FUNGAL INFECTIONS

Before starting, I have included a set of brief cases.

The first patient has a history of AML, he received a stem cell transplant and chemotherapy. A few months later, the developed fever and these painful skin lesions (*fig. 1*).
Which questions would you ask this patient?

fig. 1

One student suggested to ask the patient if he was taking immunosuppressors, the professor said that he was. Another student suggested that we should ask the patient if he was taking any new drugs that could've caused a reaction, and the professor said it is possible for drugs to give a reaction. Then, another student said we should ask the patient if he has travelled. The professor said this is important, especially if the patient has travelled to tropical countries.
Another student then asked if the patient has been recently hospitalized. The professor said no, but he said that the patient goes frequently to the outpatient hematology ward for check-ups.

Professor said that he would add the question of whether the patient has had contact with animals – domestic animals, wild animals, or any vectors (pigs, mosquitoes, flies) – and whether the patient has been swimming somewhere, kayaking, climbing, going in the woods, so any kind of contact with the outside.

Then the professor asked which test we would request. Someone said a culture of the lesions. In this case, more specifically, a skin biopsy should be requested.
The results showed fungal hyphae invading the blood vessels. These hyphae were described as being septated (walls between cells) with acute angle-branching, with some features being compatible with the fungus *Aspergillus*.

All bacterial and viral test results were negative. But a fungus few in the blood culture bottle and was visible upon Gram stain. The same fungus also grew from the tissue culture.

Based on phenotypic analysis, this organism was identified as a Fusarium species.

INTRODUCTION

Fungi are eukaryotic microorganisms. They are heterotrophic, which means that they digest their food externally by releasing hydrolytic enzymes into their immediate surroundings. This explains why fungi have the ability to invade blood vessels. There are often sources of hemorrhage on the lesions. And this is because they digest their surroundings.
They are essentially aerobic and can synthesize lysine L-α-adipic acid biosynthetic pathway.
Fungi possess chitinous cell walls, plasma membranes containing ergosterol, 80S rRNA, and microtubules composed of tubulin.

Conidia are asexual propagules (reproductive units) formed in various manners. Spores may be either asexual or sexual in origin.

CLASSIFICATION OF FUNGI – MORPHOLOGY

Yeasts are single-celled forms that reproduce by budding.
Molds form multicellular hyphae.
Hyphae can be sparsely septate to regularly septate and possess a variable number of nuclei.
In *fig. 3* it can be observed how much bigger mold is compared to bacteria.

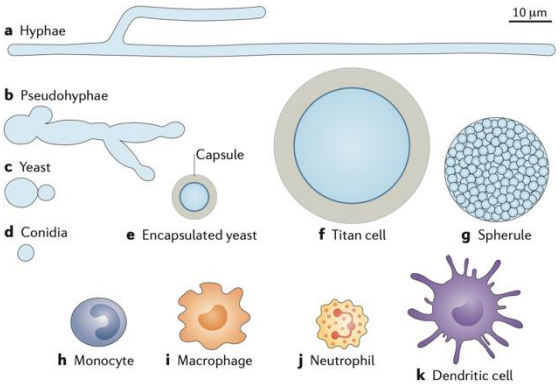


fig. 2

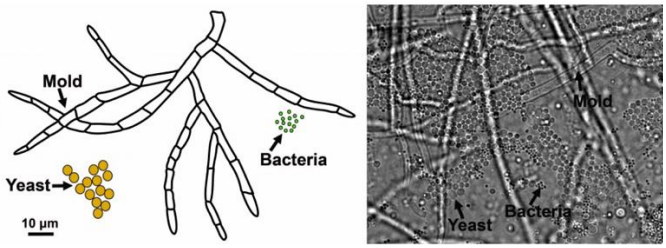


fig. 3

Dimorphic fungi grow as yeasts or spherules in vivo, as well as in vitro at 37°C, but as molds at 25°C. Dimorphism is regulated by factors such as temperature, CO2 concentration, pH, and the levels of cysteine or other sulfhydryl-containing compounds.

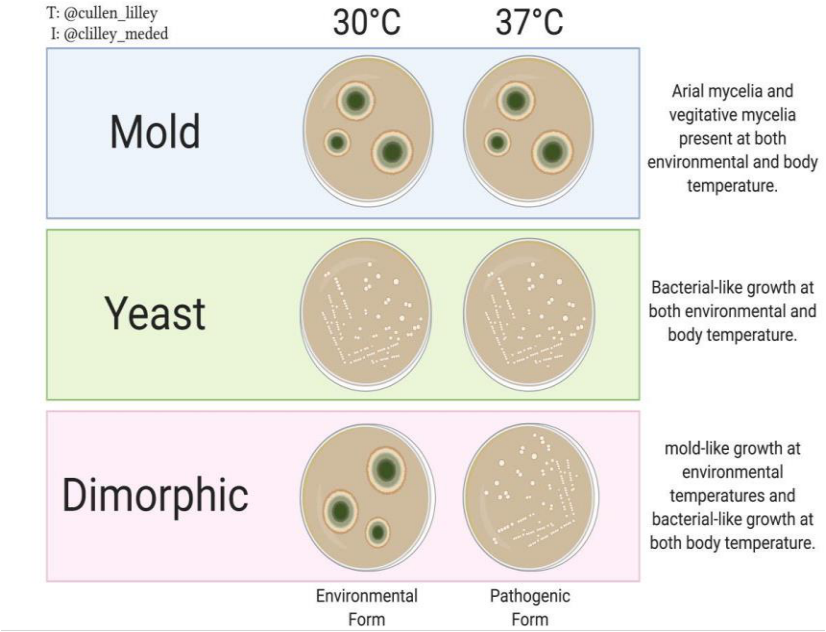


fig. 4

CLASSIFICATION OF FUNGAL INFECTIONS

The classification of fungal infections depends on a few factors. The most important from the point of view of clinical presentation is the site of infection, which can be: superficial, cutaneous, subcutaneous or systemic (deep).

