Opportunistic Systemic Mycoses

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These are fungal infections of the body which occur almost exclusively in debilitated patients whose normal defense mechanisms are impaired. The organisms involved are cosmopolitan fungi which have a very low inherent virulence. The increased incidence of these infections and the diversity of fungi causing them, paralleled the emergence of AIDS, more aggressive cancer and post-transplantation chemotherapy and the use of antibiotics, cytotoxins, immunosuppressives, corticosteroids being the primitive therapeutic to combat the COVID-19 inflammation, leads to an immune-compromised state, thereby allowing the not-so-harmful fungi to violate the immune barrier and flourish in the host. A wide range of fungal co-infection is observed in the survivors and patients of COVID-19. Fungal species of Candida, Aspergillus and Mucorales, are burdening the lives of COVID-19 patients.

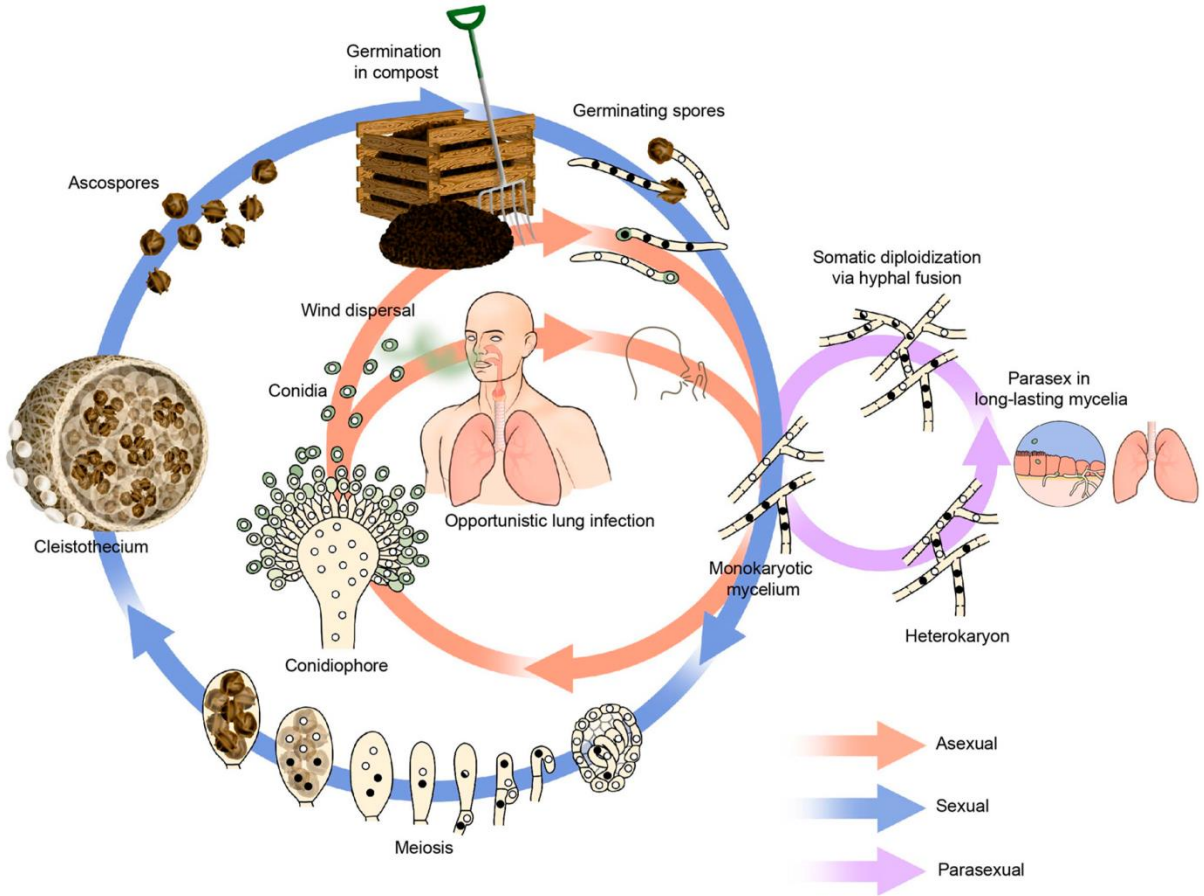
Disease	Causative organisms	Incidence
Aspergillosis	*Aspergillus fumigatus* complex, *A. flavus*, complex, *A. terreus* complex etc.	Common
Candidiasis	*Candida, Debaryomyces, Kluyveromyces, Meyerozyma, Pichia*, etc.	Common
Cryptococcosis	*Cryptococcus* spp. especially *C. neoformans and C. gattii.*	Uncommon
Hyalohyphomycosis	*Penicillium, Paecilomyces, Beauveria, Fusarium, Scopulariopsis* etc.	Rare
Phaeohyphomycosis	*Cladophialophora, Exophiala, Bipolaris, Exserohilum etc.*	Uncommon
Scedosporiosis (Pseudallescheriasis)	*Scedosporium* and *Lomentospora.*	Rare
Zygomycosis (Mucormycosis)	*Rhizopus, Mucor, Rhizomucor, Lichtheimia* etc.	Rare

