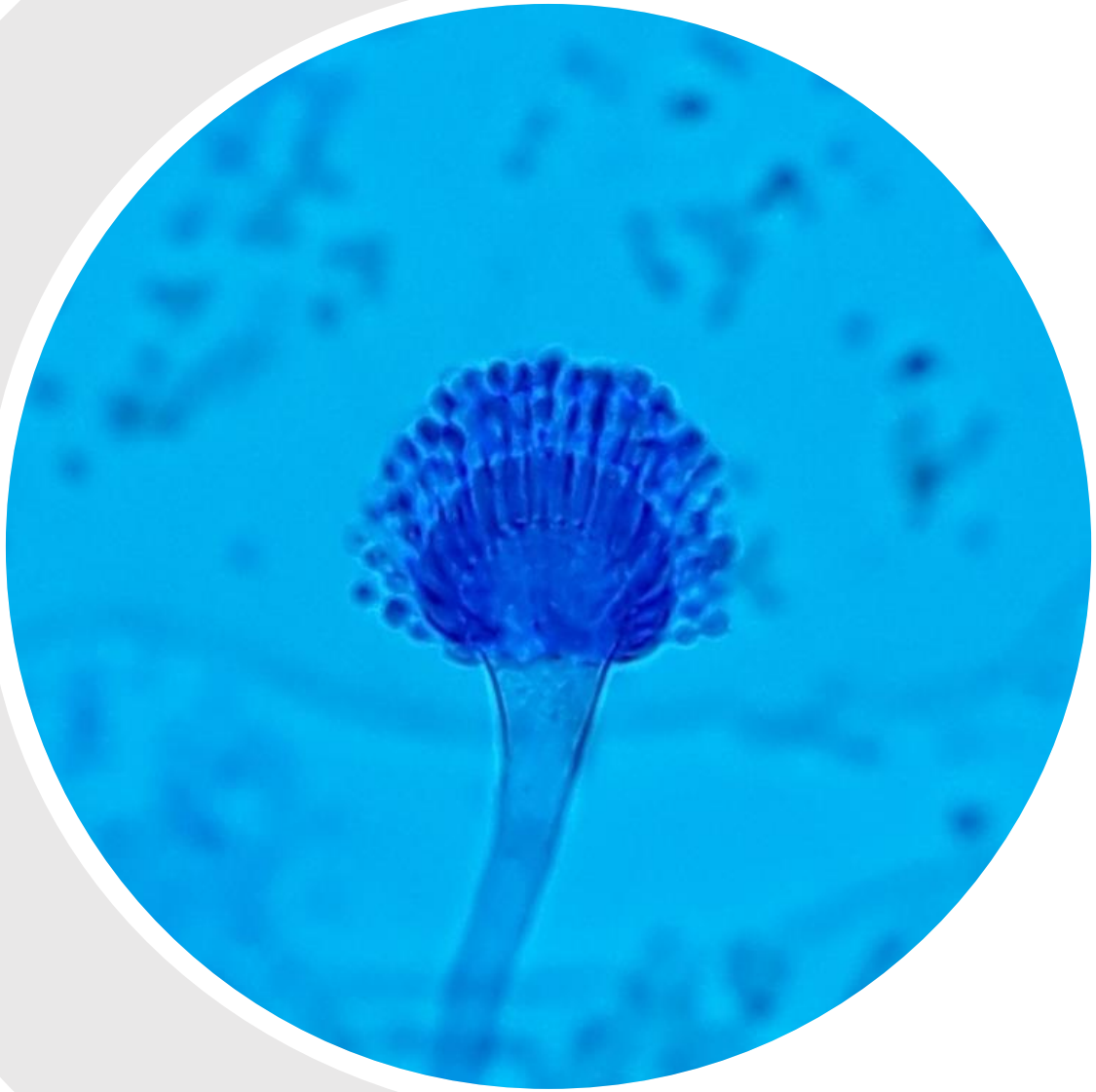


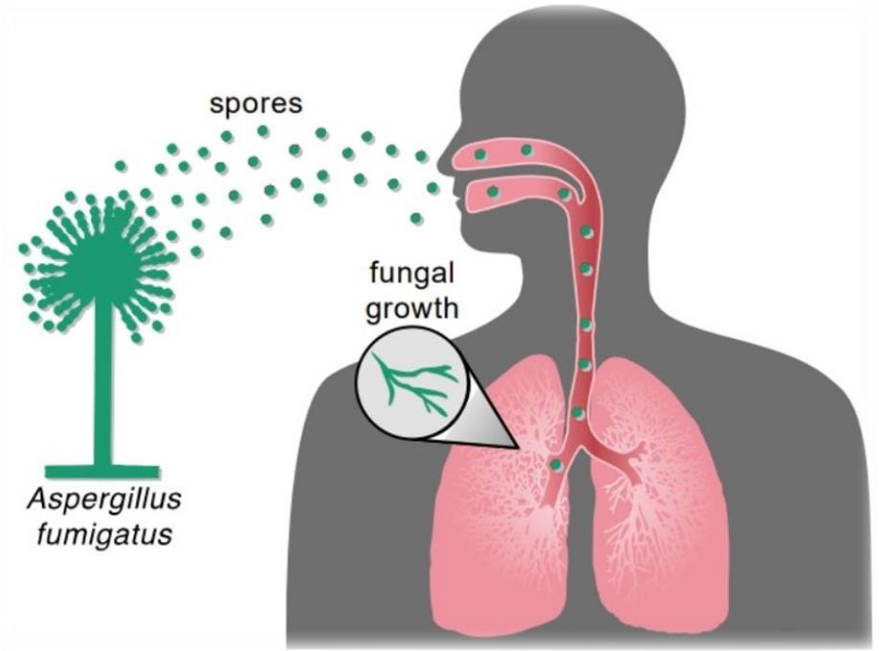
Aspergillosis

Ali Ahmadi, Ph.D.

Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction

- Aspergillosis refers to a spectrum of diseases caused by fungi of the genus *Aspergillus*, ranging from allergic responses to invasive life-threatening infection.
- 2nd most common invasive fungal infection (IFI) after candidiasis.
- It is the most common invasive mold infection (IMI) in humans.
- Important in immunocompromised patients, transplant recipients, and severe pulmonary disease.



What fungi cause Aspergillosis?

Human pathogenic

The genus *Aspergillus* comprises over 350 species, organized into species complexes based on molecular taxonomy.

