

## Healthcare industry BW

### Fungi as human pathogens

**The majority of fungal infections are unpleasant rather than dangerous. But they can be life-threatening for individuals with weakened immune systems. The number of deaths caused by systemic mycoses is currently experiencing a big increase. The pathogenicity of opportunistic fungi such as *Candida albicans* might potentially be related to their unusual reproduction abilities.**



Prof. Dr. Herbert Hof, professor emeritus of medical microbiology and hygiene, University Hospital Mannheim.  
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Among the hundreds of thousands of fungal species there are only about 150 that are known to lead to human infections and cause inflammatory reactions that are hazardous to human health. The renowned mycologist and dermatologist Prof. Dr. Herbert Hof from the Institute of Medical Microbiology and Hygiene at the University of Mannheim who retired in 2009, believes that human fungal infections are actually an (evolutionary) one-way street, because the infected individuals are usually not infectious. Fungal infections rarely spread in the same way as infections caused by pathogenic bacteria.

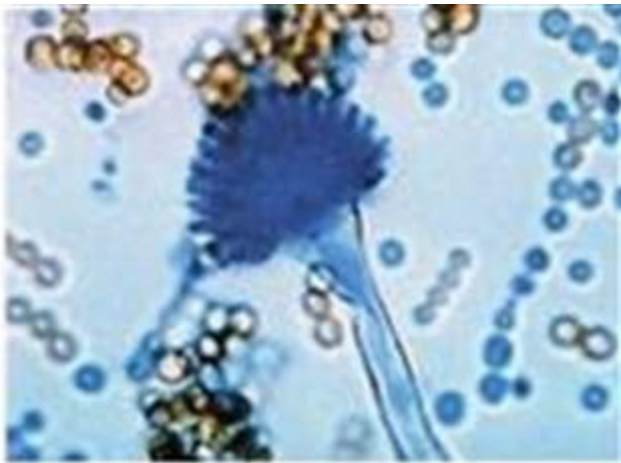
Healthy individuals can be infected by fungi, but usually only if they are exposed to a large number of pathogens over a long period of time. However, short-time exposure to fungi is sufficient for people with a weakened immune system to become infected when the fungi have favourable growth conditions. Fungal infections present a great danger to people with weakened immune systems. Even fungi that are normally harmless can lead to life-threatening infections in high-risk patients. In order to be able to understand a disease caused by fungal infections a holistic view of the patient and his/her susceptibility to infection needs to be taken into account.

Infections – allergies - intoxications

Besides their role as pathogens and active infectious agents, fungi have another effect on human health, which is of major medical importance. Sensitive people can have an allergic reaction to dead fungal cells or cell components, and not just living fungi. According to Prof. Hof, fungal antigens are the most frequent allergens of all. Even edible mushrooms or otherwise completely harmless pathogens might lead to allergic reactions.

In addition, fungal mycotoxins (metabolic products of fungi that are toxic for humans) can lead to acute or chronic intoxications. Fungus poisoning is especially frequent in autumn as a result of people collecting and eating mushrooms (see article entitled "The meat of the forest"). Another dangerous toxin is ergot alkaloids of the sclerotia of the fungus *Claviceps purpurea* that occurs in infected corn grains. In the Middle Ages, and again in the 19th century, flour contaminated with ergot alkaloids led to severe mass poisoning (ergotism). Less obvious, but no less important, are the long-term effects of mutagenic and cancerogenic mycotoxins, such as the aflatoxins of *Aspergillus flavus*, which can lead to lung carcinoma or liver cirrhosis. The number of mycotoxin-producing fungi is far higher than the number of infectious species.

## Classification problems



*Aspergillus flavus* (green mold)  
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It is difficult for general practitioners to determine pathogenic fungi. There are hardly any morphological differentiation criteria available that would enable the reliable scientific classification of pathogenic fungi. Classification is only possible if the fungi reproduce sexually. Modern molecular genetic parameters are not (yet) available or not yet suitable for practical purposes. Unfortunately, sexually reproducing fungi are virtually non-existent among the medically relevant fungi; therefore they are by necessity classified as deuteromycetes or Fungi imperfecti. Fungal nomenclature is chaotic for other species because sexual and asexual stages differ considerably in morphological terms and were therefore initially classified as different organisms. Therefore, the scientific classification is not used for practical medical purposes. Instead, medical mycology uses a simplified but practicable classification system that differentiates pathogenic fungi into 1) dermatophytes, 2) yeasts and 3) moulds.

