Sheet n. 2

Doctor 22

فريق طوفان الاقصى

Writer: Basel Ayman
Sra'a Ali

Corrector: Mahde Sabbagh

Introduction to Mycology

We are going to explore something different in the field of microbiology apart from viruses and bacteria, and that is mycology.

Medical mycology

-Medical mycology is the study of mycoses of man and their etiologic agents.
It is a branch of medical science that focuses on studying fungal infections, also known as mycotic infections. It involves understanding the causes, symptoms, and treatments of these types of infections.

-Mycoses are the diseases caused by fungi. Of the several thousands of species of fungi that are known, less than 300 are pathogenic to man.
In nature, there are thousands of types of fungi, but less than 300 of them actually infect and affect humans. Out of these, about 10-15 types are responsible for 95% of the diseases that affect humans in general. Recently, there has been a noticeable increase in fungal infections, and this is due to the increase in the number of immunocompromised individuals (people's immune systems have become weakened).
Most of the fungi around us in the environment are saprophytic, which means they rely on dead and decaying organic matter as their source of carbon, they don't cause diseases in humans. Unlike biotrophic or parasitic (pathogenic) fungi, which are the disease causing fungi (For this reason, we are not affected by all types of fungus).

-fungal invasion of human tissue was recognized in the early 1800s before the science of bacteriology was developed.
Mycology is older than bacteriology

What is a Fungus ?

- **Kingdom fungi**
- **Eukaryotic – a true nucleus , heterotrophic, do not contain Chlorophyll**

Eukaryotes and prokaryotes are different. Eukaryotes have 80s ribosomes, a true nucleus with DNA inside, and their DNA is diploid and linear. Prokaryotes have 70s ribosomes, no nucleus, and their DNA is haploid and circular. Eukaryotes also have membrane-bound organelles, while prokaryotes don't.
Fungi are Heterotrophic which means that they need oxygen to break down organic matter for their nutrition. They can't make their own food through photosynthesis like plants (do not contain chlorophyll). Instead, they depend on exogenous sources of organic material, like dead plants or animals, to get energy and nutrients.

There are two main types of fungi when speaking about the organic source that they use for carbon: saprophytic fungi (The majority) and parasitic fungi.

• Saprophytic (rely on dead tissue).Parasitic (rely on living organism).

Now, about their morphology (appearance), fungi can also be classified to:

• Yeasts (خميرة) & filamentous structures (hyphae) (عفن)

Yeast is a single-celled fungus, while filamentous fungi have long, branching filaments and tubular structure called hyphae. There are some fungi that can actually exist in two different forms or morphologies. These fungi are called dimorphic fungi. They have the ability to switch between a filamentous form and a yeast-like form depending on the environmental conditions they encounter.

• Produce spores (sexual & asexual reproduction)
In bacteria spores were related to resistance, but spores in mycology are a completely different thing, they are reproductive elements that can be produced in two ways: sexually and asexually.

Some terminology:
Teleomorph: fungi that can only reproduce sexually.
Anamorph: fungi that can only reproduce asexually.
Conidia: refers to asexual reproduction.
Spores: indicates both sexual and asexual reproduction.
(fortunately, you are not required to know details but unfortunately you are required to memorize without complete understanding).

• All fungi required organic source of Carbon associated with decaying matter

• Cell wall consist of chitin and B-glucan, both are polysaccharide which is the site of action of some antifungal drugs.
The fungal cell wall is unique because it consists of three components: glucan, chitin, and mannans. These components give the cell wall its rigidity.
These unique components have been utilized in diagnosing fungal infections. To examine a sample suspected of containing a fungal infection, we treat it with a strong alkaline agent like potassium hydroxide at a specific concentration. This breaks down cells and denatures proteins, but it cannot penetrate the fungal cell wall. This allows us to isolate fungi and then observe the intact fungal cells under a microscope.
These components of the cell wall can also be targets for antifungals.

• Cell membrane consist of ergosterol, Ergosterol is the site of action of some antifungal.
Most eukaryotes contain cholesterol in their cell wall, but fungi have a similar compound called ergosterol. It serves a similar function in their cell membranes.

