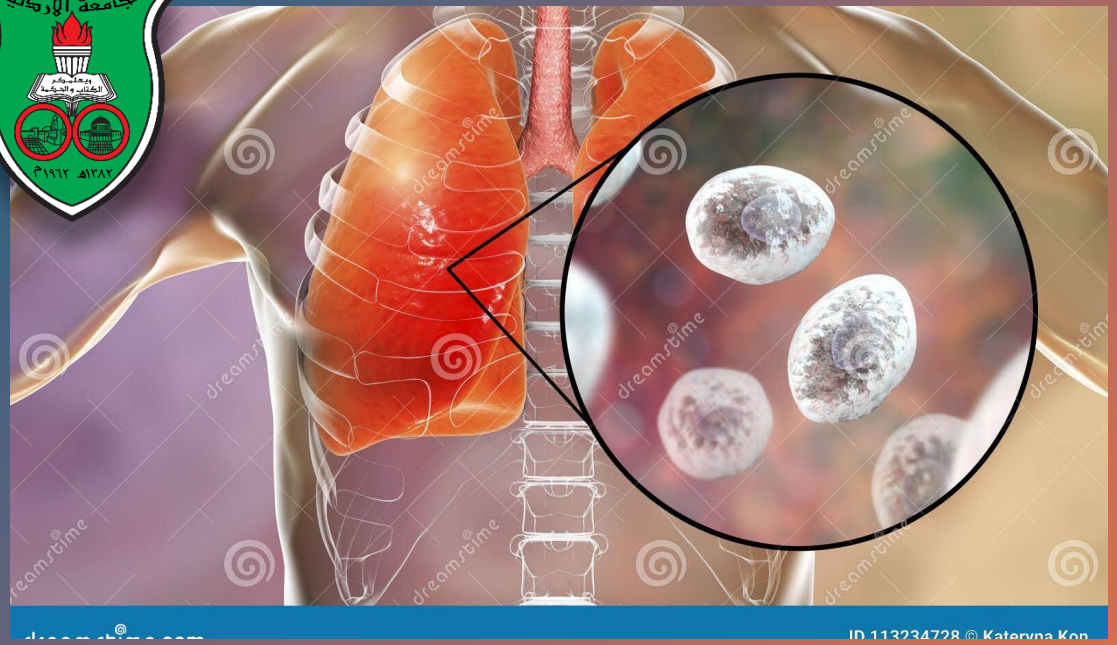
Barros, N., Wheat, J. L., & Hage, C. (2023). Pulmonary Histoplasmosis: A Clinical Update. Journal of fungi (Basel, Switzerland), 9(2), 236. https://doi.org/10.3390/jof9020236

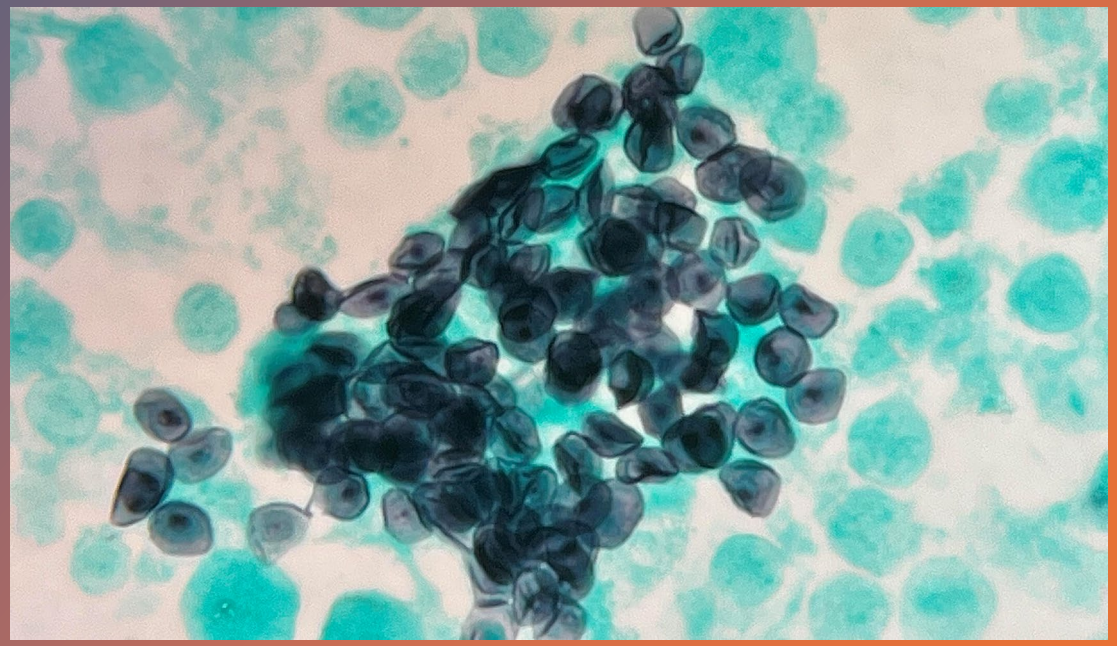
Cryptococcus: Morphology and Biological Feature