- ❑ Approximately 40 species are pathogenic to humans.
- ❑ Major pathogenic complexes:

✓ *A. fumigatus* complex → ~70–80 % of invasive aspergillosis (worldwide major agent)

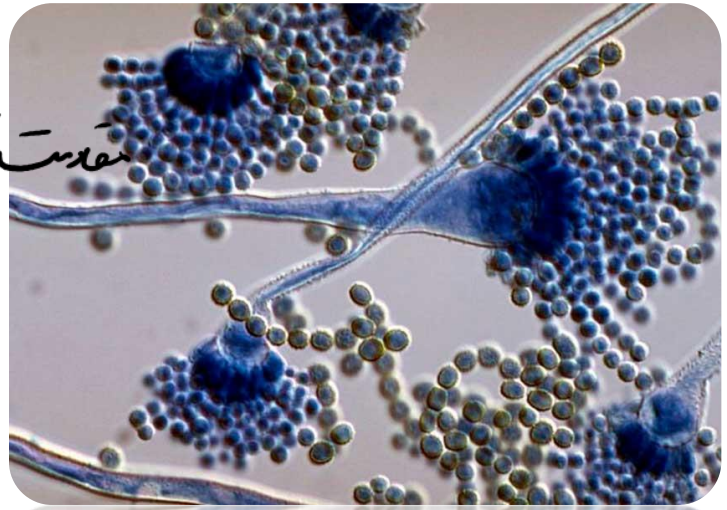
✓ *A. flavus* complex → ~10–20 %; more frequent in tropical regions (sinus & cutaneous disease)

Note: In tropical countries (including Iran), *A. flavus* may surpass *A. fumigatus*.

✓ *A. niger* complex → ~5–10 %; otomycosis, colonization

✓ *A. terreus* complex → ~2–5 %; intrinsic amphotericin B resistance

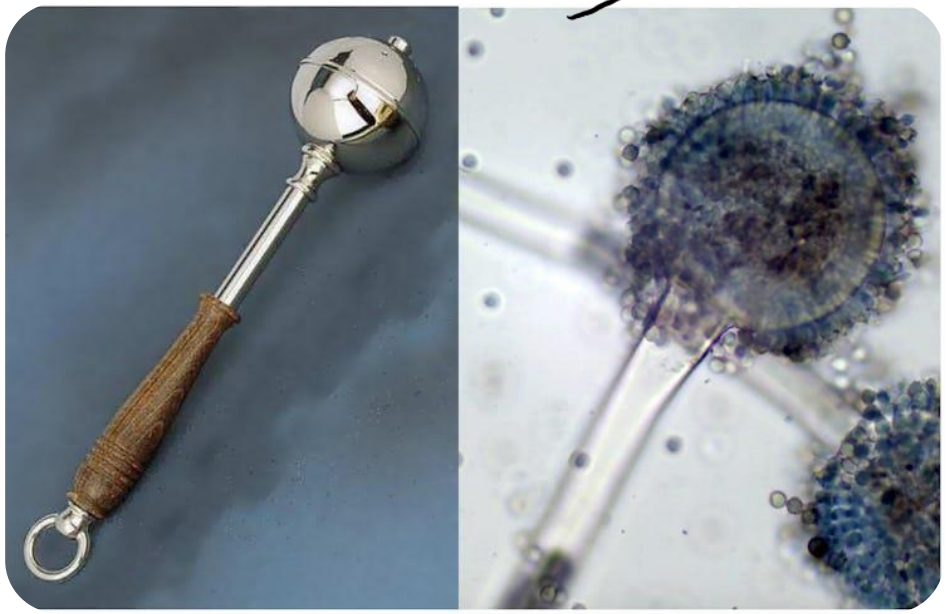
✓ *A. nidulans* complex → < 2 %; chronic granulomatous disease



Pier Antonio Micheli, 1729

Human pathogenic

طلوی سبیه



Routes of transmission

❑ *Aspergillus* spp are saprophytic molds, widely distributed in:

✓Soil, decaying vegetation, compost

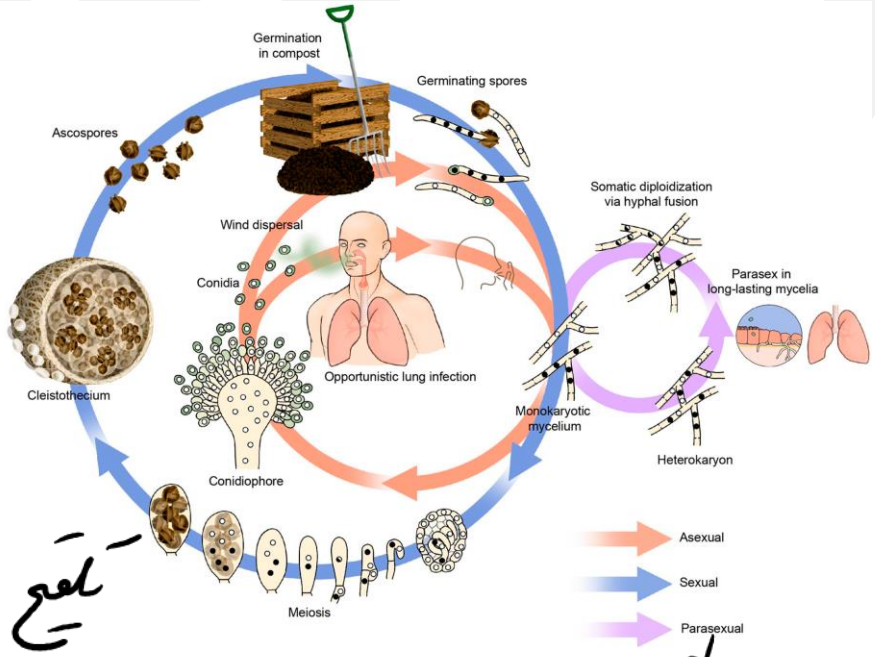
✓Airborne dust, construction sites, hospital air vents

✓Contaminated medical devices or solutions (rare)

❑ Main route of infection:

✓ Inhalation of airborne conidia → reaches alveoli.

راه اصلی



❑ Less common routes:

✓ Direct inoculation (skin, wounds, burns, IV catheters).

✓ Contaminated instruments during surgery (postoperative endophthalmitis, sinusitis).

وسایل جراحی

✓ Ingestion of spores → rare GI aspergillosis in severe immunosuppression.

موارد خیلی نادر

➢ No human-to-human transmission has been documented.

Pathogenesis

- Inhalation of airborne conidia (2–3 µm) reaching the alveoli.
- In immunocompetent hosts

Rapidly cleared by alveolar macrophages and neutrophils.

- In immunocompromised hosts

Impaired clearance → allows germination into hyphae → tissue invasion.

- Types of invasion:

Tissue invasion → hyphae penetrate parenchyma and vessels.

Angioinvasion → thrombosis, infarction, hemorrhage, dissemination.

- Outcome:

Normal immunity → allergy (ABPA)

Local structural disease → chronic (CPA)

Severe immunosuppression → invasive disease

Virulence Factors

Category	Virulence Factor	Mechanism / Role
Adhesion & Entry	Hydrophobins (RodA)	Mask PAMPs; prevent immune recognition
Immune Evasion	Melanin in conidial wall	Protects from ROS and macrophage killing
Tissue Invasion	Secreted proteases, phospholipases, elastases	Degrade epithelial & endothelial barriers
Toxin Production	Gliotoxin	Induces apoptosis of macrophages, inhibits ciliary beating, suppresses NF-κB
Iron Acquisition	Siderophores (e.g., ferricrocin)	Essential for growth in host tissue
Stress Resistance	Thermotolerance (growth up to 55°C)	Enables survival in lungs
Biofilm Formation	Polysaccharide matrix (galactosaminogalactan)	Protects from immune cells and antifungals

Epidemiology

- Estimated >300,000 cases/year of invasive aspergillosis (IA) globally.
- Mortality: 40–60% despite antifungal therapy. → درصدت عدم درمان
- Aspergillosis is now among the top 4 fungal causes of global mortality (WHO fungal priority list, 2024).
- CAPA (COVID-19-Associated Pulmonary Aspergillosis) up to 10 % of ventilated COVID patients.