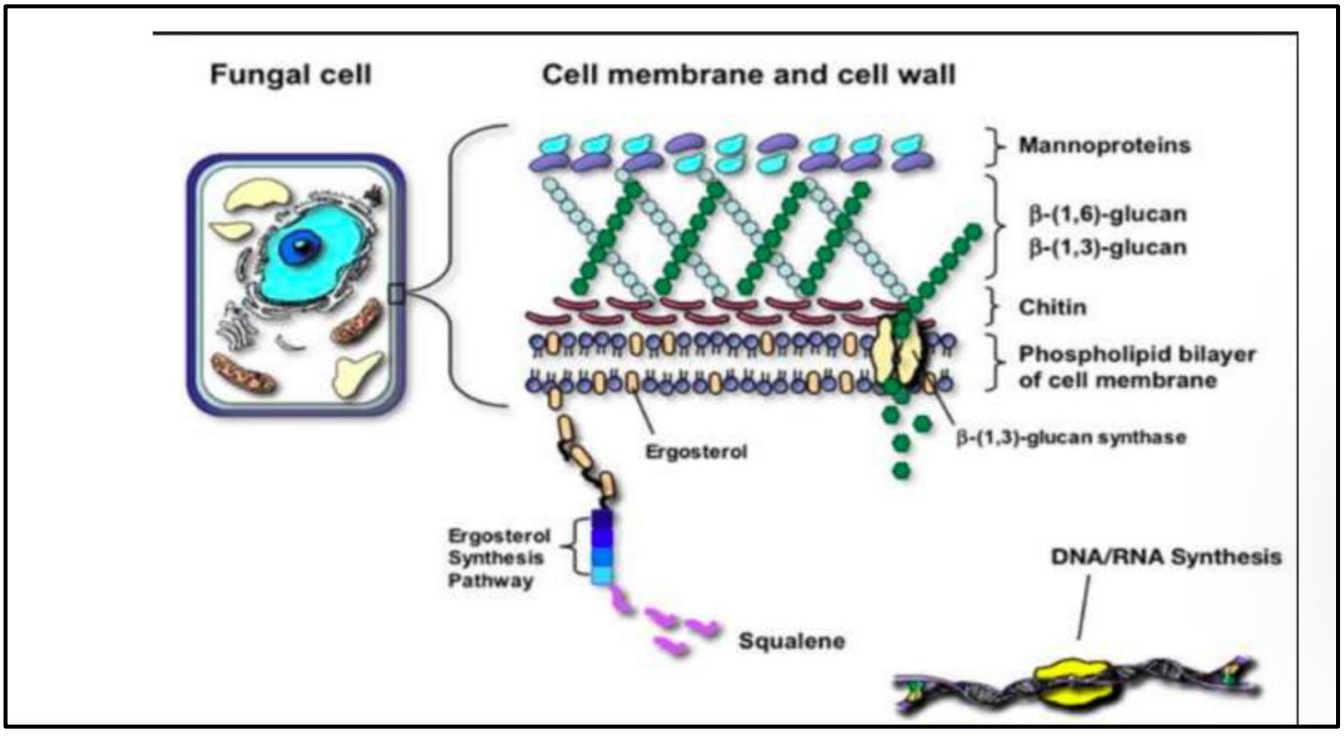
The presence of ergosterol and its synthetic pathways has become a target for three families of antifungals that specifically target the fungal cell membrane (Polyene derivatives, Azoles and Allylamines).

***Antifungal medications are different from antibiotics because they specifically target fungal infections. There are 6 families of antifungal medications, and one important family is called Echinocandins (example of a member: Caspofungin which works on the cell wall).**

• Most fungi are obligatory aerobes (which means they require oxygen to survive and grow)

However, there are some exceptions to this rule, as there are a few fungi that are facultative or even anaerobes (extremally rare).

Fungal Cell



This is a figure representing the fungal cell wall, notice the three major components (mannan, glucan and chitin), they are targets for antifungals like Caspofungin (of the Echinocandin family) which targets Beta-1,3-glucan-synthase (an enzyme) preventing its synthesis.
If you also look down a little bit at the cell membrane, you can see Ergosterol which can also be a target of some drugs, for example: polyamines fungicides, which are molecules that contain multiple amino groups. They are not a class of antifungal drugs but rather a group of compounds with diverse biological functions. They bind directly to already formed Ergosterol creating ion channels (pores), destroying the fungal cell.

Azoles (a family of antifungals) can work on the synthetic pathway of Ergosterol, preventing its synthesis.

Allylamines (a family of antifungals, an example of a which is Terbinafine) work on the earliest stages of Ergosterol synthesis by inhibiting squalene (squalene epoxidase enzyme), preventing its conversion to Ergosterol.