Table 1. show the name of disease and causative organisms with the type of Incidence

Aspergillosis

Aspergillosis is a spectrum of diseases of humans and animals caused by members of the genus Aspergillus. These include (1) mycotoxicosis due to ingestion of contaminated foods; (2) allergy and sequelae to the presence of conidia or transient growth of the organism in body orifices; (3) colonisation without extension in preformed cavities and debilitated tissues; (4) invasive, inflammatory, granulomatous, narcotising disease of lungs, and other organs; and rarely (5) systemic and fatal disseminated disease. The type of disease and severity depends upon the physiologic state of the host and the species of Aspergillus involved. The etiological agents are cosmopolitan and include *Aspergillus fumigatus* complex, *A. flavus* complex, *A. niger* complex, *A. nidulans and A. terreus* complex.

- **Lifecycle**



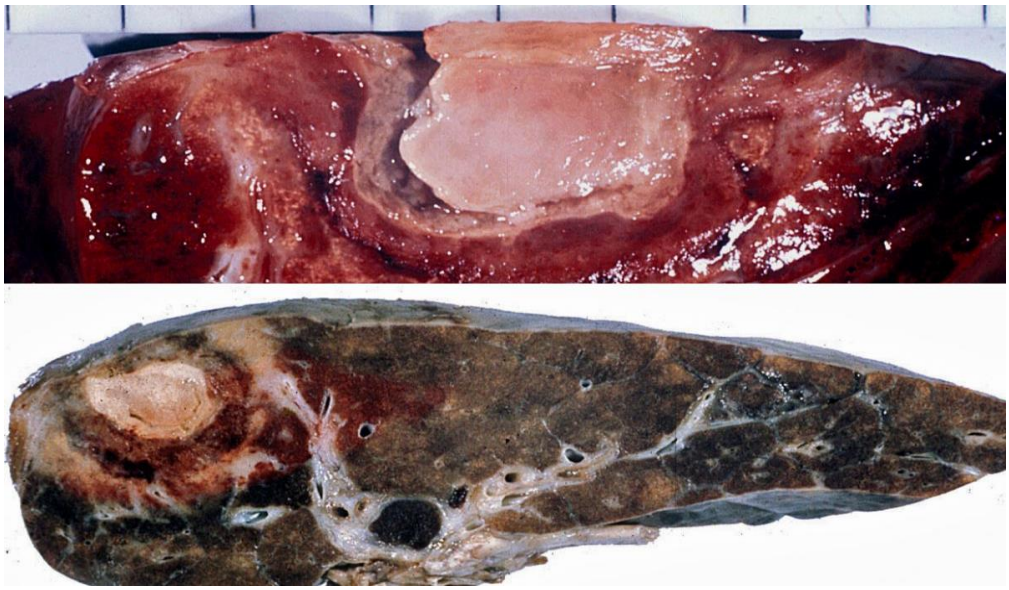
Asexual, Sexual and Parasexual lifecycle of *Aspergillus fumigatus*

Clinical manifestations:

Pulmonary aspergillosis: including allergic, aspergilloma and invasive aspergillosis.

The clinical manifestations of pulmonary aspergillosis are many, ranging from harmless saprophytic colonisation to acute invasive disease.