It can also be classified based on the route of acquisition: either exogenous (airborne, cutaneous, percutaneous) or endogenous (normal flora). For example: candida is present in our body in high amount in the GI tract. It is also present in the mouth, vagina, but in the GI tract it is present in the most significant amount. So, in a situation in which candida passes from the GI tract into the blood circulation, it can cause an infection, the so-called **candidemia**.

Lastly, it can be classified based on the virulence. Primary pathogens can establish infections in normal hosts, everyone can get an infection by these fungi, whereas opportunistic pathogens cause disease in immune-compromised hosts.

In *fig. 5*, it is possible to observe the classification of the non-invasive fungi.

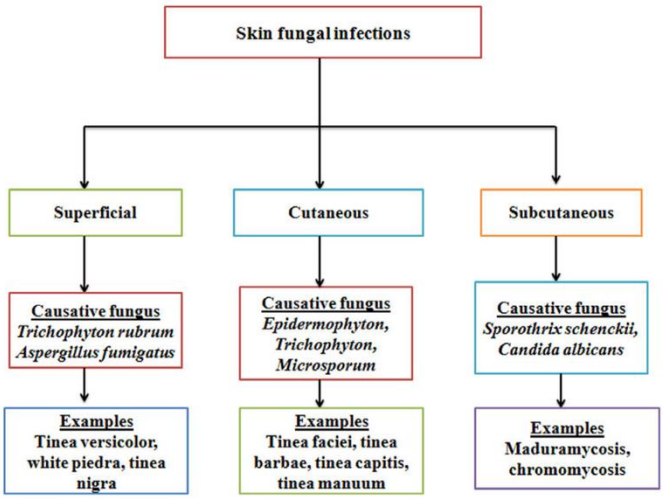


fig. 5

And in *fig. 6* the invasive pathogens are also included. The systemic ones can spread to locations other than the organs where they started. The ones in bold are the ones that we have already talked about during the course.

Superficial	Subcutaneous	Systemic	Opportunistic
Pityrisiasis versicolor	Sporotrichosis	Candidiasis	Aspergillosis
Dermatophytes	Mycetoma	Paracoccidiomycosis	Fusarosis
Candidiasis	Lobomycosis	Coccidiodomycosis	Mucormycosis
	Chromoblastomycosis	Histopalsmosis	**Cryptococcosis**
		Blastomycosis	Alternariosis
			Lomentospora
			Schedosporium
			Pneumocystis
			Talaromycosis
			Magnusiomyces

fig. 6

PITYRIASIS VERSICOLOR

Replication on the skin. It is more common in people after summer, once they have been exposed to sun. It is very easy to treat, we usually use topical antifungal agents.

fig. 7

DERMATOPHYTES

The professor didn't explain the different types of dermatophytes. He just read the names written on the images (fig. 8). Usually, topical treatment is enough to deal with these skin manifestations.

fig. 8

CANDIDIASIS OF THE SKIN – INTERTRIGO

Intertrigo is also very common, especially in hospitalized patients and diabetic patients. Very often it is caused by endogenous fungi, such as candida, which can cause these sub-mammary or inguinal lesions (*fig. 9*).

fig. 9

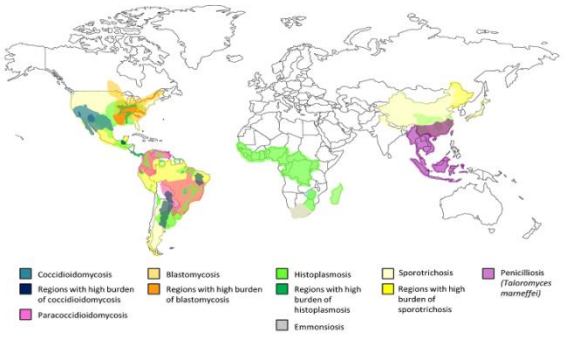
MYCETOMA OR "MADURA FOOT"

This is a very specific one. Not very common in Italy, but it is common in certain tropical countries. It is usually acquired by walking barefoot in soil. We can observe the formation of chronic hypertrophic lesions on the foot, which gets very big. Although the disease usually affects the foot, any part of the body can also be affected. The treatment is a combination of surgery and antifungal drugs.

fig. 10

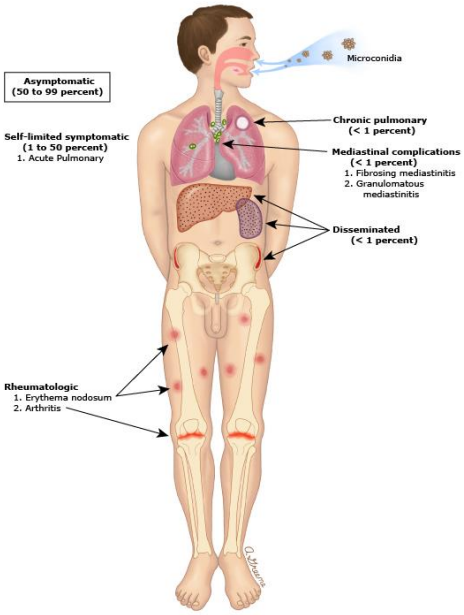
ENDEMIC MYCOSIS

There are fungal infections that are seen very specifically in certain areas of the world (*fig. 11*). There are no cases of these diseases in Europe, it is more common in parts of Africa, Asia and America. Out of these diseases, histoplasmosis is very important. Histoplasma is the main fungi affecting the African continent, as well as parts of South America and the United States. Remember that travel history of the patient is very important because it might indicate different fungi.