There is another family known as 5-Flurocytosine, which is considered a highly potent analog for cytosine in DNA and RNA synthesis. These compounds are used in cancer treatment to disrupt the growth and replication of cancer cells. By mimicking cytosine, 5-Flurocytosine interferes with the normal processes of DNA and RNA synthesis, ultimately impacting the ability of cancer cells to divide and multiply.

Don't exhaust yourself trying to memorize this information right now; we will study antifungals in details during the latter part of this lecture.

To sum up: Echinocandins like caspofungin target the fungal cell wall to stop fungal cell wall growth, polyamines fungicides directly target ergosterol, while azole antifungals and allylamines disrupt its production by two different mechanism. 5-Flurocytosine acts as a powerful substitute for cytosine, targeting cancer and fungal cells and hindering their growth.

The Importance of Fungi

1-They are common cause of damage to crops and food chain.

Fungi can indeed cause problems for crops by causing plant infestations. They can cause huge economical loss, but the real danger arises when people consume these affected crops, especially those contaminated with fungi such as Aspergillus flavus and Aspergillus Parasiticus. When these fungi enter the human body, they can produce a harmful substance called aflatoxin B1. This aflatoxin B1 can then be metabolised, which results in the formation of a highly cancer-causing compound (type 1 carcinogen) known as an epoxide (can produce hepatocellular carcinoma)

2- Few species of fungi can cause disease in human (300/200,000). However, fungal infections are increasing due to AIDS and other immunosuppressant conditions.

Fungi can produce toxins, allergies and fungal infections.

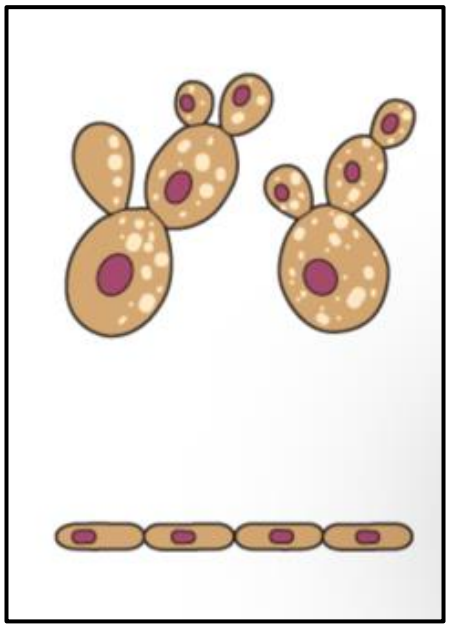
3. Production of antibiotics e.g Penicillin.

Despite all that, Fungus actually has many benefits. It's used in making cheese, bread, wine, and even the first antibiotic called penicillin. It's also used by pharmaceutical companies for the production of many compounds.

General mycology

• Fungi can be classified morphologically and according to growth forms into:

1. Yeast:



• These are oval or round single cells that reproduce by budding

Mother cell generates daughter cells by budding

• May form pseudohyphae (chains of elongated budding cells)

• Candida albicans and Creptococcus neoformans

Candida albicans (indigenous infection) is a type of fungus that can cause infections in humans. It's actually a common organism that naturally lives in our bodies as part of our normal flora. However, it can sometimes overgrow and lead to infections, especially in areas like the upper respiratory tract, GIT, and urogenital areas. These infections are often called candidiasis (can cutaneous or systemic) or yeast infections. They can occur when the fungus acquires virulence factors or when the host's immune system is compromised.
And They may suffer from arthritis, and meningitis.

Cryptococcus neoformans (exogenous infection). They are always pathogenic and can never be part of the normal flora. It's a type of fungus that can cause infections which is common among bird breeders. Cryptococcus neoformans is found in the environment(exo), especially in soil and bird droppings. When inhaled, it can enter the lungs causing initial acute inflammation and potentially spread to other parts of the body, The danger occurs when it reaches the cerebral spinal fluid, It can cause a serious condition like cryptococcosis and meningitis. Treatment usually involves antifungal medications.

Something worth mentioning about Candida albicans is that it can assume the yeast form, pseudohyphae and even some books suggest that it can assume the real hyphae morphology.

But keep in mind that pseudohyphae is different from the true hyphae, one of these differences is that pseudohyphae is an elongation of budding cells on one axis only (sausage like constriction), while true hyphae is elongated in many directions and divided into septa (septation)

• Common in immunocompromised patients and can cause multisystem infections such as meningitis, arthritis and respiratory infections.

So, what scares us about candidiasis is the development into systemic candidemia (endogenous).