- **Allergic aspergillosis** is a continuum of clinical entities ranging from extrinsic asthma to extrinsic allergic alveolitis to allergic bronchopulmonary aspergillosis (hypersensitivity pneumonitis) caused by the inhalation of Aspergillus conidia. Features include asthma, intermittent or persistent pulmonary infiltrates, peripheral eosinophilia, positive skin test to Aspergillus antigenic extracts, positive immunodiffusion precipitin tests for antibody to Aspergillus, elevated total IgE, and elevated specific IgE against Aspergillus. Plug expectoration and a history of chronic bronchitis are also common. Symptoms may be mild and without sequelae, but recurrent episodes frequently progress to bronchiectasis and fibrosis.
- **Non-invasive aspergillosis** or aspergilloma (fungus ball), is caused by the saprophytic colonisation of pre-formed cavities, usually secondary to tuberculosis or sarcoidosis. Features often include hemoptysis with blood stained sputum, positive immunodiffusion precipitin tests for antibody to Aspergillus, and elevated specific IgE against Aspergillus. However, many cases are asymptomatic and are usually found by routine chest x-ray.



Aspergilloma formed by the colonisation of a pre-formed lung cavity.

- **Acute invasive pulmonary aspergillosis** Predisposing factors include prolonged neutropenia, especially in leukemia patients or in bone marrow transplant recipients, corticosteroid therapy, cytotoxic chemotherapy and to a lesser extent patients with AIDS or chronic granulomatous disease. Clinical symptoms may mimic acute bacterial pneumonia and include fever, cough, pleuritic pain, with hemorrhagic infarction or a narcotising bronchopneumonia. The typical patient is granulocytopenic and receiving broad-spectrum antibiotics for unexplained fever. Radiological features may be non-specific and tests for serum antibody precipitins are also usually negative. Clinical recognition is essential as this is the most common form of aspergillosis in the immunosuppressed patient.

- **Chronic narcotising aspergillosis** is an indolent, slowly progressive, "semi-invasive" form of infection seen in mildly immunosuppressed patients, especially those with a previous history of lung disease. Diabetes mellitus, sarcoidosis and treatment with low-dose glucocorticoids may be other predisposing factors. Common symptoms include fever, cough and sputum production; positive serum antibody precipitins may also be detected.

- **Disseminated aspergillosis:**

Hematogenous dissemination to other visceral organs may occur, especially in patients with severe immunosuppression or intravenous drug addiction. Abscesses may occur in the brain (cerebral aspergillosis), kidney (renal aspergillosis), heart, (endocarditis, myocarditis), bone (osteomyelitis), and gastrointestinal tract. Ocular lesions (mycotic keratitis, endophthalmitis and orbital aspergilloma) may also occur, either as a result of dissemination or following local trauma or surgery.

- **Aspergillosis of the paranasal sinuses:**

Two types of paranasal sinus aspergillosis are generally recognised. (1) A non-invasive "aspergilloma" form, primarily seen in non-immunosuppressed individuals. Predisposing factors include a history of chronic sinusitis and poorly draining sinuses with excessive mucus. (2) An invasive form, usually seen in the immunosuppressed patient. This form has a similar clinical setting to that seen in rhinocerebral zygomycosis; and symptoms include fever, rhinitis and signs of invasion into the orbit.

- **Cutaneous aspergillosis:**

Cutaneous aspergillosis is a rare manifestation that is usually a result of dissemination from primary pulmonary infection in the immunosuppressed patient. However, cases of primary cutaneous aspergillosis also occur, usually as a result of trauma or colonisation. Lesions manifest as erythematous papules or macules with progressive central necrosis.

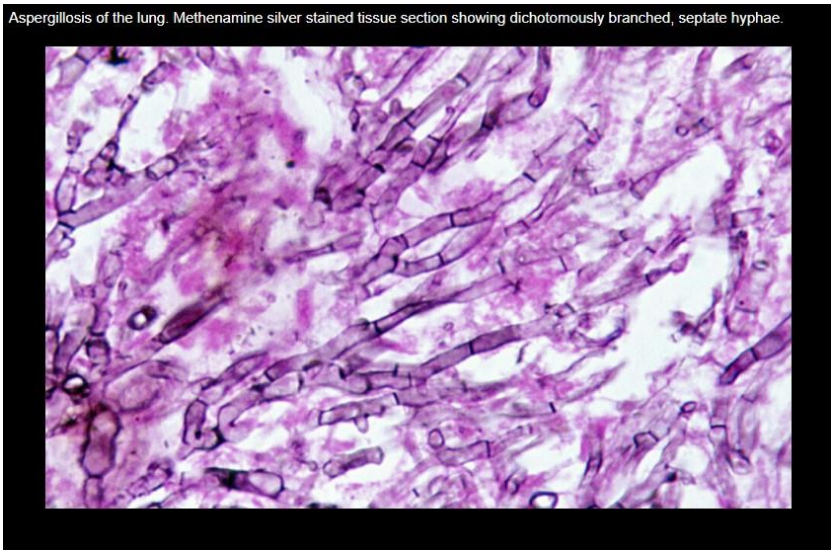
Laboratory diagnosis:

Clinical material:

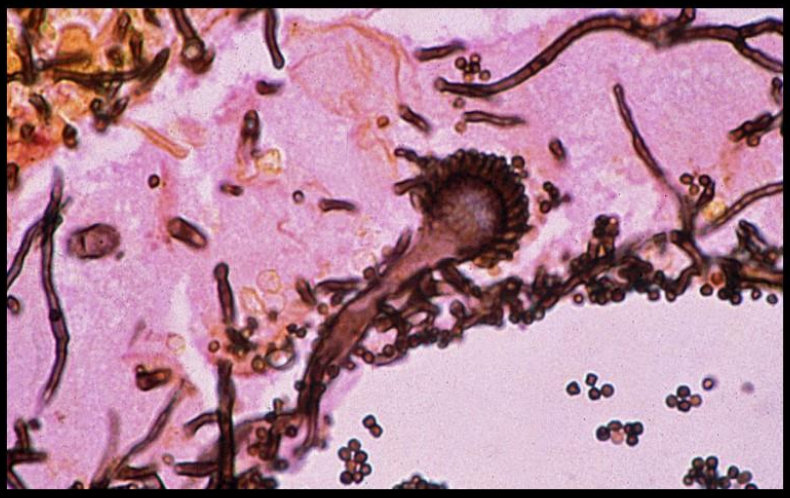
Sputum, bronchial washings and tracheal aspirates from patients with pulmonary disease and tissue biopsies from patients with disseminated disease.

Direct microscopy:

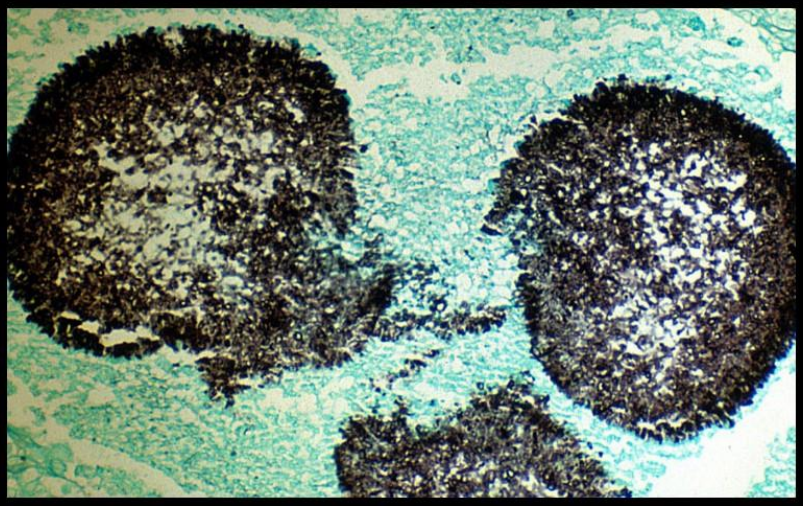
(a) Sputum, washings and aspirates make wet mounts in either 10% KOH & Parker ink or Calcofluor and/or Gram stained smears; (b) Tissue sections should be stained with H&E, GMS and PAS digest. Note Aspergillus hyphae may be missed in H&E stained sections. Examine specimens for dichotomously branched, septate hyphae.


Aspergillosis of the lung. Methenamine silver stained tissue section showing dichotomously branched, septate hyphae.

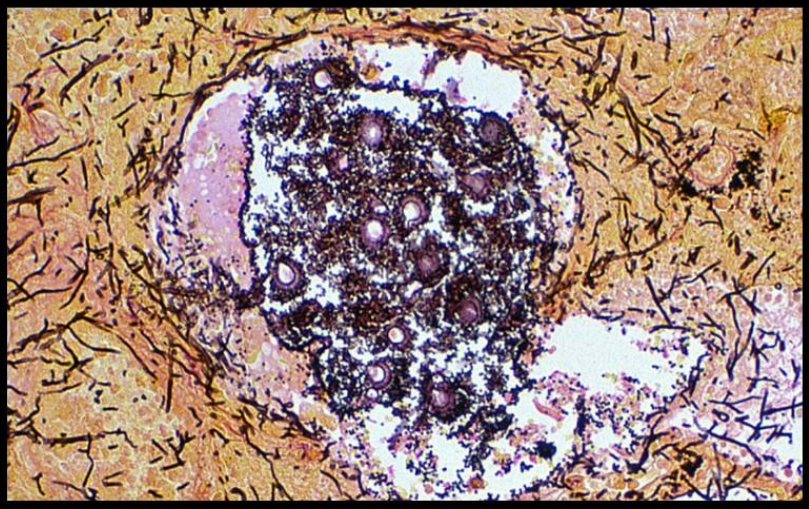
Aspergillosis of the lung. Methenamine silver stained tissue section showing a conidial head of A. fumigatus (right).