Risk factors

❑ Immunosuppression

- ✓ Neutropenia (< 500/mm³ >10 days) —IA
- ✓ Hematologic malignancy (AML, ALL)
- ✓ HSCT, SOT (especially lung & liver)
- ✓ Corticosteroid therapy (≥0.3 mg/kg/day prednisolone >3 weeks)
- ✓ Drugs: calcineurin inhibitors, anti-TNF, cytotoxic chemotherapy

❑ Structural Lung Disease

- ✓ Old tuberculosis cavities
- ✓ COPD
- ✓ Sarcoidosis
- ✓ Bronchiectasis
- ➢ predispose to CPA or aspergilloma

❑ Critical Illness

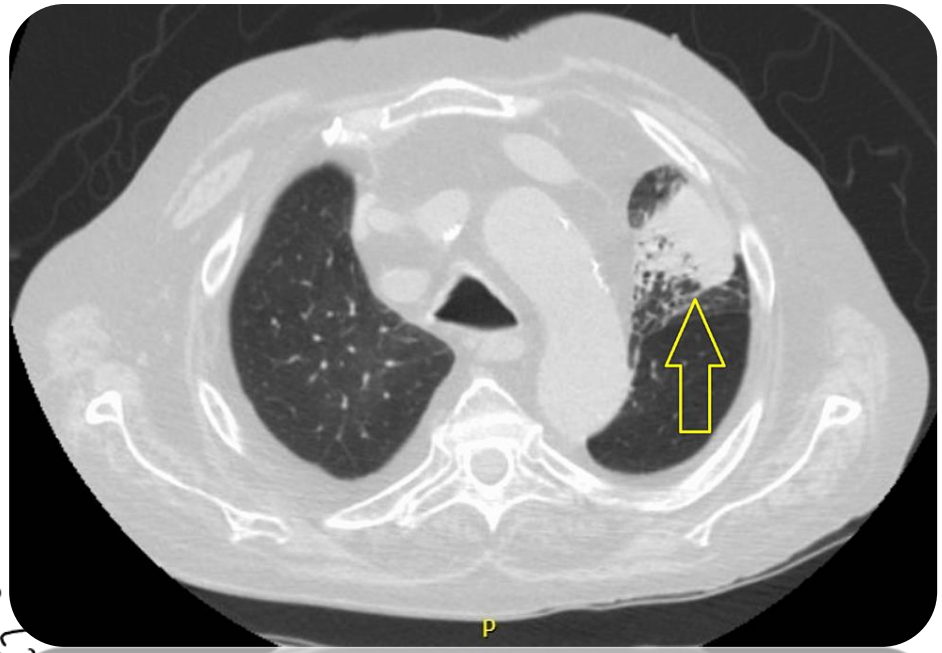
- ✓ Severe viral pneumonia → IAPA, CAPA
- ✓ Prolonged ICU stay, mechanical ventilation
- ✓ Broad-spectrum antibiotic exposure → microbiome disruption →

❑ Local or Environmental Factors

- ✓ Hospital construction → airborne spore surges
- ✓ Contaminated devices (catheters, endoscopes)
- ✓ Burns, trauma → primary cutaneous aspergillosis

Clinical Manifestations

- Allergic Aspergillus Diseases →
  - ABPA
  - AFRS
- Chronic Pulmonary Aspergillosis (CPA)
  - Aspergilloma
  - CCPA
  - CFPA
  - SAIA
- Invasive Aspergillosis (IA)
  - IPA
  - Disseminated (CNS, skin, sinus, etc.)
- Colonization (non-disease)



Allergic Aspergillus Diseases

Clinical Manifestations

❑ Allergic Bronchopulmonary Aspergillosis (ABPA)

- ➢ Occurs in asthma or cystic fibrosis.
- ➢ Type I + III hypersensitivity to *Aspergillus* antigens.
- ➢ Recurrent wheezing, productive cough with brown plugs, fleeting infiltrates.
- ➢ Labs:

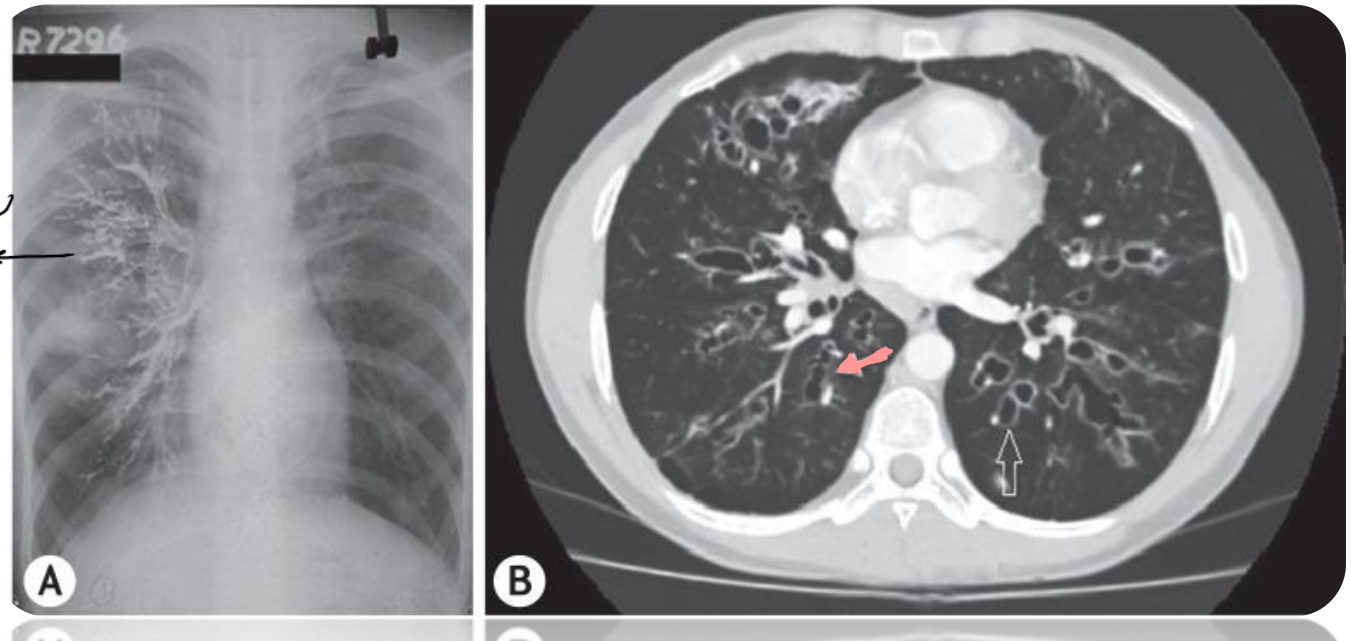
Total IgE > 1000 IU/mL.