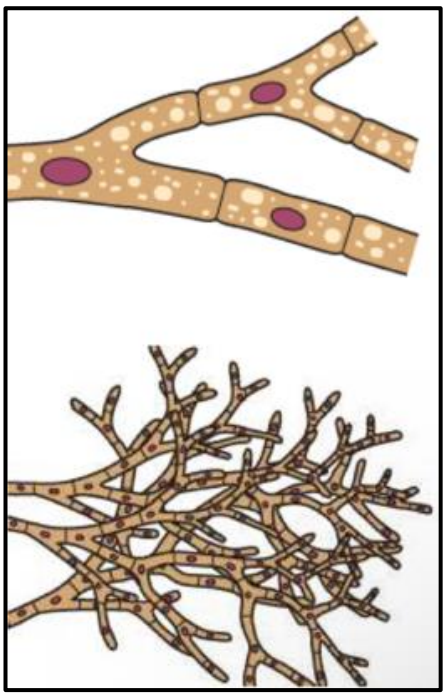
• C. neoformans found in soil and pigeon faeces and it commonly infects lung initially.

Causing cryptococcosis and meningitis (exogenous).

2. Filamentous fungi (Molds):

• They have branching tubular filaments (hyphae) which may be septate or non- septate

• Mycelium: mass of branching, interlinking hyphae



The web-like structure of hyphae is called Mycelium
The budding in Mycelium is called thallus.

• Also may produce asexual spores at the tip or side of the hyphae

They may reproduce sexually or asexually.

• Asexual spores may be contained in a sac called sporangiospores

e.g Zygomycetes, Aspergillus and Dermatophytes

There are indeed three common types of dermatophytes that cause fungal infections in humans: Trichophyton, Microsporum, and Epidermophyton. These fungi can lead to the development of ringworm lesions. These patients have an inflammatory cyrcle, and as we move towards the center of this cycle, there is a decrease in inflammation.

3. Dimorphic fungi
• These occur in two forms: yeast form in tissues or when grow at 37°C& filamentous form when grow at 22°C

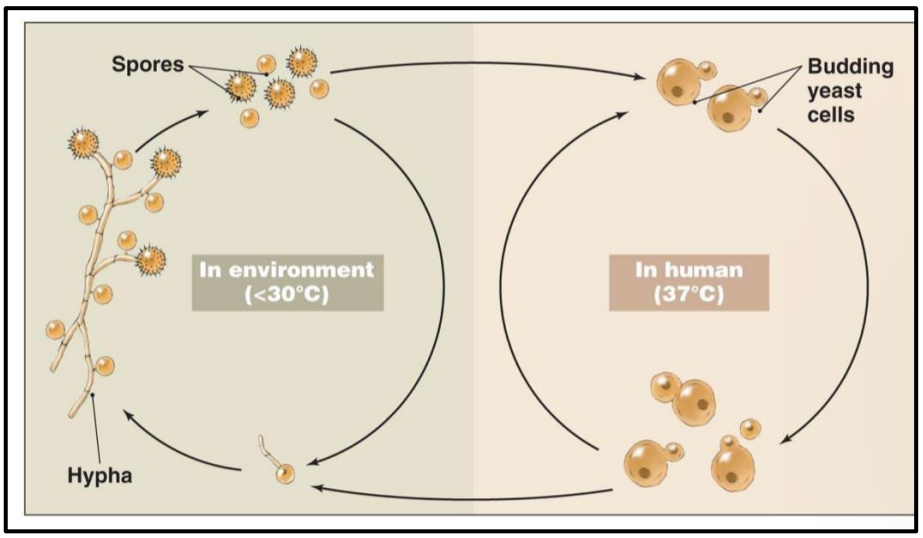
Dimorphic fungi claim both morphological forms depending on their environment. Outside the body they exist as hyphae, Inside the body, they can transform into yeast. This transformation is influenced by temperature (thermally induced) and is known as thermal dimorphism. The process is reversible, meaning the fungi can switch between the hyphal and yeast forms based on the temperature conditions.

• Examples:
Blastomyces dermatitidis

Coccidioides immitis
Histoplasma capsulatum
Paracoccidioides brasiliensis
Sporothrix schenckii
They cause systemic mycoses.

Systemic mycoses refer to fungal infections that can spread throughout the body, affecting various organs and systems.

This figure shows the reversable thermally induced dimorphism.



An example of this: some fungi switch from Yeast to Mold once extracted from the patient, they can be put in an incubator at 37C to switch back to Yeast.

They are all reversible.

They all cause systemic mycoses (will be discussed next).

