Invasive mycoses

Invasive mycoses are severe infections caused by human pathogenic fungi. They are a major cause of morbidity and mortality, particularly in immunosuppressed patients. The infection course depends primarily on the virulence and on the individual risk profile.

Prof. Dr. med. Marie von Lilienfeld-Toal

Dr. med. Maria Rüthrich

Introduction

In recent years an increase in invasive fungal infections has been observed worldwide. At the same time the number of resistant pathogens has risen. It is estimated that worldwide more than 150,000,000 new infections occur annually. The mortality rate is given as 30–90%, depending on the source. The annual incidence rate of invasive fungal infections amounts to 6 cases per 100,000 inhabitants in Germany, 20 in other European countries, and 27 cases per 100,000 inhabitants in the USA. However, comparable epidemiological data are hardly available. Variations in the frequencies of invasive fungal infections can be accounted for by factors such as socioeconomic and geoecological differences as well as the heterogeneity of patient groups at risk.

The most important human pathogenic fungi include Candida and Aspergillus spp. as well as Cryptococcus spp. and Mucorales. This article focuses on Candida and Aspergillus.

Candida infections

The most frequent pathogens of invasive mycosis are yeast fungi of the genus Candida. Further relevant yeasts are Cryptococcus, Trichosporon and Malassezia spp. In more than 90% of cases, invasive candidiasis manifests as a bloodstream infection (candidaemia). In a recently published meta-analysis, the frequency of candidaemia in Europe was given as 3.88 cases per 100,000 inhabitants per year. Other studies report 2–21 cases per 100,000 inhabitants. In Germany, the annual incidence amounts to around 5 cases per 100,000 inhabitants. It is estimated that 79 new infections occur per day. Candida spp. are the fourth most common cause of nosocomial bloodstream infections. The mortality rate is 30–55% and is comparable to that of severe bacterial or viral septicaemia. Yeasts of the genus Candida belong to the microbial flora of the skin and mucous membranes. Consequently, Candida infections are primarily of endogenous genesis and are mainly caused by disorders and damage to the natural barriers or changes in the immune defences. The entry site is often a central intravenous catheter or the gastrointestinal tract. Major risk groups are immunocompromised patients with cytopaenia or immune cell deficits, for example patients with underlying neoplastic or infectious diseases or those in intensive care. Invasive candidiasis can also occur in immunocompetent persons.

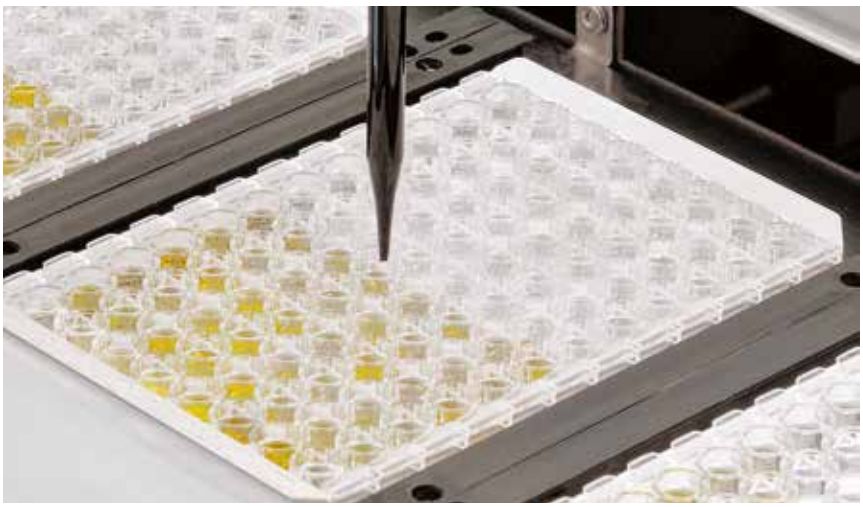
Of the 150 known Candida spp. around a dozen are clinically relevant. The causative species depends on the site of infection, patient-related risk factors and geography. The most frequent pathogen in Europe is Candida albicans. In recent years infections with non-albicans Candida spp. (NAC) have increased in frequency worldwide. NAC are often intrinsically azole resistant and are associated with a higher mortality. In most cases of NAC infection, C. glabrata is isolated. As a commensal organism of the intestinal mucosa it is often detected in non-neutropaenia patients who have undergone abdominal surgery. It is also found in many haematological patients with candidaemia. Further relevant NAC are C. parapsilosis, C. tropicalis and C. krusei. The use of azoles in therapy and prophylaxis is discussed as a cause of the increasing number of cases with non-albicans strains. Invasive Candida infections manifest clinically asymptomatically, with fever and pain, or with a highly acute septic disease pattern.