Aspergillus-specific IgE/IgG positive

Eosinophilia > 500 cells/µL

- ➢ Imaging:

Central bronchiectasis (upper lobes)



Allergic Aspergillus Diseases

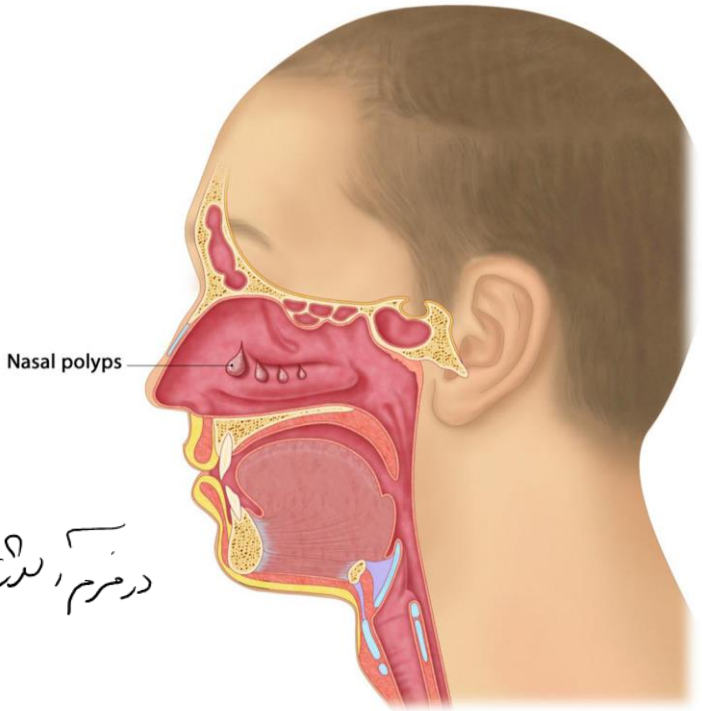
Clinical Manifestations

- ❑ Allergic Fungal Rhinosinusitis (AFRS)
  - ➢ Atopic patients with chronic sinus congestion, nasal polyps
  - ➢ Nasal obstruction, thick dark mucus discharge, nasal polyps, headache, anosmia
  - ➢ Lab:

IgE to fungi, eosinophilic mucin, no tissue invasion

  - ➢ Imaging:

Hyperdense sinus material ("allergic mucin"), often unilateral



Chronic Pulmonary Aspergillosis (CPA)

Clinical Manifestations

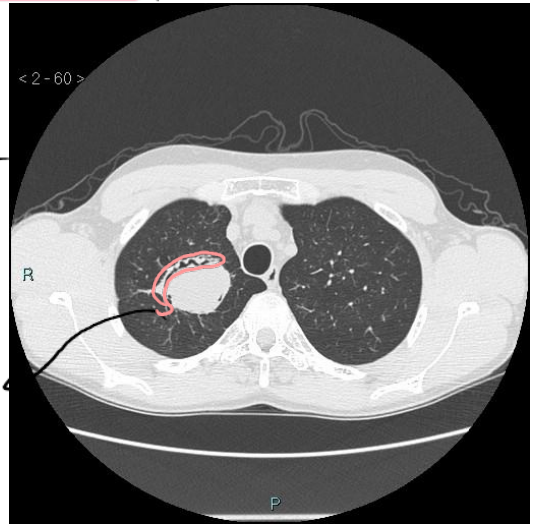
- Patients with structurally abnormal lungs (TB cavities, COPD, sarcoidosis)
- Slow tissue invasion without angioinvasion.

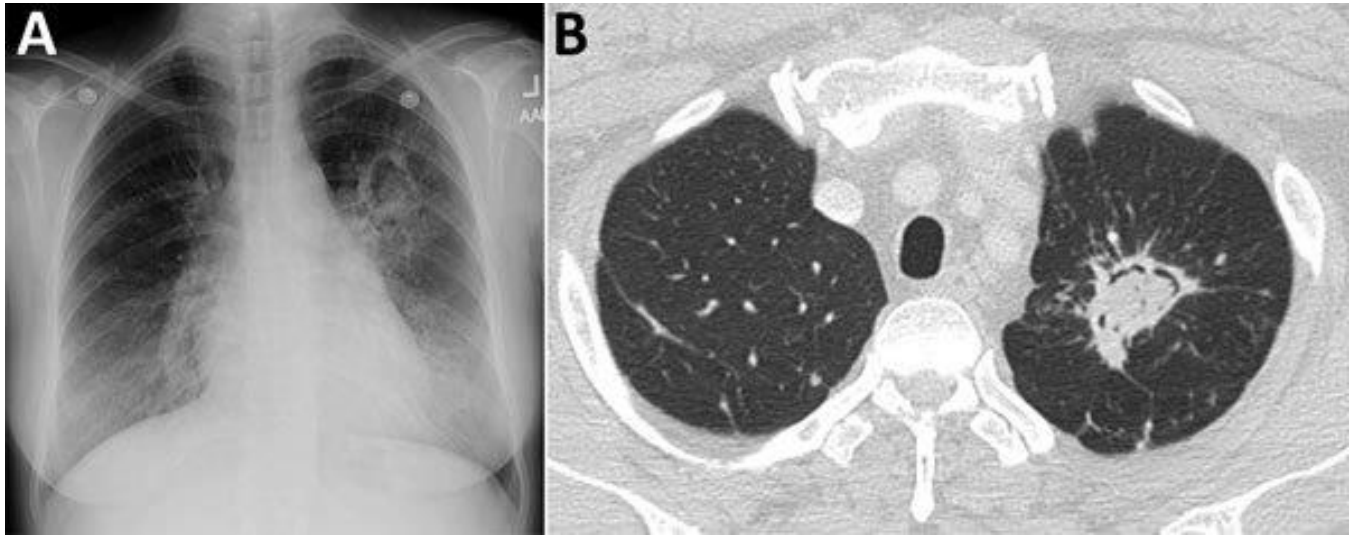
❑ Simple Aspergilloma (Fungal Ball)

✓ fungus colonizes pre-existing cavity; no tissue invasion

✓ CT: mobile intracavitary mass, air-crescent sign; often asymptomatic or mild hemoptysis

https://radiopaedia.org/





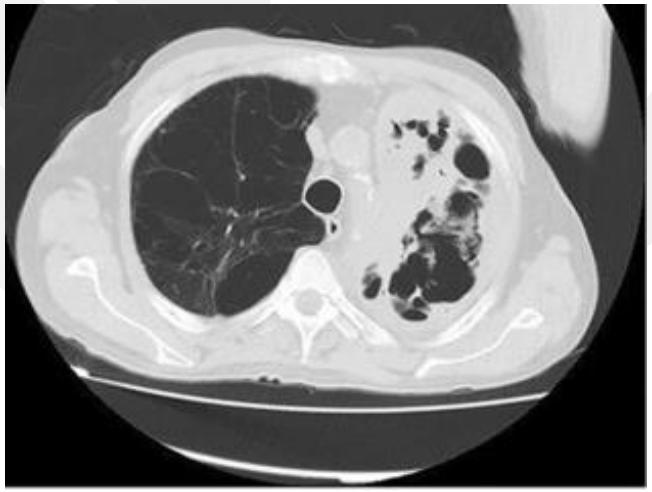
Chronic Pulmonary Aspergillosis (CPA)