Fungal diseases

- Fungal infections have recently emerged as a growing threat to human health, especially to persons whose immune systems are compromised in some way.

- There are 3 clinical entities of <u>fungal diseases</u>:

1) Fungal allergies:

- Molds grow on any damp organic surface, and spores are constantly in the air.

- As we said before, fungi reproduce through spores and conidia.

- Inhaled Spores & volatile fungal toxins may play a role in producing allergic manifestations such as asthmatic reaction (rapid bronchoconstriction mediated by IgE) and eosinophilia (hyper-eosinophilia).

- **Notable in Aspergillus fumigatus (the most known example).**

- **Those people who inhale the spores or conidia of Aspergillus fumigatus ➔ they might develop different conditions based on the site of inflammation, for example:**
  - ⇨ **If the inflammation was in the upper respiratory tract ➔ the patient is going to develop allergic rhinitis (also called Hay fever).**
  - ⇨ **If the inflammation reached the lower respiratory tract ➔ the patient is going to develop extrinsic allergic alveolitis.**

2) Fungal toxins (mycotoxicosis):

- **Aflatoxicosis:**

- **Aflatoxicosis is a poisoning condition & it results from ingestion of aflatoxins in contaminated food.**

- **Also caused by Aspergillus but the causative species are different from fumigatus.**

- **Aflatoxins are group of structurally related toxic compounds produced by certain strains of fungi (Aspergillus flavus & A. parasiticus).**

- **Aflatoxins are classified as type 1 carcinogens (type 1 carcinogen: a substance with a conclusive evidence that it can cause cancer in humans).**

- **Under favorable conditions of temperature & humidity, these fungi grow on certain foods & resulting in production of aflatoxins.**

- **The most pronounced contamination has been encountered in tree nuts, peanuts& other oilseeds including corn.**

- **Aflatoxins are metabolized in the liver to epoxide, which is potent carcinogenic.**

- **Aflatoxin B1 induce mutation in the p53 human suppressor gene (and suppresses this tumor suppressor gene), leading to loss of growth control in hepatocytes, which is the first step in a multistep process of neoplasm development.**

3) Fungal infections (mycosis):

- **Fungal infections are the most encountered entity of fungal diseases.**

- **Fungal infections are usually harmless, and sometimes they resolve spontaneously without medications. But most probably the patients will seek medical attention for cosmetic reasons.**

- **Fungal infections range from superficial infections to overwhelming infections that are rapidly fatal in compromised host.**

- **There are 5 classifications of fungal infections: Superficial, cutaneous, subcutaneous, systemic and opportunistic fungal infections.**
  We fear subcutaneous, systemic and opportunistic mycosis. Also, the status, severity and type of fungal infections depend on the host, for example, immunocompromised patients are more likely to develop systemic mycotic diseases.

- **Systemic mycotic diseases have poor prognosis (prognosis: the chance of recovery from a disease).**

- **The infection with fungi is increasing in frequency as a result of increased use of antibiotics, corticosteroids& cytotoxic drugs (immunosuppression).**

- **The number of immunocompromised people has increased in the last 2 decades; and that is due to many factors such as: immunosuppressants given to cancer patients and people who are going to undergo an organ transplantation operation, congenital and acquired immune deficiencies, taking cortisone and taking a wide spectrum of antibiotics is also considered as an immunosuppressant.**

- **Human fungal infections are commonly classified (clinically based on the site of the mycotic infection) as:**

❖ **Superficial & cutaneous infections:**

- **Infections involve the skin, mucous membrane, nail or hair with or without tissue destruction & immunological reaction.**

- **They both infect the outermost layer of the skin.**

- **Superficial mycosis for example infects only the stratum corneum of the skin. While cutaneous mycosis infects a bit deeper layer than the stratum corneum.**

- **They are characterized by low-level tissue invasion.**

- **Keratinized layer of the skin includes the nails and the hair.**

- **Superficial mycosis is characterized by no tissue damage and no immunological reaction ➔ which means that superficial mycosis has limited symptoms.**
  e.g. pityriasis versicolor, Tinea nigra, black and white Piedra.
  -Pityriasis versicolor is also called tinea versicolor, it is caused by the fungal species Malassezia furfur.
  Its symptoms include depigmentation of the skin, and depending on the host's skin color, the infection might cause hypopigmentation or hyperpigmentation. Furthermore, it can occur on the chest, on the shoulder and on the face, but it usually infects the trunk first, such as the back for example, and in this case, the patient usually doesn't notice that he has the infection because he doesn't feel any symptoms or signs.
  So, superficial mycosis is usually associated with limited or non-prominent symptoms.
  -Tinea nigra symptoms involve black macules on the palms of the hands.