	Phylum	Order	Endemic regions	Animal hosts	Disease in human
Coccidioides immitis, C. posadasii	Ascomycota	Onygenales	Southwestern USA, northern Mexico, Central and South America	Non-human primates, domesticated or wide mammals, dogs, cats, horses, llamas, snakes	Coccidioidomycosis
Paracoccidioides brasiliensis, P. lutzii	Ascomycota	Onygenales	South America	Domesticated and wild animals (monkeys and armadillos), dogs	Paracoccidioidomycosis
Histoplasma capsulatum	Ascomycota	Onygenales	Worldwide; hyperendemic in Mississippi and Ohio river valleys in USA	Cattle, sheep, horses	Histoplasmosis
Blastomyces dermatitidis	Ascomycota	Onygenales	Worldwide (endemic in North America, autochthonous in Africa, South America, and Asia)	Dogs, cats, horses, marine mammals	Blastomycosis
Emmonsia spp.	Ascomycota	Onygenales	South Africa	Wild rodents	Emmonsiosis
Sporothrix schenckii, S. brasiliensis	Ascomycota	Ophiostomales	Worldwide	Cats, occasionally dogs, horses, cows, goats, mules, pigs, rats, armadillos, camels, dolphins, birds	Sporotrichosis
Talaromyces (Penicillium) marneffei	Ascomycota	Eurotiales	Southwest and southern China; Southeast Asia	Bamboo rats, domestic animals such as dogs and cats	Penicilliosis

fig. 11



HISTOPLASMOSIS

It is common in the Midwestern and Central United States, along the Ohio and Mississippi River Valleys.
Histoplasma *capsulatum* proliferates best in soil contaminated with bird or bat droppings due to the content of nitrate and pH, which becomes the perfect environment for the fungus.
People who are infected are usually those in contact with chicken coops or farm buildings with large accumulations of bird droppings, abandoned buildings, bird roost sites, caves, and wood lots.
There is a list of activities that makes people more likely to get in contact with the fungus, such as: excavation, construction, demolition, remodeling, wood cutting and gathering, exploring caves, and cleaning structures that are encrusted with bird or bat guano.

HISTOPLASMOSIS – CLINICAL PRESENTATION

Most people are asymptomatic. And most of those with symptoms mostly present with pulmonary histoplasmosis because inhalation is the most common pathway entry.
The biggest problem for us is the histoplasma lesions in radiology (*fig. 14*) is exactly the same as tuberculosis, so the clinical presentation is cough, fever, weight loss, etc.
Sometimes we treat patients for tuberculosis and the patient doesn't respond to treatment. So, we should think of histoplasma.

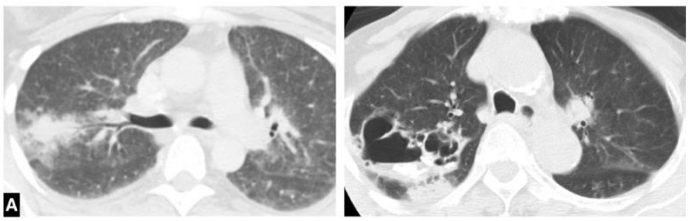


fig. 14

I have seen a case in Uganda in which histoplasmosis presented with these skin lesions (*fig. 15*) and lung lesions on a young woman who had HIV. She was tested for TB, and in the end the culture of one of her lesions came back positive for histoplasma. She had both TB and histoplasma at the same time.

fig. 13

Let's proceed by talking about fungi that we actually see in Europe.

ASPERGILLOSIS

Aspergillosis is an umbrella term that covers all illnesses due to due to allergy, airway or lung invasion, cutaneous infection or dissemination by species of Aspergillus.
Most of the cases, around 70% are caused by *A. fumigatus*, but it can also be caused by *A. flavus, niger, terreus*.
Inhalation of conidia is common (lungs or sinuses) while tissue invasion is rare.
The important thing about Aspergillosis is that microbial factors are able to inhibit macrophage phagocytosis and T-cell response, then they proliferate, leading to vascular invasion and eventually to infarction and tissue necrosis. It is similar to tuberculosis, but weaker.

ASPERGILLOSIS – RISK FACTORS

There are several risk factors. It is important to remember severe and prolonged neutropenia (neutropenia stages: from 1000 mcL to 500 mcL is mild; from 500 mcL to 200 mcL is moderate; from 200 mcL to 100 mcL is severe; below 100 mcL is extreme neutropenia). We often see this in hematological patients, in cancer patients as a reaction to chemotherapy.
Administration of high doses of corticosteroids is also a risk factor.
Besides that, immunodepression is a risk factor, including chronic granulomatous disease, hematopoietic cell transplant, AIDS. And some drugs are also considered risk factors: ibrutinib and venetoclax.
But there are cases of aspergillosis without severe immunosuppression, just moderate or no immunosuppression at all, such as:

- In COPD patients → they have two risk factors: obstruction of the airways and the administration of corticosteroids, which is a treatment for COPD.
- ICU admission
- Viral infections (influenza, SARS-CoV-2, RSV) → they impair the airways and contribute to the proliferation of Aspergillus
- High exposure (e.g. construction sites workers)

ASPERGILLOSIS – CLINICAL PRESENTATION

I want you to remember rhinosinusitis, so chronic rhinosinusitis can be fungal in origin. There is, in very immunosuppressed patients, CNS infections (ring enhancing lesions, cortical and subcortical infarction and dissemination from sinuses). Infarction is very important to be remembered because as mentioned before, Aspergillus cause vascular invasion which leads to infarction.

