Almost every clinically active doctor is confronted with fungal infections during their working life. It can be foot or nail fungi if they are a family doctor, fungal pneumonia if they are a haemato-oncologist, or irritant diaper dermatitis if they are a pediatrician. What matters is knowing these mycoses’ typical manifestations, diagnostic methods, and therapies in order to treat patients in the best way possible. This article provides a complete insight into the wide field of mycology.

General Mycology

Characteristics of fungi

Fungi are carbon-heterotrophic eukaryotes that form their own cell wall. They form a thallus and reproduce asexually or sexually. There are more than 1 million fungus species, but only about 180 can be linked to infections in humans or animals. Fungi are used in medicine to produce antibiotics or vaccines like the hepatitis B surface antigen.
The cell wall formed by fungi is made out of chitin, glucan, and mannan. The cytoplasmic membrane of fungi possesses the sterol \textit{ergosterol instead of cholesterol}, just like in humans. This ergosterol site is a suitable target for antifungal antibiotics. Unlike plants, fungi do not have photosynthetic capabilities and do not possess chlorophyll. Fungi are heterotrophs, feeding on organic materials instead.

Fungi have more \textit{chromosomes} and can be either haploid or diploid. Protein biosynthesis takes place on 80S ribosomes through a monocistronic mRNA. Perfect fungi are fungi that have a known sexual form. Fungi only known in their asexual form are called \textit{imperfect fungi} or Deuteromycetes.

**Fungal diseases**

**Allergies**

Mold antigens are the \textit{most frequent cause of allergies}, followed by grass pollen. Some symptoms of mold allergies are headaches, losses of concentration, and asthmatic complaints.

**Intoxications**

Humans can absorb mycotoxins aerogenically or through food. One of the most common toxins is \textit{Amanita phalloides} (death cap mushroom). Its \textit{amanita toxin} leads to poisoning manifestations, like nausea and diarrhea 8–22 hours after consumption. After a few days, through the inhibition of RNA polymerase II, an enzyme that helps create mRNA, there is a cessation of cell metabolism and the cell dies. Another example is \textit{Claviceps purpurea}, which grows on the ears of corn. The toxin of this fungus causes intestinal cramps, circulatory problems, and hallucinations.

**Infections**

Infectious fungi derive their pathogenicity from adherence factors, lytic enzymes, mycotoxins, and invasive abilities. They can be resistant to gastric acid and protect themselves from the immune system, e.g. through a slimy capsule in \textit{Cryptococcus neoformans}, or antigenic mimicry in \textit{Candida albicans}. Pathogenic fungi even develop \textit{defense mechanisms} against specific immune cells. \textit{C. neoformans} can thus induce suppressor cells, and \textit{Coccidioides} induces tumor necrosis factor release.

Predisposing factors for mycoses are \textit{immunodeficiencies}. Preterm birth, malignant tumors, cytostatic therapy, corticosteroids or antibiotics, \textit{diabetes}, kidney failure, \textit{burns}, polytrauma, or the use of catheters and artificial respiration can all render a patient more susceptible to mycoses.

**Fungi classification**

**Biological taxonomy according to Strassburger**

- Class I: Myxomycetes
- Class II: Chytridiomycetes
- Class III: Oomycetes
- Class IV: Zygomycetes e.g. mucor
- Class V: Ascomycetes e.g. Aspergillus
- Class VI: Basidiomycetes e.g. Filobasidiella
- Deuteromycetes (Fungi imperfecti) e.g. Candida

Some cells of the mycelium form fruiting bodies, the so-called sporangium, in which the development of sexual conidia (or spores) takes place. If these spores are formed in a tube, the fungi are called ascomycetes. On the other hand, if they are formed in a rack, they are called basidiomycetes. There is still no description of the sexual form of many medically relevant fungi, so they are classified as imperfect fungi.

Medical taxonomy

The classification of dermatophytes, yeast, and molds is more useful in medicine, although the botanic classification is more precise.

<table>
<thead>
<tr>
<th>Yeasts</th>
<th>Molds</th>
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<tbody>
<tr>
<td>Round-oval cells (budding cells = blastospores)</td>
<td>Filamentous cells (hyphen)</td>
</tr>
<tr>
<td>Pseudo micelle formation</td>
<td>Form a reticular micelle</td>
</tr>
<tr>
<td>Budding</td>
<td>Aerial micelle with fructification organs</td>
</tr>
<tr>
<td>Colony formation</td>
<td></td>
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</tbody>
</table>

Note: Identification of molds takes place microscopically through the fructification organs they form. These reproductive structures, however, only grow in cultures and rarely in tissues.