Clinical Manifestations

❑ Chronic Cavitary Pulmonary Aspergillosis (CCPA)

✓Slow expansion of cavities with mild tissue invasion

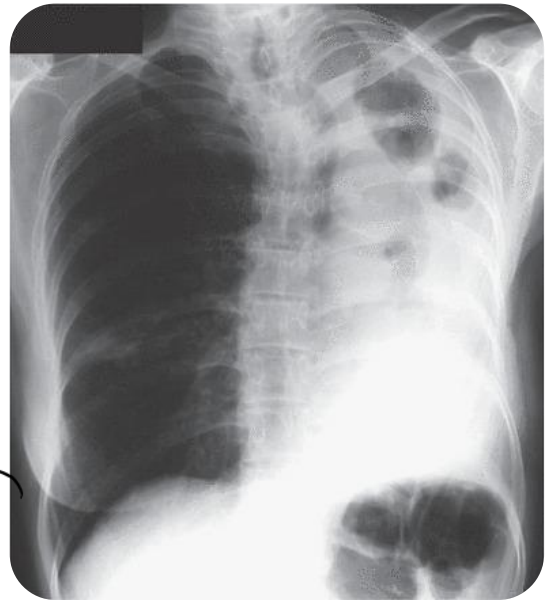
✓Multiple cavities ± fungus ball; chronic cough, weight loss, fatigue; CT shows cavity progression.



❑ Chronic Fibrosing Pulmonary Aspergillosis (CFPA)

✓End-stage fibrosis following CCPA; architectural distortion

✓lobar fibrotic destruction, volume loss on imaging; chronic respiratory symptoms



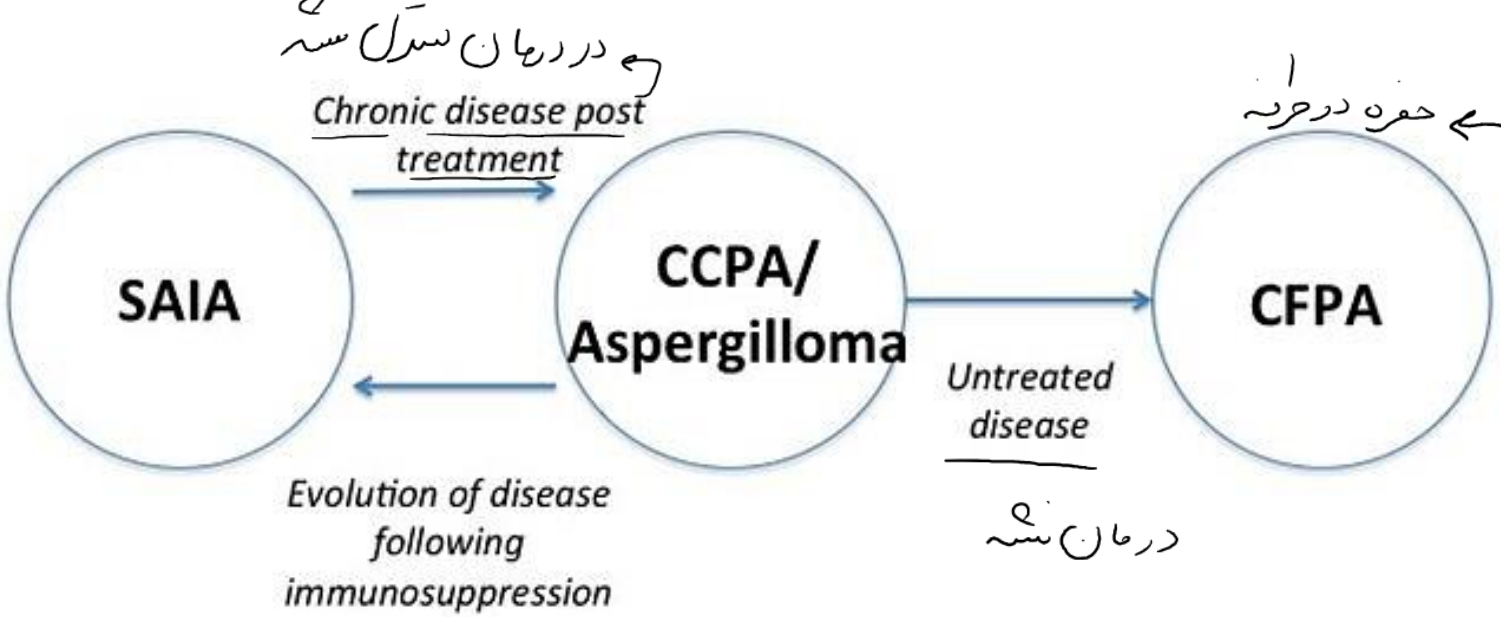
Chronic Pulmonary Aspergillosis (CPA)

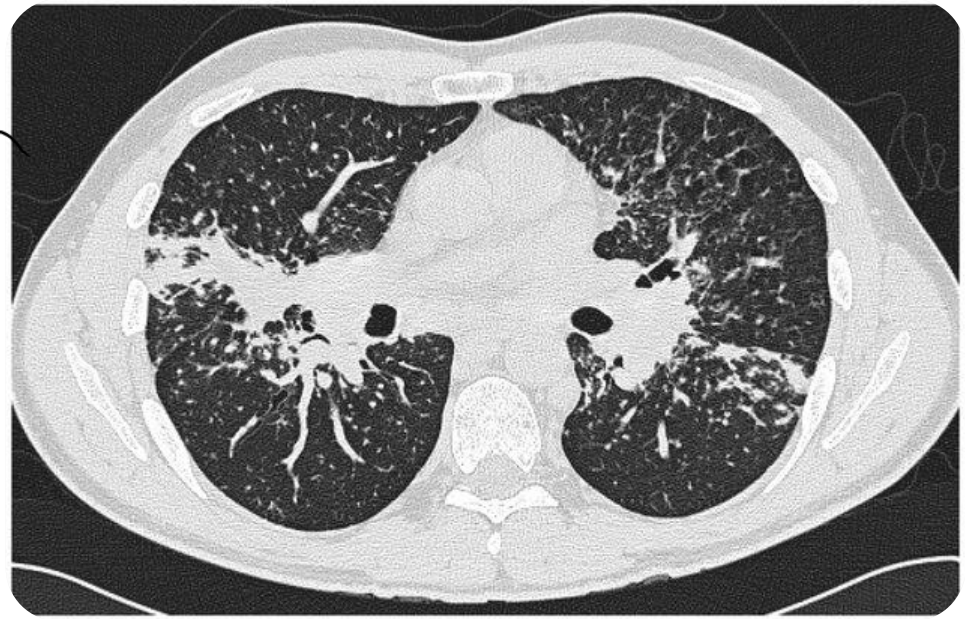
Clinical Manifestations

❑ Subacute Invasive / Chronic Necrotizing Aspergillosis (SAIA)

✓Occurs in mildly immunocompromised → slow necrotic progression

✓Progressive cavities with necrotic changes; systemic symptoms (fever, weight loss); imaging shows cavity enlargement and surrounding infiltrates.