- **Cutaneous mycosis is actually associated with tissue damage and immunological reaction, with relatively more noticeable and prominent symptoms such as inflammation and pain.**
  e.g. cutaneous candidiasis & dermatophytes.
  -Dermatophytes are also called Ringworm fungi -although they are not worms- because the lesions they cause are characterized by a ring shape with diminution (fading) of the redness toward the center of the ring.
  The names of the diseases caused by these dermatophytes consist of two parts, the first part is tinea, and the second part is a variable suffix which depends on the site of infection (lesions).
  If the lesions are on the feet ➔ then the disease is tinea pedis (athlete's foot)
  If the lesions are on the head scalp & hair ➔ then the disease is tinea capitis
  If the lesions are on a body part generally ➔ then the disease can be generally called tinea corporis
  If the lesions are on the proximal thighs ➔ then the disease is tinea cruris
  -Cutaneous candidiasis is caused by the fungus Candida, which is part of the normal flora; as it is found on the mucous membranes of the upper respiratory tract, of the GI tract and of the urogenital tract (especially in females).
  AIDS patients also suffer a lot from moniliasis (a synonym for candidiasis).
  Also, healthy individuals who have been infected with cutaneous candidiasis many times usually have typical characteristics, as they are usually obese and diabetic.
  Usually, cutaneous candidiasis occurs in body folds, for example, axillary folds, inframammary folds & gluteal folds.
  Babies also get a diaper rash (which are commonly caused by Candida) from the diaper (Candida grows best in warm and moist places such as under the diaper, and it can cause diaper rash if the wet or soiled diaper is left on too long without changing).

Cutaneous candidiasis can lead to systemic candidiasis.

❖ **Subcutaneous:**

- **In subcutaneous fungal infections, the infected layer is deeper than the layers infected by superficial and cutaneous fungal infections.**
  Examples of the layers (subcutaneous layers) infected by subcutaneous fungal infection: hypodermis, underlying fascia, cornea of the eye and even the muscle.

- **Now, the question is how would the fungus reach these subcutaneous layers and cross the skin?**
  The fungus reaches these subcutaneous layers via wounds ➔ this process is called traumatic implantation.

- **Infection is confined to sub-cutaneous tissue without dissemination to distant organs.**

- **Examples of subcutaneous fungal infections:**

  ⇨ **Chromoblastomycosis ➔ which gets access through skin cuts, abrasion, maceration.**
  ⇨ **Sporotrichoisis ➔ which is caused by the dimorphic fungi Sporothrix schenckii. Sporotrichoisis gets transmitted to humans via its spores which are found in the soil or on flower thorns, and that's why sporotrichiosis is also called "rose gardener disease" as it infects those who work at the garden like housewives and gardeners.**
  ⇨ **Eumycetoma or Madura foot ➔ which is approximately like chromoblastomycosis.**

❖ **Systemic mycosis:**

- **Are primarily pulmonary lesion that may disseminate to any organ.**

- **The individual doesn't have to be immunocompromised to be infected by those diseases as it also infects healthy individuals. However, if the individual was immunocompromised, the systemic mycotic disease would be more severe with more complications.**

- **Most Systemic mycotic diseases are cause my dimorphic fungi, they are characterized by having certain geographical distributions, as they are considered endemics in certain areas of the world.**

- **Examples of systemic mycotic diseases (they were mentioned before in the explanation of diseases caused by dimorphic fungi / the 4 fungi which cause them are quite important as they focus on them in the USMLE because their diseases are considered endemics!)**

  ⇨ **Coccidioidomycosis ➔ caused by Coccidioides immitis**
  ⇨ **Histoplasmosis ➔ caused by Histoplasma capsulatum**
  ⇨ **Blastomycosis ➔ caused by Blastomyces dermatitidis**
  ⇨ **Paracoccidioidomycosis ➔ caused by Paracoccidioides brasiliensis**

❖ **Opportunistic mycosis:**

- **The individual has to be immunocompromised so that opportunistic fungi take the opportunity to cause opportunistic mycotic diseases, they are not necessarily from the normal flora.**

- **Examples on fungi which cause opportunistic mycosis:**

  ⇨ **Candida spp (spp: species) ➔ part of the normal flora ➔ causes endogenous infection.**
  ⇨ **Cryptococcus ➔ never part of the normal flora ➔ causes exogenous infection.**