The professor didn't mention everything written on the slides, so I attached a picture containing everything (fig. 16).

1. Pulmonary Aspergillosis
2. Tracheobronchitis (obstructive, ulcerative, pseudomembranous)
3. Disseminated infection
4. Rhinosinusitis
5. CNS infections (ring enhancing lesions, cortical and subcortical infarction, dissemination from sinuses)
6. Endophtlamitis
7. Endocarditis
8. Cutaneous aspergillosis
9. Gastrointestinal aspergillosis

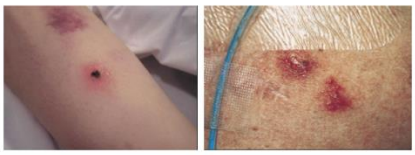


fig. 16

PULMONARY ASPERGILLOSIS

Most important form. I will show you a picture of an aspergilloma (*fig. 17*). There is a cavity, and some other radiological features are: single or multiple nodules, patchy or segmental consolidation and peribronchial infiltrates.

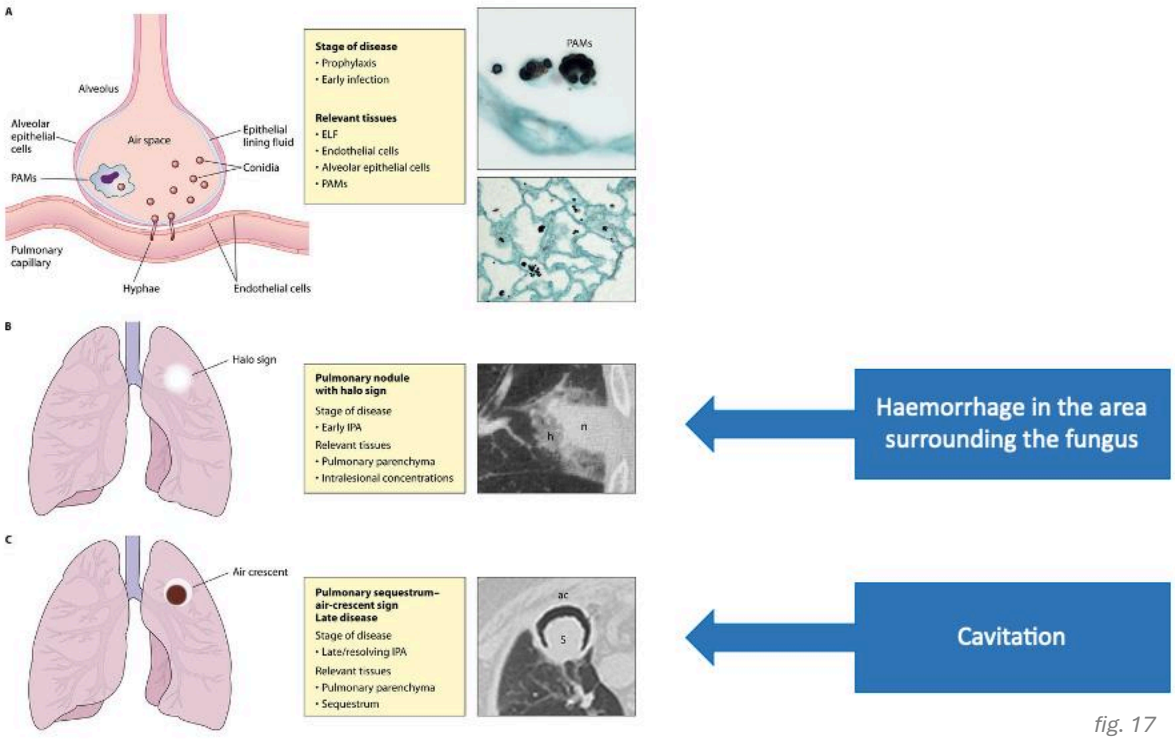


fig. 17

Some signs and symptoms of pulmonary aspergillosis are: fever, chest pain, shortness of breath, cough and hemoptysis.
There is a form of Aspergillosis called Allergic Bronchopulmonary Aspergillosis (ABPA), mostly seen in patients with asthma, which is characterized by wheezing, dyspnea, worsening of asthma symptoms, productive cough with brown mucus or mucus plugs, hemoptysis, anorexia, fever and malaise.
It is usually diagnosed based on the IgE levels.

ASPERGILLOSIS – DIAGNOSIS

The definitive criteria of diagnosis are culture + the presence of hyphae in biopsies. But we might also start by doing a sputum and BAL staining and culture (GAM and/or PCR on BAL). Imaging examinations include X-ray and CT scan.
Another option are serum biomarkers (Galactomannan, 1,3-Beta-D-Glucan) and PCR.

ASPERGILLOSIS – TREATMENT

The professor said he didn't want to go through treatment because it is too much.
According to the slides, the available treatments are: voriconazole (or posaconazole or isavuconazole when voriconazole is not tolerated) added to ecchinocandins in severe forms; amphotericin-B if azole-R >10% or DDIs/intolerance to azoles; and decrease immune-suppression if possible.