Clinically relevant moulds / aspergillosis

After Candida infections, infections with the mould genus Aspergillus play an increasingly relevant role. Whereas a few years ago the ratio of Candida to Aspergillus invasive mycoses was 15:1, it is now 4–5:1. The genus Aspergillus encompasses more than 200 species, which are ubiquitous and are found especially in soil, plants and food. The most important human pathogenic species include A. fumigatus, A. flavus, A. terreus, A. niger and A. nidulans. Of these, A. fumigatus is the most common cause of invasive aspergillosis. Other clinically relevant moulds are Fusarium spp. and Mucorales. Aspergillus infections are mostly exogenous. The spores are taken up by inhalation. Hundreds of mould spores are inhaled daily and, due to their small size, they can enter the lung alveoli. The exogenous and most clinically relevant sources of infection include building construction works, contaminated shower or washing water, potted and house plants, as well as mouldy or contaminated food. Mould infections are very rare in immunocompetent persons. They occur primarily as local infections or colonisation, so-called aspergilloma, and in patients with cystic fibrosis as Aspergillus bronchitis or Aspergillus-associated allergy syndrome. When a lung is structurally damaged, for example through preexisting cavities, which occur in tuberculosis, apergillomata can develop even in persons with a healthy immune system. In immunosuppressed patients they manifest primarily as invasive pulmonary aspergillosis (IA). An insufficient immune response leads to germination of the mould spores, tissue destruction, invasion of vessels, and eventually systemic attack. An estimated 200,000 to 300,000 life-threatening cases of IA occur annually worldwide. The mortality is dependent on the virulence and predisposing factors and is given as 30–90%. Besides underlying haematological and oncological diseases and solid organ transplantation, risk factors include prolonged corticosteroid therapy and functional granulocyte defects. An increased incidence is also found in patients with structural lung diseases as well as patients in intensive care. The most important risk factors in haematological patients include duration and degree of neutropaenia, graft versus host disease (GvHD) following allogeneic stem cell transplantation, and previous history of invasive mycoses. Clinically, IA manifests unspecifically with fever, cough, phlegm, and pleuritic complaints, or as pneumonia without detection of a pathogen.

Diagnostics

Early and reliable diagnosis of invasive mould infections is crucial for prompt initiation of targeted treatment taking into account potential resistance of the fungus. When an infection is suspected, diagnosis is made using a combination of microscopic, clinical and imaging criteria, under consideration of the local epidemiology and individual risk factors. The main predisposing factors include prolonged (>10 days) neutropaenia (<0.5x 109/L), status following allogeneic stem cell transplantation, hereditary immune deficiency, medical immunosuppression and prednisolone treatment (equivalent to at least 0.3 mg/kg/d for more than 3 weeks). Diagnosis is considered proven when yeast or mould is microbiologically directly detected in primary sterile material. Detection of Candida spp. in blood culture also provides secure evidence of invasive fungal infection (candidaemia). In contrast, detection of Aspergillus spp. in blood culture is considered as contamination due to the natural presence of the spores in the ambient atmosphere. Using indirect test procedures, specific components of the fungal cell wall can be detected, providing information for diagnosis. Detection of beta-D-glucan is specific for invasive fungal infections. However, since the fungal species cannot be identified, further investigations are necessary. A negative test result also does not exclude invasive mycosis. Due to a lack of data, serological Candida antigen/antibody detection is not recommended in current guidelines. For Aspergillus spp., on the other hand, it is possible to detect and quantify the Aspergillus-specific antigens galactomannan and galactomannoprotein in serum, bronchoalveolar lavage (BAL) fluid or cerebrospinal fluid. The two detection procedures are equivalent in sensitivity and specificity and can also be used to monitor the course of infection during antifungal therapy. False-negative results are observed in non-neutropaenic patients and in patients undergoing azole treatment. In addition, molecular infection diagnostics are possible. The combination of different detection methods is recommended for early and accurate diagnostics. Identification of the fungal species is essential due to different, species-specific resistance profiles. In Candida spp., especially C. glabrata, resistance to echinocandins is increasingly observed, in addition to the known fluconazole resistance. The proportion of fluconazole-resistant Candida isolates is 7%. In the USA, a 10% increase in echinocandin-resistant C. glabrata was observed over a time period of 10 years. In Denmark, there was an increase in resistant Candida spp. from 0.9% to 3.1% (2008 to 2013). Azole-resistant A. fumigatus strains were