Diagnosis

- **Diagnosis of fungal infections is based on a combination of clinical observation and laboratory investigation.**
- **Clinical investigation:**

- **The first indication that a patient may have a systemic mycosis is often their failure to respond to antibacterial antibiotics.**

- **Laboratory diagnosis:**

- **Recognition of the pathogen in tissue by microscopy.**
- **Isolation of the causal fungus in culture.**
- **The use of serological tests (to detect the presence of a fungal antigen via the immune response).**
- **Detection of fungal DNA by PCR (DNA probes for certain fungal antigens).**
- **Histopathological sections of a biopsy or a specimen under the microscope.**

- **Generally, fungi which cause cutaneous infections are relatively easier to diagnose.**

But in certain diseases, it is necessary to take a specimen or a sample, use microscopic methods, isolation of the fungi in cultures, use molecular or histopathological techniques to make sure we are making the right diagnosis.

Types of specimen

- **Superficial and cutaneous mycosis (such as diseases caused by the dermatophytes) affect the keratinized layers of the skin as well as hair and nails ➔ so they can be taken for diagnosis (a universal approach for easier handling of these diseases).**

- **Skin scales, nail clippings and scrapings of the scalp that include hair stubs and skin scales are the most suitable specimens for the diagnosis of ringworm; these are collected into folded paper squares for transport to the laboratory.**

- **Swabs should be taken from suspected Candida infections from the mucous membranes and preferably sent to the laboratory in 'clear' transport medium.**

- **For subcutaneous infections the most suitable specimens are scrapings and crusts, aspirated pus and biopsies.**

  So, in subcutaneous mycotic infections we need other methods to obtain the specimen, the most suitable approaches are biopsy and aspirate.

  ⇨ **Biopsy ➔ solid**
  ⇨ **Aspirate ➔ fluid**

- **For example:**
  ⇨ **Bone marrow aspirate: the fluid part of the bone marrow only.**
  ⇨ **Bone marrow biopsy: the fluid + the soft bone.**

- **In some cases of superficial or cutaneous mycosis such as pityriasis versicolor (or tinea versicolor) the patients start having hyper- or hypopigmentation as well as scrapes, so we can take these scrapes for diagnosis via microscopic methods for example.**

- **In suspected systemic infection, specimens should be taken from appropriate sites.**

- **If there was an infected organ, then the process of taking the specimen depends on the involved organ.**

Stains and Direct Microscopic Examination

- **But generally, there is actually a universal approach for the diagnosis of fungal infections:**

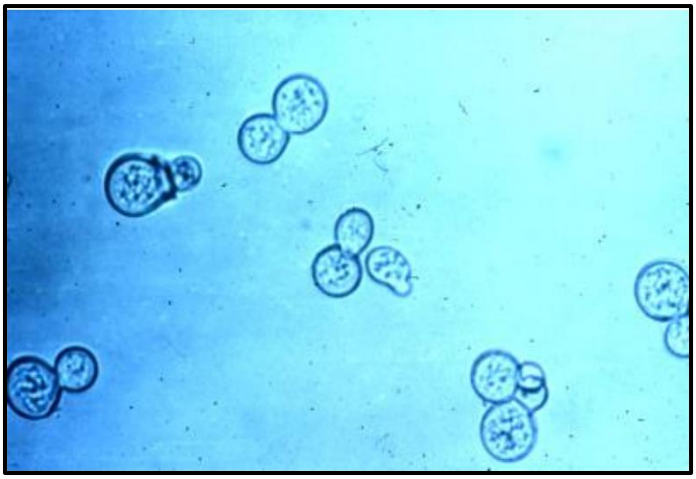
- **Most specimens can be examined satisfactorily in wet mounts after partial digestion of the tissue with 10–20% potassium hydroxide.**

  We first obtain the specimen suspected of having a fugal infection, then we put in in a 10%-20% Potassium hydroxide, which is a very strong alkylating agent that disintegrates every human cell, debris and proteins so that the fungi remain in the sample without them (wont effect the fungi since it has a string cell wall) ➔ easier to detect & observe the fungi under the microscope.