Invasive Aspergillosis (IA)

Clinical Manifestations

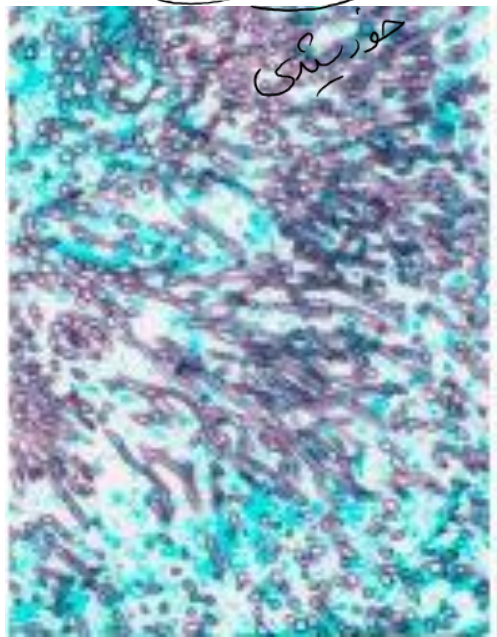
- Neutropenia >10 days, HSCT, SOT, prolonged steroids, severe viral pneumonia

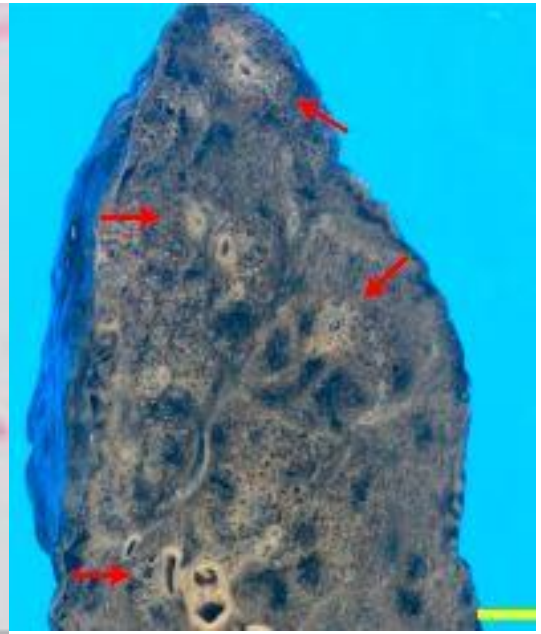
- ❑ Invasive Pulmonary Aspergillosis (IPA)

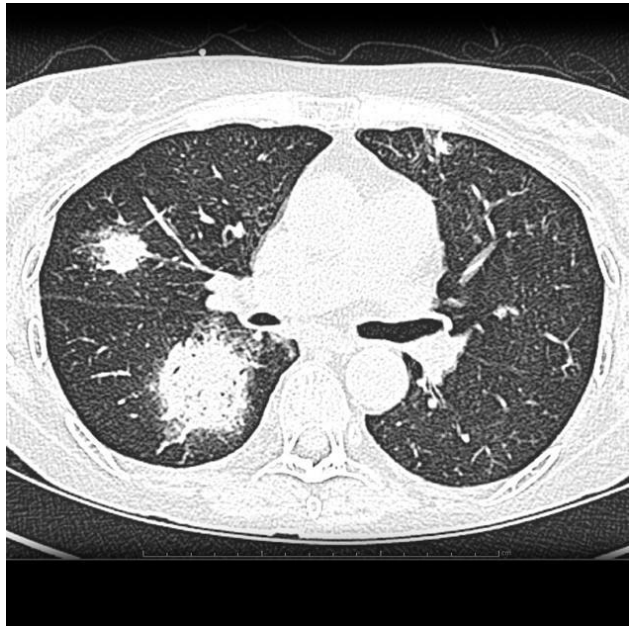
✓Persistent fever > 96 h despite antibiotics, pleuritic chest pain, dyspnea, hemoptysis

✓Angioinvasion → thrombosis → necrosis ± dissemination

✓CT: Halo sign (early hemorrhagic infarct); Air-crescent sign (recovery phase)







Invasive Aspergillosis (IA)

Clinical Manifestations

❑ Disseminated / Extrapulmonary Aspergillosis

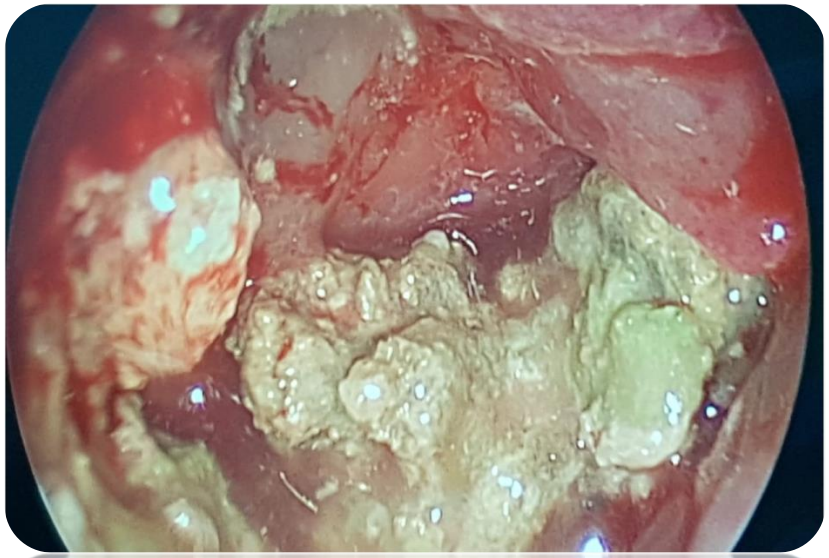
✓**CNS:** seizures, focal deficits, ring-enhancing lesions on MRI.

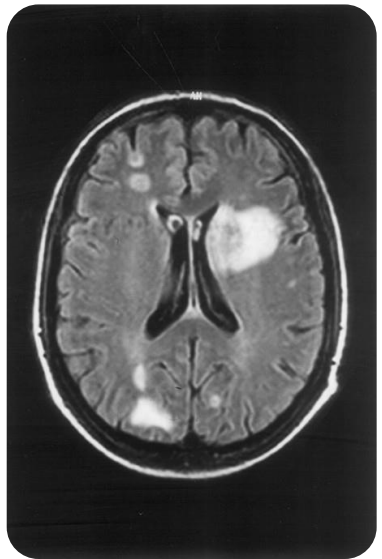
✓**Cutaneous:** necrotic papules or eschar at catheter/dressing sites (primary or secondary).