- Encapsulated yeast with thick polysaccharide capsule which provides anti-phagocytic properties.
- Detected with India ink or cryptococcal antigen test.
- *C. neoformans*: Found in pigeon droppings, immunocompromised hosts.
- Inhaled yeast causes pulmonary infection with hematogenous spread and strong neurotropism causing meningoencephalitis. Pulmonary forms: nodules, infiltrates; often asymptomatic



Source: Suo C, Gao Y, Ding C and Sun T (2023) The function and regulation of heat shock transcription factor in Cryptococcus. Front. Cell. Infect. Microbiol. 13:1195968



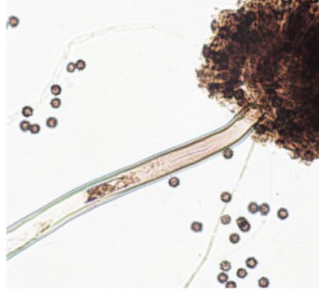


Pneumocystis jirovecii Pneumonia

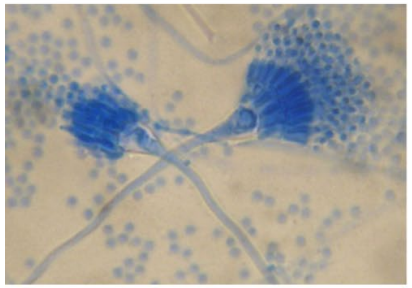
- Atypical fungus (formerly protozoan)
- Cannot be cultured in routine lab
- Exists as trophic forms and cysts
- Infects alveoli resulting in foamy eosinophilic exudate.
- Primary pathogen in AIDS (CD4 < 200) or transplant patients
- It causes diffuse interstitial pneumonia manifested in progressive dyspnea, dry cough, fever. Hypoxia is often severe relative to exam findings. CXR shows bilateral ground-glass opacities.

