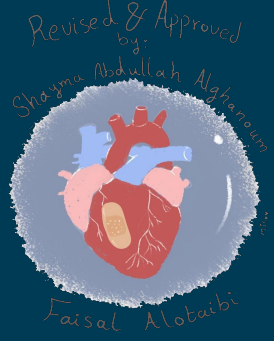
# Respiratory Fungal Infections

TEAM 439
MICROBIOLOGY




VERSION 1

# Objectives

- Acquire the basic knowledge about fungal infections of the respiratory system
- Know the main fungi that affects the respiratory system
- Identify the clinical settings of such infections
- Know the laboratory diagnosis, and treatment of these infections

## Colour index:

**Red: Important & Doctor's notes.**

**Grey: Extra info & explanation.**

**Purple: Only in girl's slides.**

**Orange: Only in boy's slides.**

**Green: Lecture notes**

**Any future corrections will be in the editing file, so please check it frequently.**

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# Etiology

**Fungi**

- **Opportunistic**
  are mostly found as normal flora in the oral cavity and URT.
  - **Yeast**
    - Candidiasis (e.g. Candida albicans)
    - Cryptococcosis (Cryptococcus neoformans, C. gattii)
  - **Mould fungi**
    - **Aspergillosis (Aspergillus species)**
    - **Zygomycosis (Zygomycetes, e.g. Rhizopus, Mucor)**
    - Other mould
- **Primary Infections**
  - **Dimorphic fungi**
    Have 2 forms depending on environmental factors
    1- it grows as yeast at body temperature
    2- grows as mould at room temperature
    - Histoplasma capsulatum
    - Blastomyces dermatitidis
    - Paracoccidioides brasiliensis
    - Coccidioides immitis

Fungal infections usually cause mild symptoms or self-limited in the immunocompetent host. In the immunocompromised host it causes severe infections and may disseminate throughout the body

# Primary Systemic Mycoses

| | |
|---|---|
| Overview | - They cause Infections of the respiratory system, (Inhalation) - **Dissemination** in **immunocompromised hosts**<br>(Infection starts with inhalation. However, if patient is immunocompromised it will go to distant organs. However, in immunocompetent patients, very mild symptoms) |
| Common in | - North America and to a lesser extent in South America. Rare in KSA<br>- Not common in other parts of the World. |
| Etiologies | **Dimorphic fungi** including:<br>- Histoplasmosis infection caused by inhaling **Histoplasma** spores, found in the droppings of bats.<br>- Blastomycosis<br>- Coccidioidomycosis<br>- paracoccidioidomycosis |
| Characteristics of dimorphic fungi | • Primary pathogens<br>• Found in nature in soil of restricted habitats<br>• Highly infectious (في اللاب يعاملونها معاملة TB) |

# Aspergillosis

Most common filamentous fungi to cause infections
(Opportunistic)

Aspergillosis is a spectrum of diseases of humans and animals caused by members of the genus Aspergillus. **They include:**

**Clinical forms of aspergillosis** ★

### Mycotoxicosis
A condition caused by the ingestion of mycotoxin metabolite, toxins produced by aspergillus
The most common is aflatoxin.

### Allergy
In normal / immunocompetent individuals, when spores are inhaled macrophages will do their job and engulf them. However, some spores might escape, requiring more inflammatory mediators to eradicate them, causing allergy. But if patient is immunocompromised, it won't be eradicated, causing an invasive disease

### Colonization (without invasion and extension) in preformed cavities
E.g. it will line TB cavities and cause a mass (aspergilloma)

### Invasive disease of lungs
In immunocompromised. It is Characterized by presence of fungal hyphae in lung tissue

### Systemic and disseminated disease

لو شخص immunocompromised وجته Aspergillosis بتصير invasive وتنتشر

لو شخص عنده TB مثلا وسوا عنده Cavities وجاه بعدها Aspergillosis . اللي بيصير أنه الكافتيز هذي بيجي فيها Aspergilloma واللي هي Fungs ball
وتصير colonized لكن ماراح ينتشروبيصير chronic