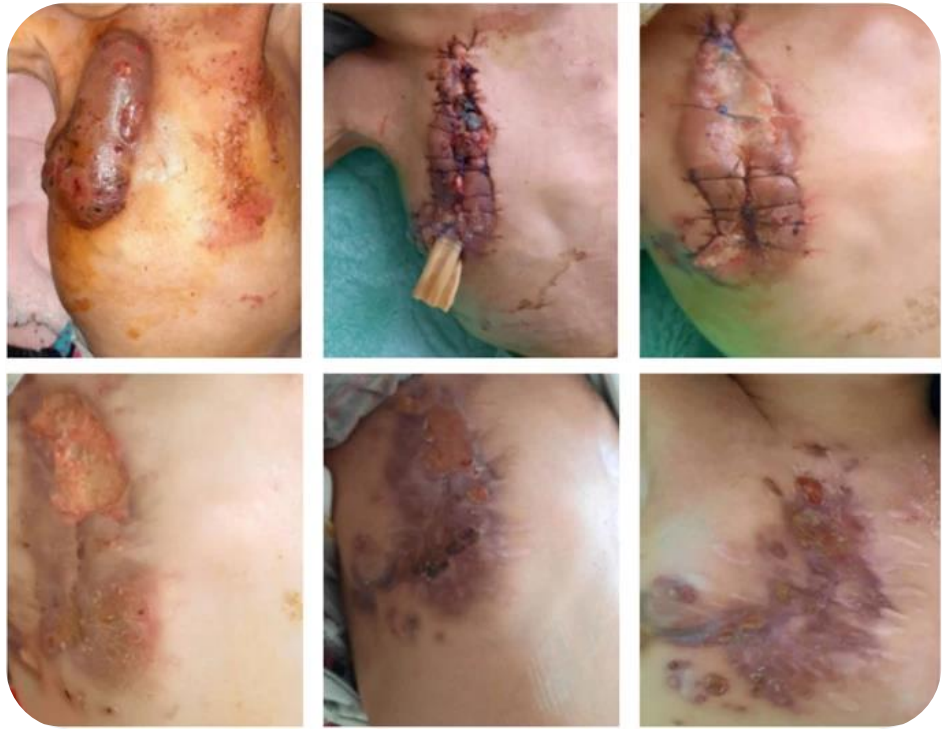
✓**Sinus:** tissue necrosis, black eschar on palate/nasal septum.

✓**Others:** endocarditis, osteomyelitis, renal involvement.

سيزس







Diagnosis

1.Clinical material:

Sputum, bronchial washings, BAL and tracheal aspirates from patients with pulmonary disease and tissue biopsies from patients with disseminated disease.

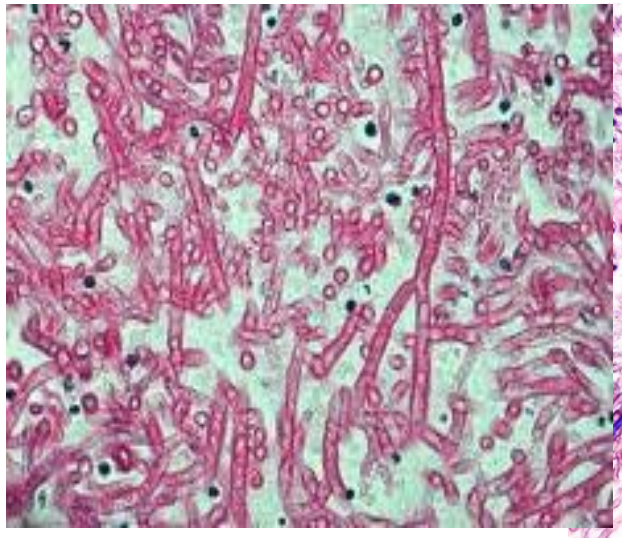
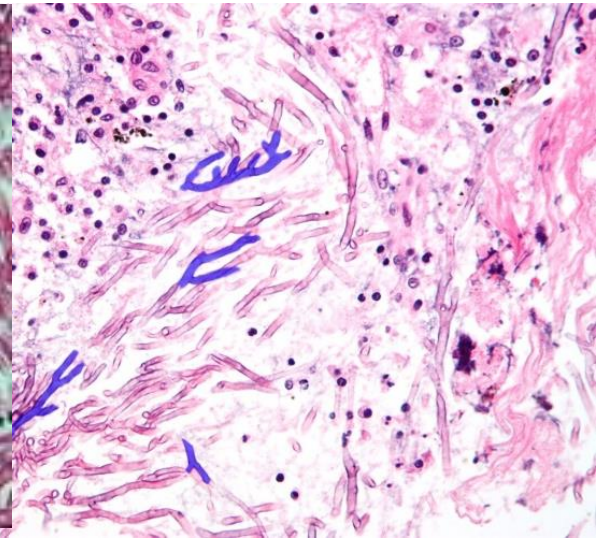
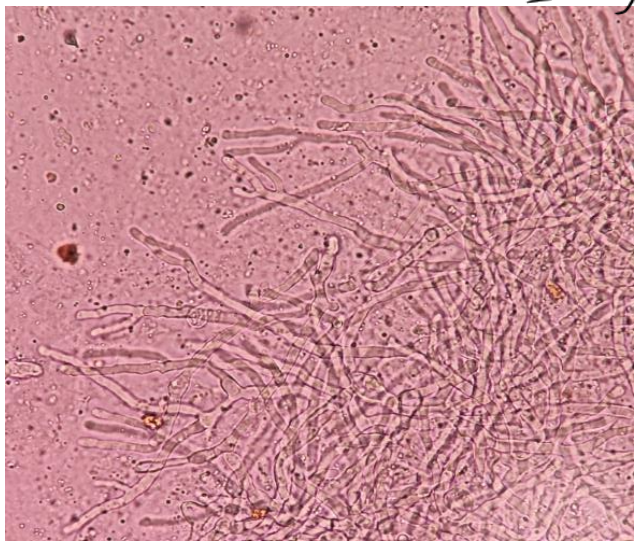
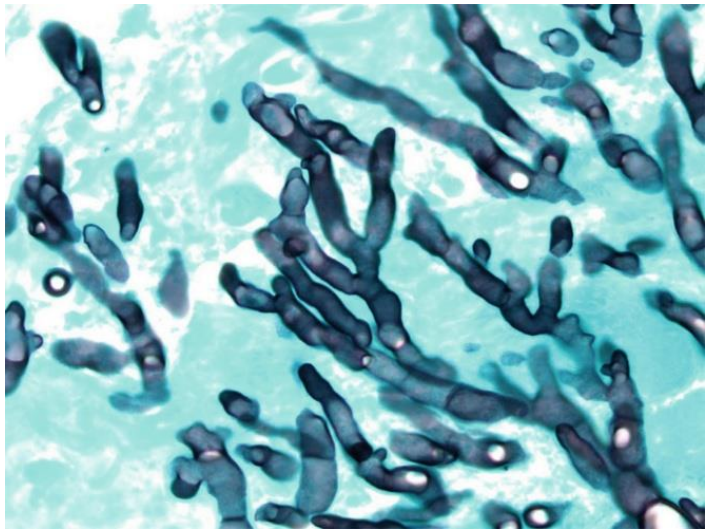
2. Direct Microscopy:

(a) Sputum, washings, and aspirates make wet mounts in either 10% KOH & Parker ink or Calcofluor and/or Gram-stained smears;

(b) Tissue sections should be stained with H&E, GMS, and PAS digest.