Lung tissue showing fungus balls of hyphae of A. fumigatus.



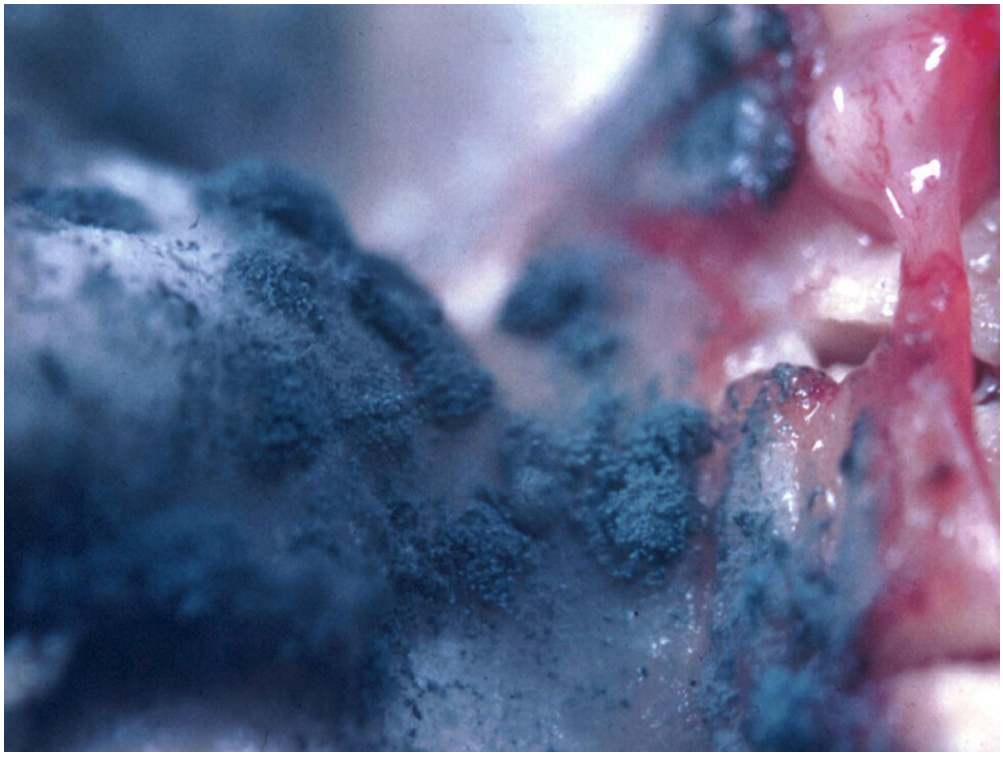
Lung tissue showing fungus balls of hyphae of A. fumigatus. Note: conidial heads forming in an alveolus.



Interpretation: The presence of hyaline, branching septate hyphae, consistent with Aspergillus in any specimen, from a patient with supporting clinical symptoms should be considered significant. Biopsy and evidence of tissue invasion is of particular importance. Remember direct microscopy or histopathology does not offer a specific identification of the causative agent.

Culture:

Clinical specimens should be inoculated onto primary isolation media, like Sabouraud's dextrose agar. Colonies are fast growing and may be white, yellow, yellow-brown, brown to black or green in colour.