CANDIDA

We have talked about candida in the lecture about STI, even though it is not an STI. We have talked about candida in the mouth, in the esophagus, etc.
The three major presentations are:

1. Local mucocutaneous infections
2. Disseminated infections in neutropenic hosts/ICU/AIDS patients
3. Invasive focal infections after candidemia or when abnormalities or devices are present (prosthetic heart valves, CNS shunts…)

Today we are going to be focusing on candidemia, which is very common because candida is on the skin. Even immunocompetent hosts can develop candidemia.

Question: Is candidemia common because it is asymptomatic or is it common because it is present on the skin?
Answer: Usually, candidemia itself can be completely asymptomatic or you can have complications. Most often candida is found due to blood cultures.

In fig. 18 you can observe the six most clinically relevant Candida species. The most important is *Candida albicans*, which is the one that is related to infections. But currently a very important type of candida is *Candida auris*, endemic in Europe and it is very resistant.

The six most clinically relevant *Candida* species

Candida albicans
- 90% of humans are colonized
- Most important species in human medicine
- Can affect nearly all organs; candidaemia is the most prevalent clinical presentation
- Less involved in otomycosis and outbreaks
- Majority of infections are from endogenous sources
- Resistance is rare

***Candida parapsilosis* species complex**
- 10% of adults are colonized
- The majority of infections are exogenous
- Affects neonates and the older population
- Associated with total parenteral nutrition and poor hand hygiene
- Strong biofilm producer in vivo
- Increased fluconazole resistance, tendency to clonal outbreaks
- Prevalent in southern Europe and southern Africa

***Pichia kudriavzevii* (formerly *Candida krusei*)**
- Transient inhabitant of mucosal membranes in healthy individuals
- Widely distributed in nature (vegetables and fruits)
- Affects individuals with haematological malignancies and transplant recipients
- Intrinsically resistant to fluconazole, rapidly acquiring multidrug resistance (echinocandins and azoles)
- Highest frequency of isolation in Europe (Czech Republic, 7.6%) and North America and lowest in Indonesia, South Korea and Thailand

***Nakaseomyces glabratus* (formerly *Candida glabrata*)**
- Colonizer of the healthy microbial flora
- Infection source is generally endogenous, some studies found horizontal transfer for this species
- Widely distributed in the environment (water and soil)
- Second most important species in the USA and north-western Europe, where infection leads to substantial morbidity and mortality (40–60%)
- Rapidly acquires resistance to echinocandins, high frequency of azole resistance

Candida tropicalis
- Can be found on skin, nails and mucosa
- Widely distributed in the environment (soil, water, Amazon forest)
- Most important species in India and Pakistan, second in Latin America; in the northern hemisphere, patients with cancer are at risk
- Resistance to fluconazole, mainly in India followed by Turkey, Spain and Algeria
- Strong biofilm producer
- Horizontally transferred in hospitals

Candida auris
- Skin colonizer, with ~10% of colonized people going on to develop invasive infection
- Infection source is either endogenous (skin) or exogenous from the immediate contaminated health-care environment
- Associated with large health-care-related outbreaks
- Rapidly becoming a major pathogen causing invasive infection, particularly in low-income and middle-income countries
- Clade-specific resistance patterns with clade I more resistant than clade III and IV (clades II and V are rarely associated with invasive infection)

fig. 18

There are some regional differences (*fig. 19*). And those in red are reports of *Candida auris* in the world.

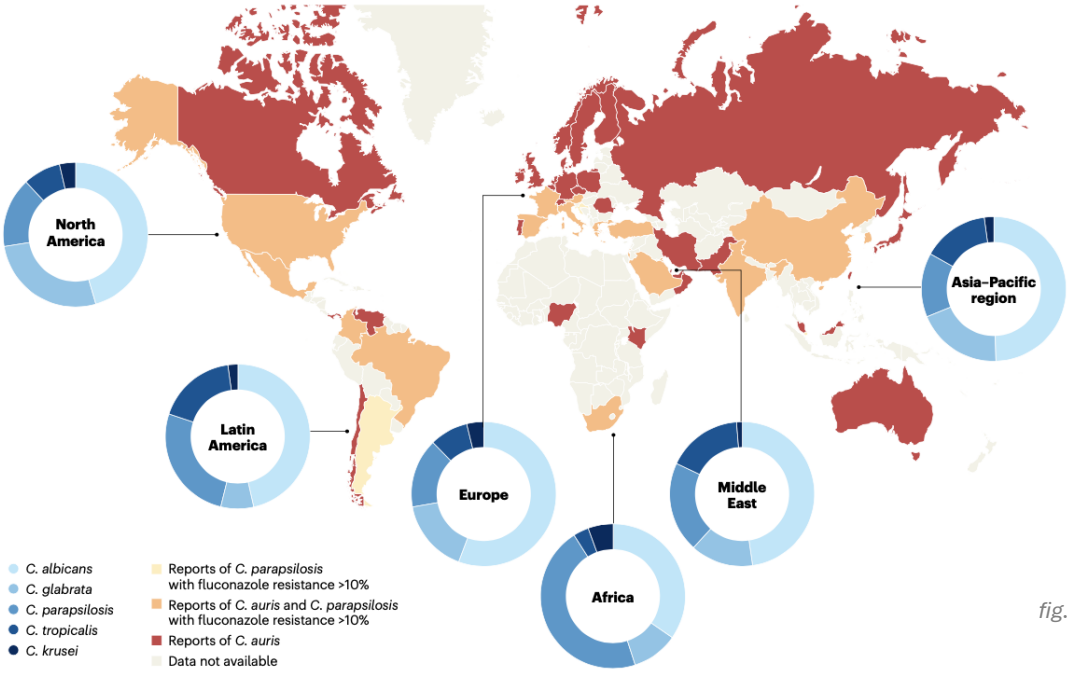


fig. 19

The local mucocutaneous types of candida infection are:

1. Oropharyngeal

2. Esophagitis
3. Vulvovaginitis
4. Balanitis
5. Chronic mucocutaneous candidiasis → common in children, which have repeated skin or nail infections, and it is common in the setting of autoimmune syndromes
6. Mastitis

INVASIVE CANDIDIASIS

It always starts with candidemia. The one exception is peritonitis. But all the others (kidneys, lungs, liver) are usually related to candidemia.