Aspergillus flavus

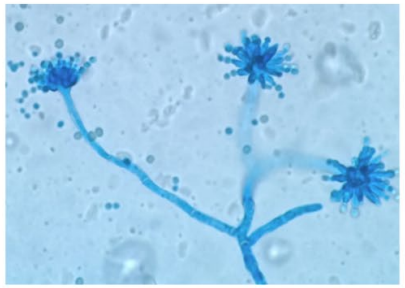
Aspergillus fumigatus



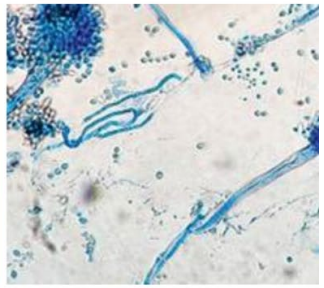
Aspergillus nige



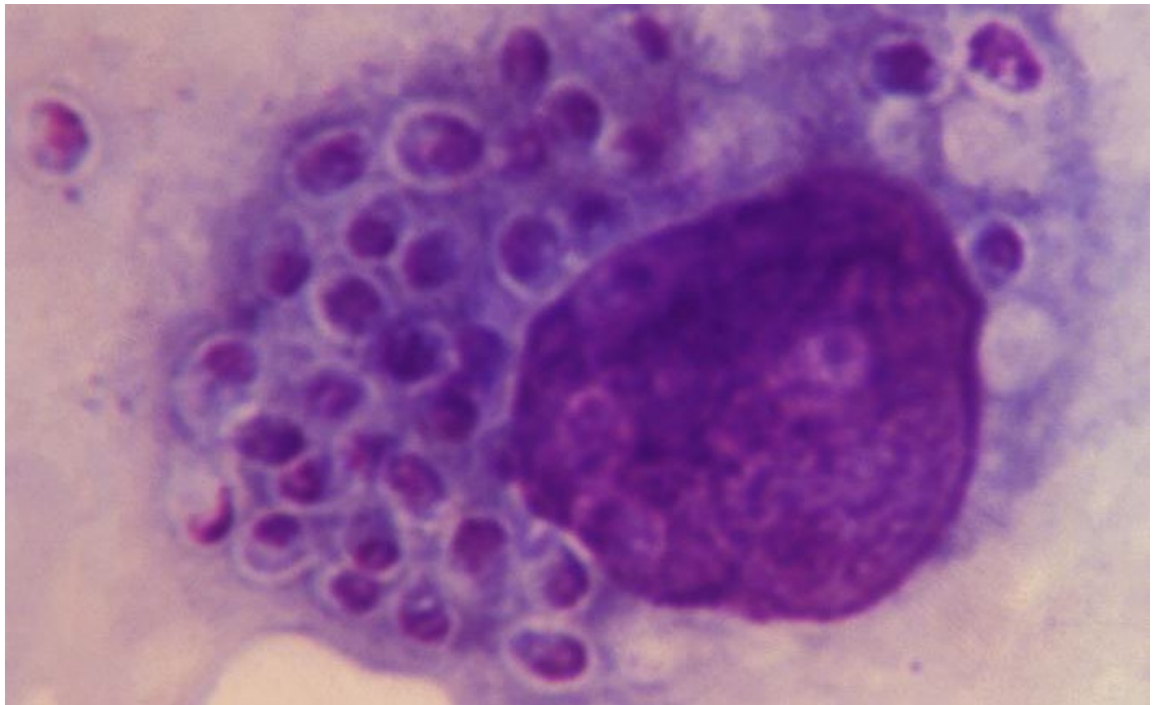
Aspergillus terreus



Aspergillus glaucus



Aspergillus nidu

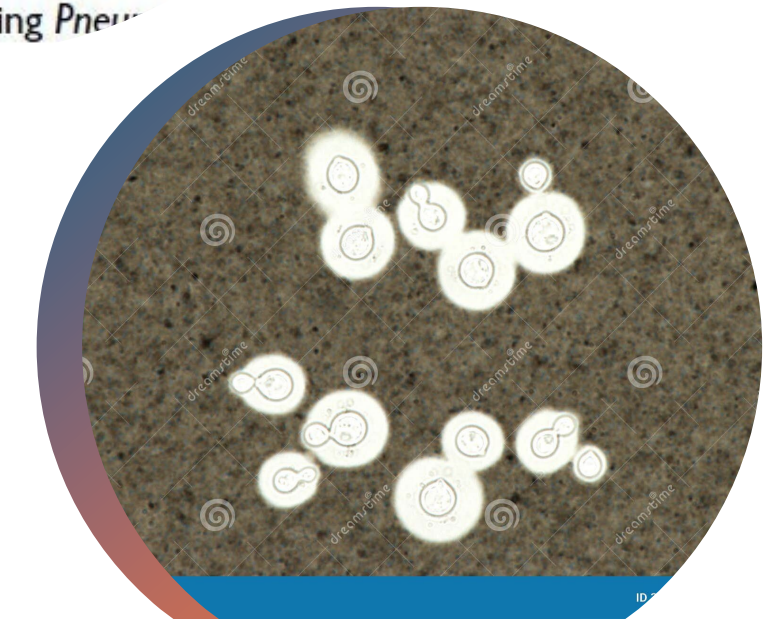


Mycological Diagnostics

- *Aspergillus*:
- Galactomannan antigen (serum/BAL).
- Culture and microscopy (45 degree septate hyphae)
- CT: halo sign (early), air crescent sign (late)
- *Histoplasma*:
- Histoplasma antigen (urine/serum): highly sensitive.
- Yeasts inside macrophages on biopsy
- Culture is slow but definitive

Mycological Diagnostics

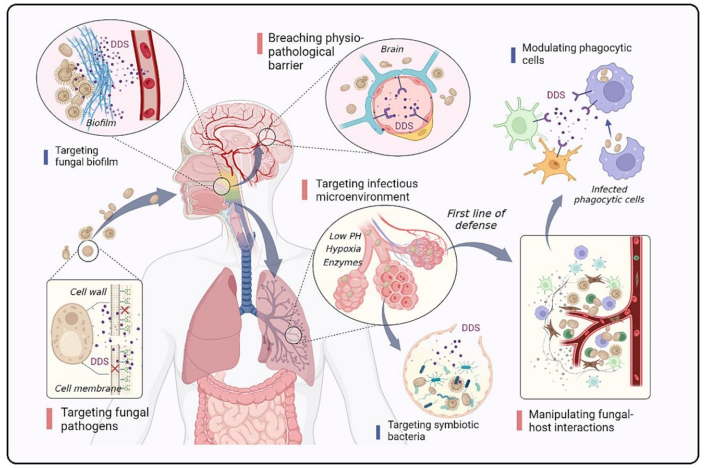
thenamine silver stain of bronc
patient showing Pneu



- *Cryptococcus*:
- Cryptococcal antigen (CrAg) in serum/CSF: very sensitive.
- India ink stain (CSF): encapsulated yeasts.
- *Pneumocystis*:
- PCR on BAL fluid.
- DFA staining (silver stain shows cysts).
- CXR/CT: ground-glass opacities

Antifungal Therapies

- *Aspergillus*: Voriconazole (first line). Alternatives: amphotericin B, echinocandins.