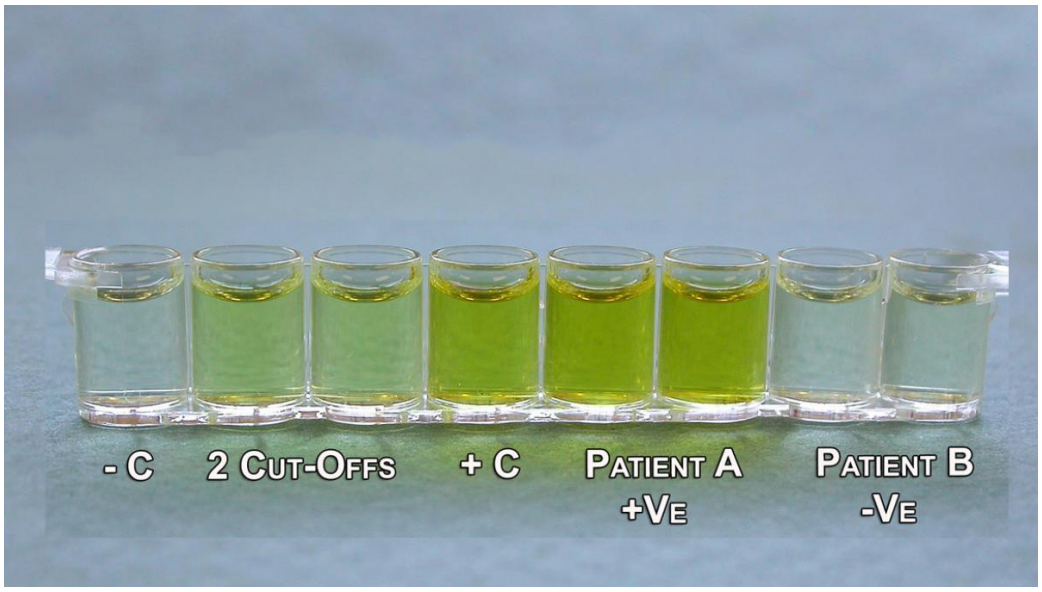


***A. fumigatus* growing in air sacs, during epidemic aspergillosis.**

Interpretation: Aspergillus species are well recognised as common environmental airborne contaminants, therefore a positive culture from a non-sterile specimen, such as sputum, is not proof of infection. However, the detection of Aspergillus (especially *A. fumigatus* and *A. flavus*) in sputum cultures, from patients with appropriate predisposing conditions, is likely to be of diagnostic importance and empiric antifungal therapy should be considered. Unfortunately, patients with invasive pulmonary aspergillosis, often have negative sputum cultures making a lung biopsy a prerequisite for a definitive diagnosis.

Serology:

Immunodiffusion tests for the detection of antibodies to Aspergillus species have proven to be of value in the diagnosis of allergic, aspergilloma, and invasive aspergillosis. However, they should never be used alone, and must be correlated with other clinical and diagnostic data. Several antigen tests for the detection of Aspergillusfrom blood, urine and CFS are now available. The (1→3)- β-D- glucan test detects a wide variety of fungal pathogens including Aspergillus, Candida, Fusarium, Trichosporon and several commercial kits (FungiTec G, Fungitell) are available.



Platelia Aspergillus ELISA galactomannan test.

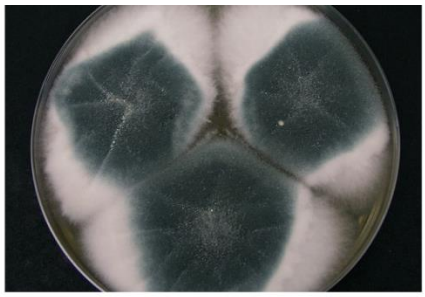
However the most widely used system is the Aspergillus galactomannan ELISA test (Platelia® Aspergillus ELISA kit). The Aspergillus galactomannan (GM) test has a reported specificity of 89-93%; sensitivity of 61-71%; NPV of 95-98%; PPV of 26-53% (Meta-analysis 27 studies Pfeiffer et al. CID 2006). However as galactomannan is rapidly eliminated from blood - serial screening twice weekly for optimal diagnosis is recommended.

Identification:

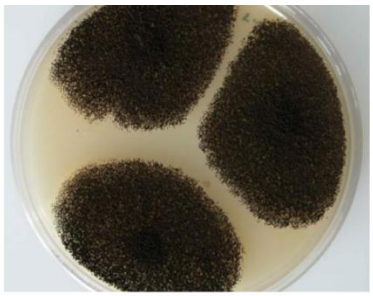
Aspergillus colonies are usually fast growing, white, yellow, yellow-brown, brown to black or shades of green, and they mostly consist of a dense felt of erect conidiophores. Conidiophores terminate in a vesicle covered with either a single palisade-like layer of phialides (uniseriate) or a layer of subtending cells (metulae)

which bear small whorls of phialides (the so-called biseriate structure). The vesicle, phialides, metulae (if present) and conidia form the conidial head. Conidia are one-celled, smooth- or rough-walled, hyaline or pigmented and are basocatenate, forming long dry chains which may be divergent (radiate) or aggregated in compact columns (columnar). Some species may produce Hülle cells or sclerotia.