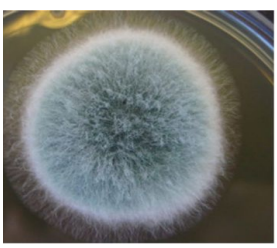
A. Fumigatus > A.flavus

- A. terreus
- A. nidulans
- **Aetiological Agents** (common Aspergillus species) (Mold)
  - **A. fumigatus**
  - **A. flavus**
  - A. niger

Most common in **lung** infections

# Risk factors

- Bone marrow / organ transplantation
- Cancer: Leukemia, lymphoma,.. etc
- AIDS
- Drugs (immunosuppressive) : Cytotoxic drugs, steroids,.. etc
- Diabetes
- Others



Aspergillus fumigatus

Aspergillus niger

# Classification of Aspergillosis

## Airways/nasal exposure to airborne Aspergillus

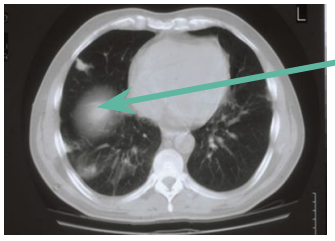
We are repeatedly exposed to fungal spores and our immunity can eradicate them but in cases where it is weakened diseases can happen

- **Persistence without disease**
  - Colonisation of the airways or nose/sinuses
- **Allergic**
  - Allergic bronchopulmonary aspergillosis (ABPA) > in lung
  - Allergic Aspergillus sinusitis >in sinuses
- **Invasive Aspergillosis**
  - Immunocompromised patients
- **Chronic Aspergillosis**
  - Lung aspergilloma
  - Maxillary (sinus) aspergilloma

**Aspergilloma** is a clump of mold which exists in a body cavity such as a paranasal sinus or an organ such as the lung or a cavity caused by a disease like TB or tumors.

| | **Chronic Aspergillosis**<br>Colonizing aspergillosis<br><br>(Caused by **Aspergilloma**, aka. fungus ball) | **Invasive pulmonary Aspergillosis** | **Allergic bronchopulmonary Aspergillosis** |
|---|---|---|---|
| Signs/ symptoms | Cough, hemoptysis, variable fever | Cough, hemoptysis, fever, leukocytosis | Symptoms of asthma, bronchial obstruction, eosinophilia, wheezing |
| **Radiology** | **Mass in the lung, radiolucent crescent**<br><br>**يجي مرض زي الـTB ويسوي Cavities، وبعدين يصير Fungal infection بالمكان ويعبي الفراغ هذا ويطلع Aspergilloma أو Fungus ball** | **Lesions with Halo sign (Invasive)**<br>A zone of ground glass opacity surrounding a pulmonary nodule or mass and represents hemorrhage | - |
| Tests | - | Tissue specimen from lung biopsy is very important for diagnosis | ❖ Skin test reactivity to Aspergillus<br>❖ Serum antibodies to Aspergillus<br>❖ Serum IgE > 1000 ng/ml<br>(usually total IgE is not enough but **IgE specific to aspergillus is important**) |

**Air crescent**
Air surrounds the mass
**Aspergilloma, Fungus ball**



**Halo sign**
**Invasive pulmonary aspergillosis**
بالوسط فيه nodule وحولها شفافية، الشفافية ذي بسبب الـ hemorrhage

# Diagnosis of Aspergillosis

## 1 Specimen

- Respiratory specimens: Sputum, BAL (BronchoAlveolar Lavage), **Lung biopsy**.
- Other samples: Blood, etc.. For serology & detection of antigens

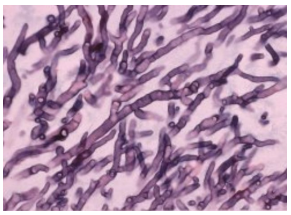


Figure A

## 2 Lab Investigations

- **Direct Microscopy:**

We use Giemsa Stain, Grocott methenamine silver stain (GMS)

★ Will show fungal **septate** hyphae**,** **dichotomous branching** (45°)(Fig.A)

- **Culture on SDA,** Sabouraud Dextrose Agar

- **Serology:**
  - Test for Antibody
  - ELISA test for galactomannan Antigen (specific for aspergillus)

- **PCR:**
  - Detection of Aspergillus DNA in clinical samples

For invasive disease, tissue biopsy is the best.
For allergic disease, igE.