- **Addition of Calcofluor white and subsequent examination by fluorescence microscopy enhances the detection of most fungi (clearer morphology) as the fluorescent hydroxide– Calcofluor binds to the fungal cell walls.**

- **special stains (methylene blue, lactophenol blue, periodic acid-Schiff (PAS), ink, etc) could be added after the KOH treatment, and the stain depends on the type of fungi you are looking for.**
  - ⇨ **Methylene blue could be used to distinguish fungi under the microscope, for example, Candida is Gram-positive.**
  - ⇨ **Lactophenol blue is used for staining Dermatophytes (Epidermophyton, microsporum and Trichophyton).**
  - ⇨ **PAS stains the fungi with a hot pink color for better observation.**
  - ⇨ **Ink is used to stain Cryptococcus neoformans (which causes Cryptococcosis and it is also characterized by a capsule)**
    In Cryptococcus infection we fear the dissemination of the fungus from the lungs to the cerebrospinal fluid (CSF) of the patient. So we take a CSF sample from the patient to know if the Cryptococcus neoformans had reached the CSF or not.
    We add ink to the sample to delineate the capsule of Cryptococcus neoformans.

- **After the treatment of the specimen with KOH alkylating solution, we put a coverslip on it, and we observe it under the microscope.**



KOH wet mount
(notice the budding yeasts)

Culture

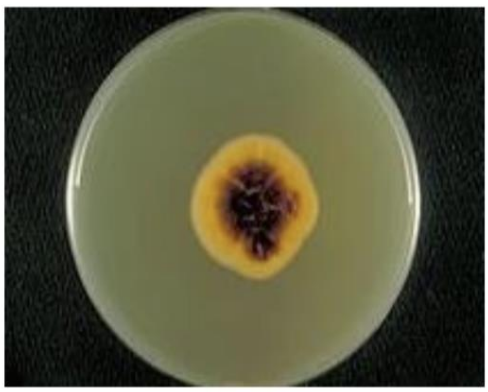
- **After I treated the sample with KOH, I can grow the fungus (remember that fungi are molds, which means they can grow on most culture medias. However, there is a universal approach)**
- **Most pathogenic fungi are easy to grow in culture (they can grow on bacterial agar plates).**

- **Sabouraud dextrose medium :**

- **commonly used (universal agar for culturing).**

- **may be supplemented with:**
  - ⇨ **chloramphenicol ➔ to minimize bacterial contamination (prevention of bacterial growth).**
  - ⇨ **Cycloheximide ➔ to reduce contamination with saprophytic fungi (fungi present in the environment, which is non-pathogenic).**

- **It is a customized agar plate for the growth of pathogenic fungal species.**



The right figure shows Candida Albicans culture, it is described as white, creamy, blubberous and waxy colonies.

The left figure shows Dermatophytes culture, specifically Trichophyton rubrum, we view the culture and look at it from below the plate.

Antifungal therapy

- **The drugs used to treat bacterial diseases have no effect on fungal infections.**
- **Antifungals are too toxic to be used for long periods.**
- **it depends on presence of ergosterol in fungal cell membranes.**
- **Amphotericin B and nystatin are polyenes (Fungicidal) & various azoles (fungistatic) are commonly used for treatment of fungal infection.**
- **Amphotericin B can't be prescribed. Instead, it is given IV in the hospital.**
- **There are 6 groups of antifungals for the treatment of fungal diseases:**

1) **Polyene derivatives (The only fungicidal group of antifungal, which means they kill the fungi directly + it is composed of 2 members):**
   - ⇨ **Amphotericin B ➔ systemic member which is given IV.**
   - ⇨ **Nystatin ➔ oral, ointment and cream.**
- **They bind to the ergosterol present in the membrane of the fungus and cause its disruption.**

All the remaining antifungals are fungistatics (they inhibit the growth of fungi rather than killing them directly).

2) **Azoles (The most famous fungistatic group of antifungals):**
   - ⇨ **Ketoconazole**
   - ⇨ **Fluconazole**
   - ⇨ **Itraconazole**
   - ⇨ **Voriconazole**
   - ⇨ **Posaconazole**
- **They interfere with the pathway of ergosterol synthesis.**

3) **Griseofulvin (fungistatic):**

- They only work on Dermatophytes (ringworm diseases).
- They are isolated from a fungus.

4) 5-fluorocytosine (5-FC) (fungistatic):
- They are a cytosine analogue.
- They are very potent DNA and RNA replication inhibitors.
- They are too toxic to be used for long periods.
- They are used in cancer treatment.

5) Allylamines (fungistatic):
   ⇨ Terbinafine (Lamasil)
- They are used a lot.
- They inhibit the enzyme squalene epoxidase which is involved in the early stages of ergosterol biosynthesis.

6) Echinocandins (fungistatic):
   ⇨ Caspofungin
- Inhibits the synthesis of glucans in the cell wall.