- *Histoplasma*: Mild: itraconazole. Severe: amphotericin B with itraconazole maintenance.
- *Cryptococcus*: Induction: amphotericin B and flucytosine. Maintenance: fluconazole.
- *Pneumocystis*: TMP-SMX (first line). Alternatives: pentamidine, atovaquone. Adjunctive steroids for severe hypoxemia
- Azole resistance in *Aspergillus* increasing due to environmental fungicides
- *Cryptococcus*: emerging fluconazole resistance in some regions
- *Pneumocystis*: TMP-SMX resistance rare but documented



Source: Wu S, Song R, Liu T, Li C. Antifungal therapy: Novel drug delivery strategies driven by new targets. Adv Drug Deliv Rev. 2023 Aug;199:114967. doi: 10.1016/j.addr.2023.114967. Epub 2023 Jun 17. PMID: 37336246.

Prevention

- High-risk patients (transplants, hematologic malignancy): Posaconazole or voriconazole prophylaxis
- Avoidance of construction zones (*Aspergillus*-rich air)
- AIDS patients: PCP prophylaxis by TMP-SMX when CD4 < 200. Cryptococcal antigen screening in some high-prevalence regions. Early ART initiation.
- Reduce bird/bat exposure in endemic areas (*Histoplasma*). Control pigeon populations (*Cryptococcus*)

Thank You!
Wishing you all the best!