# Treatment of Aspergillosis

- **Voriconazole (Gold-standard)**

- Alternative therapy:

1- Amphotericin B

2- Itraconazole

3- Caspofungin

# Fungal Sinusitis

| | |
|---|---|
| **Clinical Presentation** | ❖ Nasal polyps (لحمية) – and other symptoms of sinusitis.<br>❖ **In immunocompromised:** Could disseminate adjacent structures e.g. the eye then go to → cranium and become (**Rhinocerebral**).<br>❖ The most common cause in KSA is **Aspergillus flavus**<br>❖ In addition to Aspergillus, there are other fungi that can cause fungal sinusitis.<br>❖ Aspergillus sinusitis has the same spectrum of Aspergillus disease in the lung. See below |
| **Spectrum** | **Invasive**:<br>Could disseminate to brain & eye. Mostly in immunocompromised |
| | **Non-invasive:**<br>Aspergilloma, **(localized), .** |
| | **Allergic (Very common),** nasal polyps. |
| | **Chronic** |
| **Diagnosis** | ❖ Clinical and radiology<br>❖ Culture<br>❖ **Histology** (to see eosinophils)<br>❖ Precipitating antibodies useful in diagnosis (serological test in case of invasive fungal infection)<br>❖ Tissue biopsy (best for invasive)<br>❖ Measurement of IgE level, RAST test*<br><br>*A radioallergosorbent test is a blood test using radioimmunoassay test to detect specific IgE antibodies, to determine the substances the patient is allergic to.<br>The diagnosis is very important to know if it's allergies or chronic or invasive (doctor) |
| **Treatment** | Depends on the type and severity of the disease and the immunological status of the patient.<br>For example: if there is a polyp, it will be removed<br>If the patient is immunocompromised, antifungals will be given. |

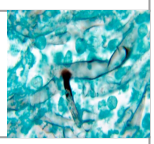
# Zygomycosis

Rarely occurs in immunocompetent individuals

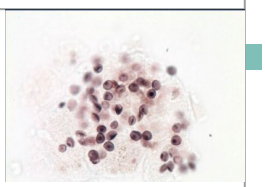
**Pulmonary** zygomycosis
Less common clinical form

**Zygomycosis**
**2 types**

**Rhinocerebral** zygomycosis
Most common clinical form
Starts as acute sinusitis

| | |
|---|---|
| **Presentation** | ❖ **Acute** (Unlike aspergillosis)<br>❖ **Rapid** evolving clinical course (Rapidly progressive & needs urgent intervention)<br>❖ Consolidation, nodules, cavitation, pleural **effusion**, hemoptysis<br>❖ Infection may extend to chest wall, diaphragm, pericardium.<br>❖ Pulmonary infarction and hemorrhage. As it has more affinity to infect blood vessels.<br><br>★ Dr: you must know that the hallmark of this disease is **tissue invasion, infarction, necrosis**, hemoptysis, pneumonia etc.. |
| **Etiology** (Mould) | **Zygomycetes** ,broad **Non-septate** hyphae e.g. Rhizopus (Remember that aspergillosis has septated hyphae)  |
| **Risk Factors** | ❖ Transplant patients<br>❖ Malignancy<br>❖ AIDS<br>❖ **Diabetic ketoacidosis** a life-threatening problem that affects people with **diabetes**. It occurs when the body starts breaking down fat at a rate that is much too fast. |
| **Diagnosis** | **Specimen:**<br>❖ Respiratory specimens:<br>- Sputum<br>- BAL, BronchoAlveolar Lavage<br>- Lung biopsy<br>❖ Other samples. |
| | **Direct Microscopy:**<br>- Giemsa stain, GMS stain (Silver stain)<br>Will show broad **non- septate** fungal hyphae.<br>- Culture on SDA (no cycloheximide) |
| | **Serology:** Not available |
| **Treatment** | ❖ **Amphotericin B**<br>❖ Surgery (in many cases surgery is needed) |