## Cumbersome dermatophytes

Dermatophyte infections are very frequent; the best-known example, athlete's foot, occurs in almost one third of the world's population. In general, dermatophyte infections are harmless, but might

become problematic if for example pathogenic bacteria enter the body through the skin lesions caused by the fungi. Tinea corporis is a superficial fungal infection characterised by flare-ups and has a variety of appearances. Tinea corporis can be caused by a broad range of dermatophytes, the most frequent being *Trichophyton rubrum*. Recently, *Trichophyton tonsurans* infections have been on the increase, in particular among athletes and in fitness circles. The infection is known as Tinea gladiatorum, which spreads by way of fungal spores in the mats and sports equipment used by athletes and sportspeople.

Fungal infections of finger- and toenails are also very frequent. These infections are known as onychomycoses (Tinea unguium). Such infections are commonly caused by *Trichophyton rubrum*. A prerequisite for an infection to occur is prior damage to the nails. Treating the disease is challenging and takes a long time. At best, treatment only leads to permanent success by combining a range of methods (removal of the dystrophic nail material; local and oral application of antimycotics). Antimycotic drugs such as azole or amorolfine only act on growing fungal cells, but not on the fungal resting stages (spores). These drugs inhibit the synthesis of ergosterol which is found in the fungal cells in place of cholesterol.

Other anti-mycotic drugs such as terbinafine must be used with care because of their negative affect on the liver. In addition, they are expensive. Since such onychomycoses are more cumbersome than harmful to human health, great care should be taken to weigh the advantages and disadvantages of such treatments.

## Life-threatening mycoses



*Candida albicans*, grown on Sabouraud agar for characterisation.  
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Of greater medical importance are fungal infections of the mucosa such as canker sore of the tongue and the oral cavity, food pipe and vaginal inflammations or even systemic infections of internal organs. The number of deaths caused by systemic mycoses has increased considerably since the 1970s, affecting mainly immunocompromised individuals, in particular AIDS sufferers and patients undergoing immunosuppression in the case of leukaemia, transplantation, severe surgery and intensive therapy. The majority of infections are caused by *Candida* species, a yeast-like genus that reproduces asexually by budding. The 200 known *Candida* species are a heterogeneous group of which the majority of species are not closely related to each other. The most frequent cause of human infections, *C. albicans*, is diploid, while the second most frequent species, *C. glabrata*, is haploid and a close relative of the baker's yeast *Saccharomyces cerevisiae*. According to molecular and biochemical properties, all *Candida* species are classified as ascomycetes, while another clinically important fungus, *Cryptococcus*, is a basidiomycete that occurs in humans in asexual form, but can also reproduce sexually in specific ecological niches and is more correctly classified as *Filobasidiella*.

# Homosexuality and heterosexuality in yeasts

For more than one hundred years, *Candida albicans* was regarded as a strictly asexually reproducing organism. However, in 2005, a pheromone was discovered in *Candida* that is responsible for the sexual differentiation of this yeast species. The majority of *C. albicans* strains are heterozygous for this gene locus ( $a/\alpha$ ) and sterile. However, they can separate into diploid homozygous strains ( $a/a$  and  $\alpha/\alpha$ ), which switch between white and opaque phenotypes, and can unite into a tetraploid heterozygous cell ( $a/a/\alpha/\alpha$ ), where budding (without recognisable meiosis) gives rise to diploid offspring ( $a/a$ ,  $\alpha/\alpha$  and  $a/\alpha$ ). According to a publication in the scientific journal "Nature" by scientists from Brown University, Providence, R. I., USA, the fusion of unisexual homozygous cells ( $a/a$  and  $a/a$ ) can give rise to a tetraploid zygote; in this case, the homozygous cells previously also switched from white to opaque phenotypes. The fusion of the cells requires  $\alpha$ -cells to be present and to contribute their pheromone – a ménage-à-trois among yeasts. In addition, unisexual *Candida* strains may also fuse without giving rise to further differentiation. It is assumed that this type of self-fertilisation leads to the sterile clones found in pathogenic strains.

Although the pathogenic yeast *Cryptococcus neoformans* has a sex cycle ( $a - \alpha$ ), the natural populations mainly have unisexual  $\alpha$ -cells. These haploid cells might homosexually fuse to become a diploid  $\alpha/\alpha$  zygote. Meiosis leads to haploid infectious  $\alpha$  spores, in contrast to the parasexual chromosome reduction of *Candida albicans*.

This creates the impression that these pathogenic yeasts do exactly as they like. Since both of them *Candida* (an ascomycete) and *Cryptococcus* (a basidiomycete) are not related to one another, the ability of unisexual populations to sexually reproduce developed independently from one another and is most likely more common than it is believed to be. Nobody has yet looked closely for this phenomenon. The discoverers of the phenomenon assume that the infectious and pathogenic properties of these fungi are related to their ability to alternate between unisexual and bisexual reproduction. The effective permanent abatement of these fungi requires a detailed understanding of these mechanisms.

## References:

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## The article is part of the following dossiers



Fungi – an introduction