Diagnostic techniques

Evidence of microscopic fungi
Skin scrapings, hair, and nails often serve as examination materials. First, they have to be coated with potassium hydroxide or sodium hydroxide to dissolve animal or human cells, while the fungal cells survive. Furthermore, many fungi are difficult to recognize under the microscope in their natural form, so they must be stained. Lactophenol or Gram staining are the simplest forms of staining.

Evidence from tissue sections is easier to find through differential staining with periodic acid-Schiff staining (PAS reaction) or Grocott-Gomori silver staining. Optic brighteners like calcofluor, which binds with glucan and chitin on the cell wall, are also highly suitable.

Evidence of fungi via culture
Most medically relevant fungi do not have a rapid growth phase in culture. As a result, dermatophytes often need several weeks to form a visible colony. On **Sabouraud dextrose agar** or Kimmig agar, fungi have a growth advantage over bacteria due to a lower pH level of the medium.

Means of differentiation are also available. Colonies of *Candida albicans*, *C. tropicalis*, and *C. krusei* thus grow on CHROMagar in different colors, allowing a direct identification on isolation sheets.

**Biochemical yeast differentiation**

Biochemical differentiation, along with the measuring of species-specific metabolic performance e.g. the utilization of different nitrogen and carbon sources or sugar
splitting, is only performed on yeasts. Dermatophytes and molds are distinguished through their conidia genesis.

Serologic diagnostics for fungi

EIA, immunohemagglutination, and immunodiffusion are methods for detecting the presence of circulating fungus-specific antibodies. However, evidence of these antibodies is less relevant since they can already be formed during non-invasive fungal colonization and are not always proof of invasive infection. In immunosuppressed patients, on the other hand, antibodies are often absent, even in the case of a fungal infection.

Consequently, positive antigen detection is not diagnostically relevant. Yeasts, for instance, release certain mannans and the capsule material of cryptococcus is composed of special glucurono-xylo-mannans. Tests on these particular fungus antigens are only positive in advanced fungal infections because macrophages only eliminate small amounts of antigens.

Other diagnostic methods for identifying fungi

The evidence of specific gene sequences through PCR is increasingly used in identifying fungi, particularly for very resistant candida phyla.

Clinical diagnosis with regard to skin and mucosal infections is also relevant. Many dermatophytes can thus be identified through their typical manifestations on the skin.

Specialized Mycology

Dermatophytes

Cutaneous mycoses, also called dermatophytoses, are caused by dermatophytes, which are ubiquitous parasites. Dermatophytes are keratinophilic filamentous fungi. Infections occur through contact with infected people or as autoinfection, usually in a warm, damp environment e.g. in the pool.

They are subdivided based on microscopically differentiable asexual reproductive organ forms (macroconidia and microconidia) into Trichophyton, Microsporum, and Epidermophyton.

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Localization</th>
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<tbody>
<tr>
<td><em>Trichophyton</em> spp.</td>
<td>Skin, hair, nails</td>
</tr>
<tr>
<td><em>Microsporum</em> spp.</td>
<td>Skin, hair</td>
</tr>
<tr>
<td><em>Epidermophyton</em> floccosum</td>
<td>Skin, nails</td>
</tr>
</tbody>
</table>

The dermatophytes can be transmitted via zoonotic vectors (*Trichophyton* spp), anthropods (*Microsporum* spp.), or geophilically (through the ground). All 3 means of transmission rely on close contact to transit the fungi.

Note: Immunosuppressed patients are not more prone to dermatophytes than the non-immunosuppressed, but dermatophyte infections represent entrance gates for other pathogens, especially bacteria.
Symptoms of superficial dermatomycosis include dry itchy patches of skin where the fungus is present. They are called tinea or ringworm. The name of the infection is related to the body site where the dermatophyte is located; tinea capitis on the head, tinea inguinalis in the inguinal region, and tinea corporis in the stem body. In 80% of cases, it is a T. rubrum infection, and in 15%, a T. interdigitale infection. Rarer pathogens are M. canis and T. mentagrophytes. Allergic tissue reaction is apparent among mycoides in dermatophyte infections.

Tinea pedis

Tinea pedis, colloquially called foot fungus, is the most common dermatomycosis in industrialized nations. Up to 75% of the population develop symptoms of itchiness in the spaces between toes. Simultaneously, a toenail infection, called onychomycosis, can also often found.

Tinea favosa

Favus (latin for honeycomb) is a dermatomycosis caused by Trichophyton schoenleinii. Patients have the dermatophyte in their hair. Clinical characteristic is hair infection with yellow-brownish desquamation. These scales, also called scutula, are pathognomonic for this disease and consist of the mycellium including hair follicles. Healing takes place with scarring alopecia.
Tinea capitis

*Microsporum audouinii* and *Trichophyton tonsurans* are the typical pathogens of head mycosis, particularly in children. These fungi are highly contagious and mainly infect the hair. These are fully covered with spores and break off at a height of about 7 mm. The mucosa is not infected.