# Pneumocystosis (PCP)

| | |
|---|---|
| **Overview** | ❖ It is **interstitial** pneumonia of the alveolar area. Affect compromised host **(common in AIDS patients).**<br>❖ Pneumocystis pneumonia (PCP) is Opportunistic fungal pneumonia |
| **Etiology** | **Pneumocystis jiroveci (Yeast)**<br>❖ Naturally found in rodents (rats), other animals (goats, horses), Humans may contract it during childhood.<br>❖ Previously thought to be a protozoan parasite, but later it has been proven to be a fungus. |
| **Risk Factors** | ❖ Especially **common in AIDS patients** |
| **Diagnosis** | **Specimen:**<br>- Bronchoscopic specimens<br>- BAL, BronchoAlveolar Lavage<br>- Sputum, Lung, biopsy tissue. |
| | **Histological sections or smears stained by:**<br>❖ GMS stain.<br>❖ **Immunofluorescence** (better sensitivity)<br>If positive —> will see **cysts** of hat-shape, Cup shape,crescent<br>  <br>**Cysts** |
| | Does not grow in laboratory media e.g. SDA |
| **Treatment** | ❖ Trimethoprim "The drug of choice"<br>❖ Sulfamethoxazole<br>❖ Dapsone<br>Note that it is treated by antibiotics, not antifungals. |

## Summary

# MCQs

*Note that the girls' dr said there probably won't be any cases only straightforward Qs

| | | | |
|---|---|---|---|
| **Q1: A 14-year-old girl with leukemia had been neutropenic for 5 weeks when she developed fever, cough, shortness of breath, pleuritic chest pain, and hemoptysis. The causative organism is seen in a lung biopsy stained with methenamine silver. With which antimicrobial should she be treated?** | | | |
| A- Ciprofloxacin | B- Amphotericin B | C- voriconazole | D-Itraconazole |
| **Q2: A 45 year old man came to the hospital with a fever and hemoptysis. A chest CT scan showed multiple lesions with a halo sign. He was later diagnosed with invasive pulmonary aspergillosis. What is the most likely etiology of this disease?** | | | |
| A- Aspergillus fumigatus | B- Aspergillus niger | C- Rhizopus | D- Pneumocystis jiroveci |
| **Q3: A 24-year-old male presents with fever, headache, chills, cough, and chest pain a few weeks after visiting caves in the Ozark Mountains of northern Arkansas. A chest radiograph reveals patchy lung infiltrates and hilar lymphadenopathy. An immunodiffusion test detects antibodies in the patient's serum to the H antigen of the causative fungal agent. Which organism caused the patient's clinical manifestations?** | | | |
| A- Candida albicans | B- Aspergillus flavus | C- Cryptococcus neoformans | D- Histoplasma capsulatum |
| **Q4: A patient developed pulmonary zygomycosis, a specimen was taken and stained with Grocott methenamine silver stain. What will be seen under a microscope?** | | | |
| A- Hat shaped cysts | B- Microbe not visible | C- Septate hyphae | D- Broad Non-septate hyphae |
| **Q5: A patient infected with HIV presented with fever, cough, and hemoptysis. After doing a radiology test the doctor was able to exclude chronic aspergillosis. Which sign did he NOT find?** | | | |
| A- Cavitation | B- Aspergillus fungus ball | C- Halo sign | D- Pleural effusion |
| **Q6: Which of the following is not risk factor for rhinocerebral zygomycosis?** | | | |
| A- Immunocompetent | B- Bone marrow transplant | C- Diabetic ketoacidosis | D- Malignant tumors |
| **Q7:The most common cause of fungal sinusitis in saudi arabia is?** | | | |
| A- Aspergillus fumigatus | B- Aspergillus flavus | C- Rhizopus | D- Pneumocystis jiroveci |

| Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 |
|---|---|---|---|---|---|---|
| C | A | D | D | B | A | B |

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