Now the first line of treatment for candidemia is (I couldn't understand what he said so I wrote what I found according to my research online) echinocandin, like caspofungin and anidulafungin.

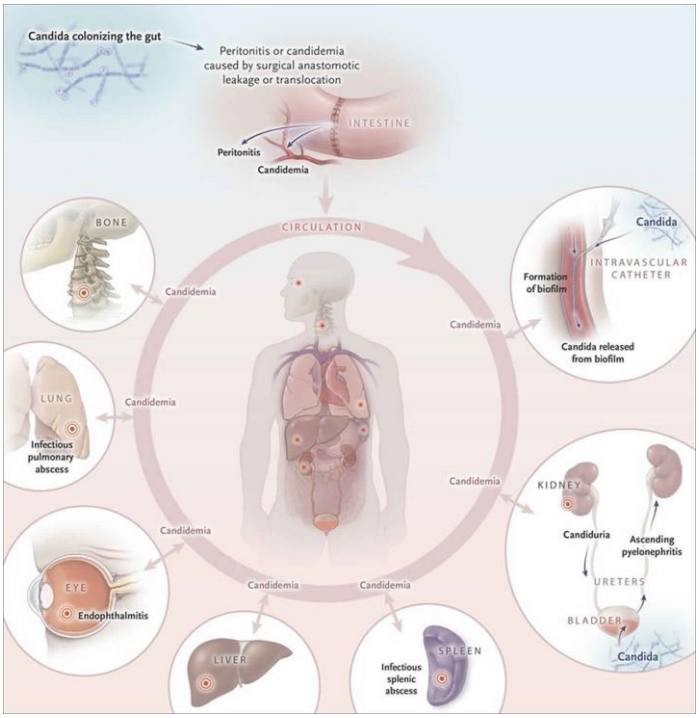


fig. 20

INVASIVE CANDIDA INFECTIONS – RISK FACTORS

1. Over proliferation of Candida → in skin or mucosal flora, with documented culture-based colonization at multiple body sites, can be risk factors when the following medical interventions are performed:
    - Broad-spectrum antibiotics use
    - Long-term stay in an acute-care facility or ICU
    - Mechanical ventilation

2. Breaches in skin or mucosal barriers, either related to an underlying condition or iatrogenic:
    a. Extensive burns
    b. Gastrointestinal perforation
    c. Acute or necrotizing pancreatitis
    d. Gastrointestinal surgery
    e. Chemotherapy-induced mucositis
    f. Indwelling intravascular catheters
    g. Hemodialysis or peritoneal dialysis
    h. Total parenteral nutrition

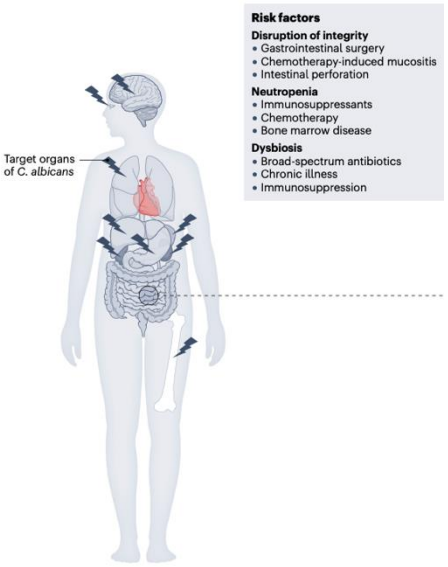


fig. 21

i. Indwelling prosthetic materials, including left ventricular assist devices, ventriculo-peritoneal shunts or external ventricular drains
j. Intravenous drug use
k. Urinary tract instrumentation

3. Intrinsic or acquired immunosuppression
    a. Genetic susceptibility to invasive candidiasis by variations in immune-related genes
    b. Extremes of age (in particular, small, vulnerable newborns)
    c. Diabetes mellitus
    d. Viral infections such as COVID-19
    e. Profound and prolonged neutropenia
    f. Solid organ transplant and hematopoietic stem cell transplant recipients
    g. Immunosuppressive treatment, including corticosteroids
    h. Graft-versus-host disease

DIAGNOSIS OF CANDIDA INFECTIONS

Once again, he did not say anything about diagnosis during the lecture, so I added the image present on the slides.