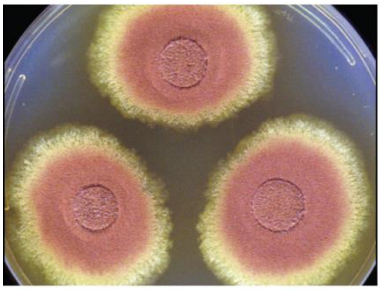
Aspergillus flavus



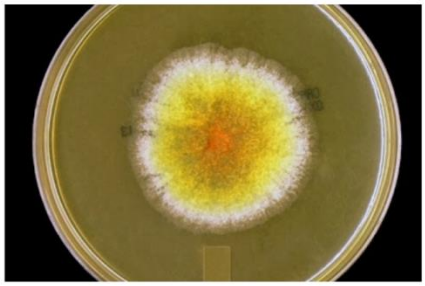
Aspergillus fumigatus



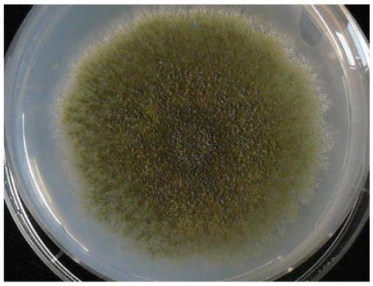
Aspergillus niger



Aspergillus terreus



Aspergillus glaucus



Aspergillus nidulans

Classification

Kingdom: Fungi - Division: Ascomycota - Class: Eurotiomycetes

Order: Eurotiales - Family: Trichocomaceae - Genus: Aspergillus

Symptoms of Aspergillosis

The different types of aspergillosis can cause different symptoms.
The symptoms of allergic bronchopulmonary aspergillosis (ABPA) are similar to asthma symptoms, including:

- Wheezing
- Shortness of breath
- Cough
- Fever (in rare cases)

Symptoms of allergic Aspergillus sinusitis include:

- Stuffiness
- Runny nose
- Headache
- Reduced ability to smell

Symptoms of an aspergilloma ("fungus ball") include:

- Cough
- Coughing up blood
- Shortness of breath

Symptoms of chronic pulmonary Aspergillosis include:

- Weight loss
- Cough
- Coughing up blood
- Fatigue
- Shortness of breath

Virulence Factors

Virulence factors play a major role in the pathogenicity of Aspergillus species, host immune status also plays a key role in enhancing the production of virulence factors of fungi in a host. Virulence factors have been identified for different Aspergillus species such as adhesins, pigments hydrolytic enzymes such as proteases, phospholipases, ribonucleases, restrictocin; catalases, superoxide-dismutases, mycotoxins and low-molecular-weight non-protein metabolites. Mycotoxin mainly gliotoxin is one of the powerful virulence factor, produced by *A. fumigatus* and *A. terreus* isolates in patient samples, however production of aflatoxins are mainly seen in *A. flavus* cases, it is reported that mycotoxins can play a major role to enhance pathogenesis of invasiveness of aspergilli. Also reported that the gliotoxin is produced in vivo in tissues of animals infected with *A. fumigatus* and it was recently found in serum of patients with invasive Aspergillosis.

Treatment for Aspergillosis

Type of aspergillosis	Examples	Recommended Treatment
Allergic aspergillosis	• Allergic bronchopulmonary aspergillosis (ABPA) • Allergic *Aspergillus* sinusitis	• Itraconazole • May consider corticosteroids
Invasive aspergillosis	• Invasive aspergillosis • Cutaneous aspergillosis • Chronic pulmonary aspergillosis	• Voriconazole • Other options: lipid amphotericin formulations, posaconazole, isavuconazole, itraconazole, caspofungin, and micafungin
Aspergilloma		• May include surgery and/or antifungal medications

Treatment for invasive and cutaneous aspergillosis: When possible, immunosuppressive medications should be discontinued or decreased. People with severe cases of aspergillosis may need surgery.

Expert guidance is needed for infections not responding to treatment, including antifungal-resistant infections.

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