The laboratory diagnostic detection is based on cultivation or microscopy. However, cultivation in particular is only successful in around 50% of cases. The detection of Aspergillus antigen in body fluids has become established as an additional investigation. It enables sensitive detection even of early aspergillosis. For this reason, the detection of Aspergillus antigen has been incorporated into the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) as a criterion for probable invasive aspergillosis. The detection method of established test systems is based on the determination of cell wall polysaccharides.

first described in the Netherlands in the mid-1990s. Now they are observed worldwide at an increasing incidence. At the same time, the mortality rate has increased by 21–31%. The proportion of resistant strains varies depending on the underlying disease and geography. For example, the resistance rate in the USA in patients who have undergone allogeneic stem cell transplantation is given as 7%. The Mycology Reference Centre Manchester determined a rate of 28% and an increase in the annual prevalence from 5% to 20% within 6 years. In the Netherlands, azole-resistance rates were found to be 5–10% in the general population and 29% in the risk group of haematological patients. In Germany, azole-resistance was first described in 2012. The rate varies significantly and is given, for example, as up to 30% in patients who have had stem cell transplantation. The use of fungicides in agriculture and the use of antimyotics in therapy and prophylaxis are discussed as reasons for the increase in resistant pathogens. Resistance testing is recommended in invasive fungal infections as well as in cases of insufficient response to treatment.

Therapy options

Early initiation of antimycotic therapy is associated with improved overall survival. Since diagnosis of invasive mycoses is complex, therapy should be started already in strongly suspected cases in patients at risk. Fungal prophylaxis is recommended in high-risk patients with haematological neoplasia (AML/MDS) undergoing induction chemotherapy or after allogeneic stem cell transplantation. The data availability for other risk groups is limited, but prophylaxis is discussed particularly for patients with a complicated course of abdominal surgery, patients in intensive care and following lung transplantation. However, there are no clear recommendations. Generally, substances from three classes of antimycotic are used for treatment of invasive fungal infections: polyenes, echinocandins and azoles. Echinocandins (caspofungin, anidulafungin) are preferred for first-line therapy of invasive Candida infections. Fluconazole should only be used for primary treatment of noncritically ill patients who have not previously been treated with azoles, or in follow-up oral treatment following successful primary therapy with echinocandins. Treatment should be continued for at least 14 days after the time point of the last positive blood culture, or for longer when symptoms do not abate. Treatment with L-AmphB is recommended in cases of disseminated invasive candidiasis or resistance. Since Candida spp. adhere to synthetic surfaces and form a biofilm, central venous access devices should be removed. An ophthalmologist should be consulted during therapy to exclude Candida colonisation of the eyes. For primary treatment of invasive aspergillosis the use of voriconazole or isavuconazole is recommended. In cases of previous treatment with azoles, suspected azole resistance due to local epidemiology or confirmed azole resistance, L-AmphB is the preferred medication. In addition, surgical treatment of the infection should be considered. The duration of therapy encompasses 6–12 weeks depending on the clinical course and the individual risk factors.

Summary

Invasive mycoses are a frequently overlooked infection and underestimated risk for hospitalised and immunosuppressed patients. The often unspecific initial symptoms can impede early diagnosis. Prompt diagnosis is necessary to reduce mortality and enable implementation of therapy as soon as possible. Diagnosis is based on clinical, radiological, microbiological and molecular investigations. Due to the increase in intrinsic and acquired resistance, resistance testing is recommended in addition to species identification. New antifungal substances and combination therapies are the subject of various studies. In general, therapy of patients with invasive fungal infections should be interdisciplinary, in cooperation with experienced specialists. Moreover, diagnostic algorithms and therapeutic strategies should be critically reviewed at regular intervals, and guidelines should be adapted to local epidemiology and risk groups in collaboration with specialists.

Information

■ **Prof. Dr. med Marie von Lilienfeld-Toal**
Dr. med. Maria Rüthrich
Clinic for Internal Medicine II
Department of Haematology and Internal Oncology
University Clinic Jena
Am Klinikum 1
07747 Jena, Germany
onkologie@med.uni-jena.de

■ **Prof. Dr. med Marie von Lilienfeld-Toal**
National Centre for Invasive Mycoses
Leibniz Institute for Natural Product Research and Infection Biology
Hans Knöll Institute
Adolf-Reichwein-Straße 23
07745 Jena, Germany
www.nrz-myk.de

■ **EUROIMMUN AG**
Scientific information service
Aspergillus Antigen ELISA
Seekamp 31
23560 Lübeck, Germany
www.euroimmun.com