Diagnostic test	Advantages	Limitations	Comments
Microscopy	Proof of infection, if positive from sterile body specimens; rapid turnaround time and broad applicability	Lack of genus or species identification; needs a high amount of fungal cells to be visible; low sensitivity	Fluorescent brighteners increase sensitivity and typical fungal morphologies may enable tentative diagnosis; histopathology shows tissue invasion and inflammation
Culture	Supports species identification and antifungal susceptibility testing; easy and cheap	Low sensitivity in candidaemia (~50%); difficult to distinguish between colonization and infection from non-sterile body sites; time-consuming	Not all fungi grow in culture (for example, *Pneumocystis jirovecii*); detection of polymicrobial infections is supported by using chromogenic media
Serology	The 1,3-β-D-glucan assay has a high negative predictive value; in invasive infections, sensitivity and specificity range from 75% to 80% and 60% to 80%, respectively; the combined mannan antigen and antimannan antibody assay displays a sensitivity of 89% and specificity of 63%	1,3-β-D-glucan is a fungal cell-wall component, and therefore is a panfungal marker with no differentiation between the various fungi; does not cover Mucorales and *Cryptococcus*; false positive results may occur when treated with intravenous immunoglobulin and albumin; may decline slowly despite appropriate therapy; mannan antigen and antimannan antibody assay shows limited specificity due to normal commensalism or colonization by *Candida* species	Specificity improves using serial samples; different companies provide various thresholds; most useful in patients in the intensive care unit; lower sensitivity for *Candida krusei* and *Candida parapsilosis*; the sole use of mannan antigen test shows variable sensitivity (52–85%) and specificity (86–98%), whereas antimannan antibodies give sensitivity of 57–80% and specificity of 60–87%
Molecular assays	Culture-dependent systems are highly sensitive and specific; have a short turnaround time and contain fully automated platforms; culture-independent tests have a moderate sensitivity and specificity, with high negative predictive value; enable a broad range of pathogen detection	Detect only defined *Candida* species; panfungal PCRs are less helpful from non-sterile sites and display poor performance in mixed infections; metagenomic assays are highly sensitive but less specific (target all microorganisms)	Fungal DNA isolation techniques are critical; best data when used in tissue-positive specimens; early detection of infection has been reported

fig. 22

CANDIDEMIA

First of all, if candida is present in the blood culture, it is NEVER a contaminant. But if you see candida in the urine, mucus or in the sputum, it most likely a contaminant; therefore, we do not treat candiduria, for example. But if it's in the blood it is an infection, a severe infection, which means it requires <u>treatment</u> and <u>source control</u>:

- Caspo/anidulafungin for 2 weeks after first negative blood culture (repeated every day or every other day until negative)
    - In neutropenic patients, neutropenia also should be resolved for stopping antifungal therapy
- Negative eye fundus examination (2-20%) and cardiac ultrasound → for source control
- CVC removal (or individualized management in neutropenic patients) → also source control

Candidemia presents with minimal fever to full-blown sepsis. In case of invasive candidiasis, it may affect the eye, kidney, heart and CNS.

Disseminated candidiasis might present skin manifestations, such as in *fig.23.*

fig. 23

ZYGOMYCOSIS (MUCORRMYCOSIS)

Then, just to finish I would like to spend one slide talking about mucormycosis (or zygomycoosis). It is caused by a family of fungi called Mucorales, and includes: *Rhizopus, Cunninghamella, Mucor, Rhizomucor, Saksenea, and Absidia*. The hyphae are broad, it has 5-15 micon diameter, and it is irregularly branches with rare septations (fig 24).

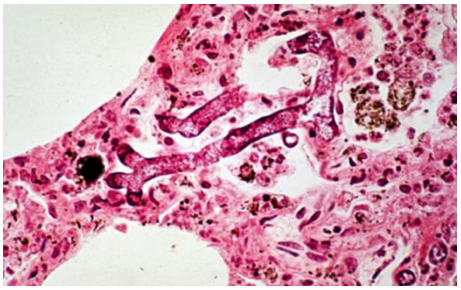


fig. 24

The risk factors for this disease are:

- Diabetes mellitus (ketoacidosis!)
- Treatment with glucocorticoids
- Hematologic malignancies
- Hematopoietic cell transplantation
- Malnutrition
- Trauma/burns
- Solid organ transplantation
- Treatment with deferoxamine
- Iron overload
- Recent COVID-19
- AIDS
- Injection drug use

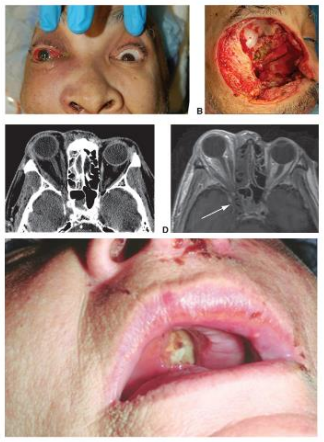


fig. 25

They are very important because they can cause a lot of damage: rhino-orbital cerebral (the most severe, from the sinus it spreads to the eyes and to the brain), pulmonary, gastrointestinal, cutaneous, renal, isolated CNS, disseminated. *Fig. 25* shows the rhino-orbital cerebral condition, in which from the sinus it also spread down to the oral cavity. The treatment requires a combination of medical therapy and surgery to remove all of this tissue of fungal infection.

DIAGNOSIS

We have already talked about it:

- Gram stain → fungi are Gram positive.
- Histopathology
    - Superficial infection – acute, subacute or chronic dermatitis with folliculitis

- Subcutaneous & systemic infections – granulomatous reaction with fibrosis or pyogenic inflammation
- Routine stain – Hematoxylin & Eosin (HE)
- Special stains – PAS (Per Iodic acid), GMS (Grocott Gomori Methanamine Silver), Mayer's mucicarmine, Gridley's stain

- Fluorescent- antibody staining
  - To detect fungal Ag in clinical specimen such as pus, blood, CSF, tissue sections
  - Adv – can detect fungus even when few organisms are present
- Fungal Culture
  - Sabouraud Dextrose Agar (SDA) → Contains 2% dextrose, antibiotics (gentamicin, chloramphenicol) and cycloheximide
  - Selective media
    - Corn meal agar (CMA) – sporulation, chlamydospore formation
    - Bird seed agar – cryptococcus, forms brown colonies
    - Brain Heart Infusion (BHI) agar – dimorphic & other fastidious fungi
- Non-culture-based markers (the most important according to the professor) → focus on galactomannan and beta-glucan
  - In *fig. 26*, we can see the cell wall of different fungi.