Examine specimens for **septate hyphae, dichotomously branched 45°,**

Rapid, not species specific

3. Culture:

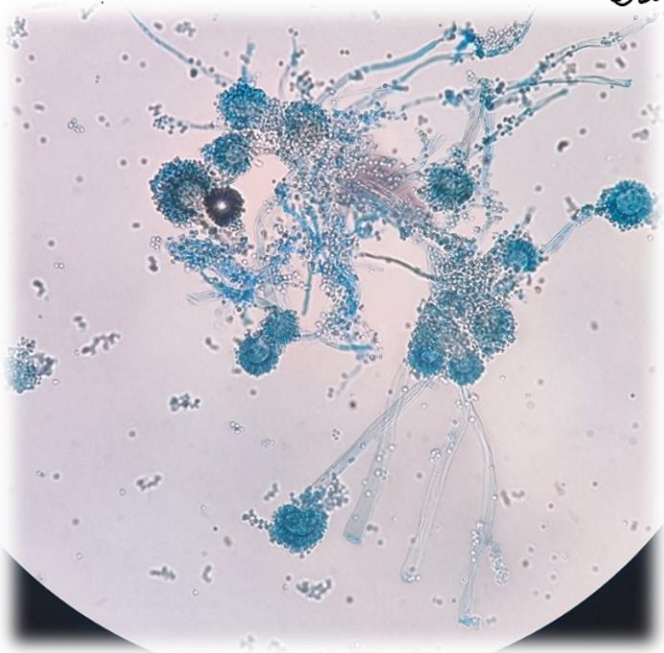
Clinical specimens should be inoculated onto SDA.

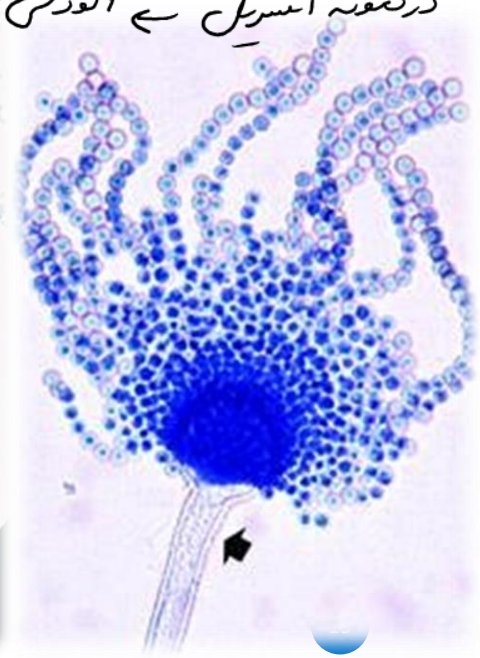
Colonies are fast-growing and may be white, yellow, yellow-brown, brown to black, or green in color.

Aspergillus species are well recognized as common environmental airborne contaminants; therefore, a positive culture from a non-sterile specimen, such as sputum, is not proof of infection. → توی محیط کشت آلوده شده * → در نمونه غیر استریل یا چند بار تکرار

Confirm species & do susceptibility

در نمونه استریل به آلودگی نداره





4. Serology:

- The galactomannan (GM) is a polysaccharide antigen that exists primarily in the cell walls of *Aspergillus* species.
- GM may be released into the blood and other body fluids even in the early stages of *Aspergillus* invasion, and the presence of this antigen can be sustained for 1 to 8 weeks.
- Serum GM > 0.5 index positive; BAL > 1.0
- Sens 70%, Spec 90%

β-D-Glucan

- > 80 pg/mL → pan-fungal (Screening only)

Diagnosis is based on the EORTC/MSGERC

❑ Proven:

Histopathologic evidence of fungal invasion (e.g., hyphae with angioinvasion) OR culture from a normally sterile site

❑ Probable:

Requires all three of: (1) a host risk factor, (2) clinical/radiologic features consistent with IFD, and (3) mycological evidence (non-sterile site culture, microscopy; antigen, PCR)

❑ Possible

Host risk factor + clinical/radiologic features, but lacking mycological evidence (or insufficient)

Treatment

Clinical Form	First-Line Treatment	Dose & Duration	Alternative / Salvage	Notes
ABPA	Prednisolone 0.5 mg/kg/day × 2 wk → taper 3 mo	+ Itraconazole 200 mg BID × 16 wk (↓ fungal load & IgE)	Voriconazole / Posaconazole (resistant cases);	Monitor total IgE & chest CT for improvement
AFRS	Functional endoscopic sinus surgery + oral corticosteroids	–	Itraconazole 200 mg BID × 3 mo (reduce recurrence)	Avoid nasal packing; monitor relapse
CPA	Itraconazole 200 mg BID × ≥6 mo	Voriconazole 200 mg BID / Posaconazole 300 mg daily (if intolerance)	Surgical resection for localized aspergilloma / massive hemoptysis	Check serum azole levels (1–2 µg/mL)
Invasive Aspergillosis (Pulmonary/CNS)	Voriconazole 6 mg/kg IV q12h × 2 doses → 4 mg/kg q12h (PO 200 mg BID) × 6–12 wk	Isavuconazole 372 mg IV/PO q8h × 6 → 372 mg daily	Liposomal Amphotericin B 3–5 mg/kg daily; +Echinocandin (Caspofungin) for refractory cases	Reduce immunosuppression, add G-CSF if neutropenic
Cutaneous / Sinus Invasive	Voriconazole ± Surgical debridement	6–12 wk	Liposomal AmB 5 mg/kg daily	Early surgery crucial
Colonization (Non-invasive)	None (observation only)	–	–	Avoid unnecessary antifungal therapy

Category	Typical Host	Pathogenesis	Major Clinical & Radiologic Features	Key Diagnostic Clues
Allergic (ABPA, AFRS)	Asthma, CF, atopic	IgE-mediated hypersensitivity	Wheezing, brown plugs, fleeting infiltrates, central bronchiectasis	↑Total IgE, +Aspergillus-specific IgE/IgG, eosinophilia, CT: bronchiectasis
Chronic Pulmonary Aspergillosis (CPA)	TB, COPD, sarcoidosis	Slow local invasion & fibrosis	Chronic cough, fatigue, hemoptysis, apical cavities ± fungal ball	Imaging: cavities ± air-crescent, positive culture/IgG
Invasive Aspergillosis (IA)	Neutropenic, transplant, steroid therapy	Angioinvasion → infarction, necrosis, dissemination	Persistent fever, pleuritic pain, hemoptysis, nodules, halo/air-crescent signs, CNS lesions	Galactomannan +, PCR +, GMS stain: septate hyphae at 45°, culture positive
Colonization	COPD, ICU, ventilated	Non-invasive presence	Often asymptomatic; may appear in sputum or BAL	No radiologic lesion, negative biomarkers

MEDICAL MYCOLOGY

2025