**Therapy for dermatomycosis**

Local therapy is via topical imidazole antimycotics in the form of lotions or nail polish. Patients are also encouraged to keep the affected area dry. The treatment lasts for 4-6 weeks. In some cases, systemic therapy with azoles or griseofulvin can be used as a supplement. Systemic therapy has a longer duration than topical therapy because it takes time for antifungals to reach the keratin layer of the skin.

**Dermatomycoses prophylaxis**

*Nail and skincare* are very important, especially in people with underlying immunosuppressive diseases like diabetes mellitus. Care should be taken by these patients to avoid warm, damp rooms, like saunas. They should also check their skin for evidence of infection.

**Yeast**

Yeast multiply through budding. This means that a bud grows from the mother cell through evagination, with an ingrown copy of the nucleus of the cell. The so formed daughter cell eventually becomes independent.

*Image: Microscopic image (200-fold magnification) of Candida albicans ATCC 10231. By: Y tambe. License: CC-SA BY 3.0*

**Candida albicans**

*Candida* spp. is a dimorphic fungus that can form pseudomycelia. Candida is part of the saprophytic human local flora. Thus candida strains are detectable in test materials from the oropharynx (30%) and feces (65%). Candida species are possible pathogens, in certain conditions.

Factors favoring yeast colonization are:

- Reduction of the physiological bacterial flora on the skin and mucosa due to
antibiotics
- pH level increase in the vagina or excess estrogen due to hormonal contraceptives or pregnancy
- Skin barrier damage due to burns
- Immunosuppression e.g. in AIDS, radiotherapy, or cytostatic therapy

Damp, warm, and dark areas of the skin like in the spaces between the toes or adiposities in skinfolds allow the formation of inflammatory, flush lesions that can macerate and tear, forming rhagades. They are called intertrigo. Candida infections can form in these areas.

Vulvovaginal candidosis can arise in women, especially if they are taking hormonal contraceptives or are pregnant. Typical symptoms are itching and burning, along with whitish fluor vaginalis. In men, it is called balanitis. In babies, in patients with hematologic disorders and those who have received antibiosis, a whitish layer can be formed on the oral mucosa. Typical presentation of oral thrush is a white fluffy layer that can be wiped away.

Invasive or systemic candida mycoses can lead to direct or hematogenous sepsis. Typical consequences are microabscesses in the liver, kidneys, and lungs. However, uveitis, meningitis, arthritis, and pericarditis are also a possibility.
Evidence of candida

Evidence of the candida genus can readily be found microscopically in a native preparation or after gram staining. Grocott-Gomori impregnation with silver salts or treatment with optic brighteners like calcofluor is effective for identifying candida. Typically, **cream-colored, porcelain-like colonies** develop in culture.

**N.B:** Evidence of candida in skin swabs, sputum, urine, and solid faces is not proof of an infection, but only the expression of colonization. Quantity is crucial in determining infection. If detection via culture and microscopy is not successful, antigenic evidence of fungus can be useful. The sensitivity of antigen and antibody tests is 20–80% and its specificity is unknown.

**Candidiasis therapy**

Treatment of candidiasis is via the topical application of fluconazole or imidazole. Oropharyngeal and vulvovaginal infections are both treated with local and systemic antimycotics. In systemic mycoses, the infectious cause must first be removed, then therapy begins with high-impact triazole and echinocandin.

*Cryptococcus neoformans*
*Cryptococcus neoformans* is a yeast-like fungus with a **polysaccharide capsule**. The capsule protects it from phagocytosis by granulocytes and macrophages. The fungus occurs in the ground and can be particularly found in **pigeon feces**. It is transmitted via respiratory droplets. Typically, the fungus will go unnoticed in the immunocompetent host. However, in immunocompromised patients, such as AIDS patients, the fungus can spread hematogenously to the brain; 10% of all AIDS patients will develop cryptococcosis.

Patients with cryptococcal meningitis will have symptoms of nausea, headache, confusion, and cranial nerve deficits. Diagnosis occurs via a lumbar puncture, where the CSF will be stained with **India Ink**. The polysaccharide capsule will pick up the dye and a diagnosis can be made.

Treatment is a **triple combination** (amphotericin B, 5-fluorocytosine, and fluconazole). The therapy must be conducted over a period of 4–8 weeks. Male patients also need **lifelong maintenance therapy** because reactivations from the prostate can occur.

Cryptococcus can also cause pneumonia, skin ulcers, and bone lesions.