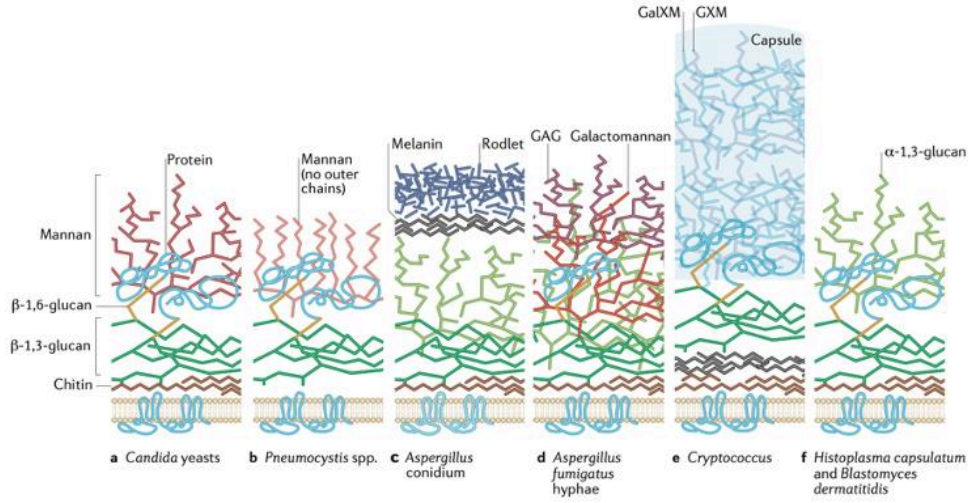


fig. 26

  - Galactomannan is only in Asprgillus, it is a very specific test.
  - 1, 3-β-D-Glucan (βDG) is common to all fungi, but Mucor *(couldn't understand clearly if this is what he said)*.

	Origin	Unit of measure	Threshold	Applications	Limitations
Galactomannan (GM)	Soluble polysaccharide antigen, released by Aspergillus species during fungal growth	Optical density index (ODI) (ratio relative to the OD of a threshold control)	>0.5 serum/BAL >1 on all samples >0.7 serum and >0.8 BAL	One of the criteria for probable IA Monitoring for pre-emptive treatment in high-risk patients	• Only Aspergillis • False-: patients on prophylaxis and non-neutropenic • False+: bacterial infections, beta-lactams, haemodyalisis, etc.
1, 3-β-D-Glucan (βDG)	Cell wall of *Aspergillus, Candida, Pneumocystis, Coccidioides, Histoplasma, Trichosporon, Fusarium and Exserohilum*	Pg/mL	>80 pg/mL	Pre-emptive treatment in high-risk patients High NPV in certain patients (SOT, immunesuppresive drugs…) and for deep-seated infections (IAI)	• Low sensitivity in low-risk patients • Lower sensitivity with *C. krusei and parapsilosis* • Not for Cryptococcossu and Mucor • BAL poor sensitivity • False +: haemodyalisis, beta.-lactams…

fig. 27

Remember that some antibiotics are produced in fungal cultures, so there are pieces of fungi in certain antibiotics, such as beta-lactams. If the patient is taking such antibiotics, it could lead to false positive results for Galactomannan.
False positive results might also occur in βDG if the patient is in haemodialysis.

TREATMENT

The Professor finishes the lecture by showing a slide of antifungal drugs. He says he usually doesn't ask for treatment in the exam, but I have added the table of antifungals (fig. 28) to the SBOBINA for the sake of completeness.

Antifungal	Frequency	Route	Notes and considerations
Fluconazole	Daily	PO, IV	Liver test abnormalities, drug–drug interactions (strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A4), xerosis, cheilitis and alopecia with long-term use
Voriconazole	Twice daily	PO, IV	Liver test abnormalities, significant drug–drug interactions (strong inhibitor of CYP3A4, moderate inhibitor of CYP2C19 and weak inhibitor of CYP2C9), photosensitivity, hallucinations and confusion, and photopsia; voriconazole is extensively metabolized by CYP2C19 and CYP3A4, and genetic polymorphisms cause wide variations in pharmacokinetics
Isavuconazole	Daily	PO, IV	Liver test abnormalities, electrolyte abnormalities; drug–drug interactions as a moderate inhibitor of CYP3A4
Caspofungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug interactions potentially mediated via organic anion-transporting polypeptides such as OATP-1B1
Micafungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug–drug interactions with cyclosporine and sirolimus, other interactions uncommon
Anidulafungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug–drug interactions uncommon
Rezafungin	Weekly	IV	Infusion reaction with rapid administration, electrolyte abnormalities; drug–drug interactions uncommon
Flucytosine	Four times daily	PO, IV	Haematological abnormalities, including agranulocytosis, anaemia, pancytopenia, abdominal pain, diarrhoea and nausea; drug–drug interactions not apparent but agents with similar toxicity may be additive
Amphotericin B deoxycholate	Daily	IV	Systemic therapy: infusion reactions, nephrotoxicity, renal tubular abscess, hypokalaemia
			For bladder irrigation, amphotericin B is used in sterile water and administered as continuous bladder irrigation daily for 5 days
Liposomal amphotericin B	Daily	IV	Infusion reactions, nephrotoxicity, renal tubular abscess, hypokalaemia

fig. 28

There are 3 types of fungi that are very important when we are talking about drug resistance: Candida auris, azole-rsistant Aspergillus fumigatus and Trichophyton indotineae.