**Malassezia furfur**
Malassezia furfur is the pathogen for pityriasis versicolor or tinea versicolor, which is a superficial infection of the skin. Tinea versicolor presents itself clinically through hypopigmentation of the infected area. In rare cases, M. furfur can also lead to catheter-associated sepsis in parenteral feeding with lipid solutions.

Diagnosis can be made with skin scrapings and potassium hydroxide under a microscope. Treatment includes dandruff shampoo applied to the area. Topical antifungals can also be used in severe cases.

Aspergillus

The typical micromorphological characteristic of Aspergillus is conidia ending in a vesicle.

This fungus can cause 3 different conditions: Allergic Bronchopulmonary Aspergillosis (ABPA), aspergilloma, and invasive aspergillosis. Inhalation of aspergillus spores can cause an allergic reaction and mediate the release of IgE antibodies. This is a type I hypersensitivity.

In patients with previous episodes of tuberculosis with lung cavitations, inhaling aspergillus spores could cause an aspergilloma, which is a localized ball of fungus that might have to be surgically removed.

In immunocompromised patients, an aspergillus infection can spread and cause frequent bleeds and a bloody cough secondary to aspergillus lung nodules. This disease is very fatal and treatment is with strong antifungal medications.

Aspergillus can also create a toxin called aflatoxin. This toxin grows on grains and peanuts. If ingested in large quantities, this toxin causes liver damage that can lead to liver cancer.
Zygomycetes

Zygomycetes are primitive dermatophytes, among which Mucorales like rhizopus and mucor are particularly important in human medicine. These ubiquitous fungi are typical pathogens in neutropenia, with vessel affinity. The illness can present itself as:

- **Cutaneous mycosis**: e.g. in extensive burns
- **Rhinocerebral mycosis**: Originates in a colonization of the respiratory tract and paranasal mucosa. Spread into the CNS can occur, especially in diabetic metabolic conditions (ketoacidosis).
- **Pulmonary mycosis**: Particularly common in leukemic patients; through ingrowth in lung vessels it can lead to lung infarction.
- **Gastrointestinal mycosis**: The fungus can grow inside the vessels and lead to intestinal infarction.
These fungi have an affinity for the sinuses and cranial bones. They are highly likely to infect diabetics, burn patients, and people who take iron chelators.

**Dimorphous fungi**

Dimorphous are fungi that grow as yeasts in their parasitic form and as filamentous fungi in their saprophytic form. They are pathogens that cause *systemic mycosis*.

**Histoplasma capsulatum**

This fungus is present in dry, hot climates and is confined to endemic areas in South America, the USA, and Africa. Its spores are spread through *bird and bat feces-contaminated dust*. Since *H. capsulatum* is highly contagious, it is classified into risk group III.

**Note:** It is not transferrable from human to human.

After inhalation, microconidia are phagocytized and multiply themselves in alveolar macrophages. This leads to the symptoms of histoplasmosis. This illness often progresses subclinically, but it can also result in acute *pneumonia*. In immunosuppressed patients, there is a danger of hematogenous metastasis in the *lymph nodes*, liver, *spleen*, and bone marrow.
In X-rays, *Histoplasma* granulomas appear as nodules. They are also called 'blizzard' or 'cloudburst'. Culture takes relatively long, and since *Histoplasma* can grow again in the culture medium as filamentous fungus, there is a high risk of infection for laboratory personnel. Serologic antigenic evidence is more suitable.

**Blastomyces dermatitis**

Blastomyces dermatitis is the pathogen for North American blastomycosis. Infection takes place through inhalation or transcutaneously through skin wounds. *Tuberculosis*-like symptoms and spread to the bones and skin with the formation of fistulas can occur. The developing granulomatous nodules ulcerate and heal with a central scar. Without therapy, the lethality of blastomycosis is high. Amphotericin B is indicated for treatment.
Note: Men are affected by blastomycosis 10 times more often than women.

**Pneumocystis jirovecii**

*Pneumocystis* is a peculiar fungus, because, unlike other fungal cells, its cells do not possess ergosterol in their cytoplasmic membrane. Because of this, it is resistant to antifungals. Pneumocystis-pneumonia is an endogenous reinfection in a weakened immune system. About two-thirds of the population go through inapparent infections for as long as 3 years, during which the pathogen stays in their lungs as a saprophyte. In up to 80% of AIDS patients, an infection occurs.

*Pneumocystis* can be detected directly in cysts—plasmatic cells that were attacked in the interstitium (plasmatic cell pneumonia).

This disease is lethal if not treated. Therapy should consist of cotrimoxazole or pentamidine-isethionate, and prophylaxis is also important in AIDS patients and highly immunodeficient patients.
References


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