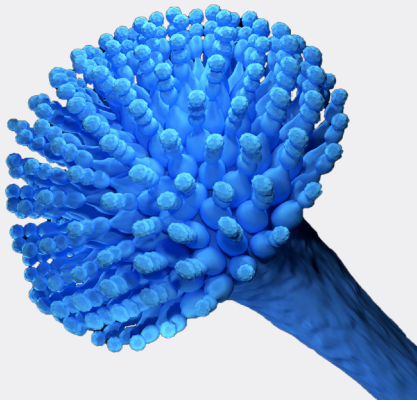
ACADEMYCOTIKA™ 2021

In September 2021, under the supervision of Prof. Martin Hoenigl and Prof. Peter Schellongowski the first edition of ACADEMYCOTIKA™ took place. The aim of this academic meeting was to offer clinically relevant knowledge regarding systemic fungal infections and to train physicians, practicing intensive care medicine or infectious diseases.



An educational event co-organised by ECCM and Gilead

Fungi and Evolution

Prof. Hoenigl opened the two-day event with an overview on the significance of fungal infections in view of evolution in general. The increase in body temperature of mammals most likely proved to be a survival advantage at the expense of an increased basal metabolic rate.[1] In this regard, the expansion of certain fungal species due to global warming, like *Coccidioidomycosis*, could serve as an alarming example.[2]

Epidemiology of Fungal Infections

On the one hand, the development and usage of various therapeutic options, including antibiotics, immunosuppressants and stem-cell transplantation, have resulted in an increase in invasive fungal infections and on the other hand – in a shift in its epidemiology over the last decades.[3]

According to Prof. Hoenigl, Candida and Aspergillus ssp. are still the most common pathogens with a gradual increase of the infections with other fungi. A surge has been observed in invasive fungal infections among non-neutropenic patients, not receiving anti-mycotic prophylaxis. Fungal infections represent a frequent medical challenge in intensive care units (ICU) in the course of the ongoing COVID-19 pandemic, leading to the definition of COVID-associated pulmonary aspergillosis (CAPA).[4]

What Patient Groups Are at Risk of Fungal Infection?

Neutropenia is a well-established risk factor for the development of clinically relevant fungal infections. It is often registered as a consequence of immunosuppressive therapy (solid organ transplantation or autoimmune disease), cytostatic chemotherapy, hematologic malignancies or after stem-cell transplantation. Other diseases or physical conditions associated with an increased incidence of fungal infections include untreated solid malignant tumors, COPD, liver cirrhosis, diabetes, burn injuries, malnutrition, as well as acquired or inherited immunodeficiencies (e.g. untreated HIV infection).[5–7] Screening for fungal infection is justified and recommended in case one or more of these risk factors have occurred.

Fungal Infections at Intensive Care Units

As per prognoses, invasive mold, Candida and Pneumocystis infections are anticipated complications with patients at ICU.[8–11] The risk of fungal infections increases with the duration of the stay and is linked to treatment with broad-spectrum antibiotics, long-term usage of central venous catheters, parenteral nutrition, underlying diseases and the relevant administered therapy.[8–11]

Invasive pulmonary aspergillosis (IPA) and candidiasis account for the substantial number of patients with acute respiratory failure (ARF), often associated with fatal outcome and represent the only likely versatile risk factor.[12]

Clinical and radiological features of IPA often differ between neutropenic and non-neutropenic patients. Accordingly, the described radiological features include non-specific infiltrations instead of the characteristic „halo sign“ or „air crescent sign“ in IPA. Therefore, invasive aspergillosis is often diagnosed only during autopsy.[13,14]

A precise and final diagnosis through biopsy with patients with hematological disease is not often achievable due to thrombopenia or coagulation disorders. Thus, the EORTC include proven and probable criteria for diagnosis, relying on the patient's characteristics, microbiological and radiological findings.[15]

Prof. Hoenigl presented an overview on available diagnostic algorithms based on different methods, sample materials, clinical findings and radiological features.[16–19] When in doubt, an appropriate therapy should be initiated with high-risk patients with corresponding symptoms and in critical state.[20]

Diagnosis of Fungal Infections

A prompt and reliable diagnosis of invasive fungal infection allows for choosing the adequate therapy which significantly reduces associated lethality.[21]

Prof. Willinger has presented an overview on various techniques for microbiological diagnosis which are based on different approaches. These include cultural, microscopic, serological, and biomolecular methods. Those are associated with variant sensitivity, specificity, time requirements and individual issues. The method of detection depends on the patient's characteristics, their immune system and the available sample material.

When suspicion for systemic fungal infection arises, blood cultures should be prepared several times per day. Samples in sufficient quantities should be drawn through venous puncture and not by using catheters. Blood cultures allow for identification of the pathogen and evaluation of susceptibility for avail-

able antifungal drugs at moderately low costs. The disadvantages of this method include long duration, suboptimal sensitivity and limited informative value for non-sterile specimen.[22]

As blood cultures alone do not offer optimal sensitivity and take several days for delivery of the results, additional methods for establishing diagnosis should be employed.[23]

Detection of fungal antigens such as 1-3-ß-D-glucan, a cell membrane component of most fungi, by using commercially available test systems represents one such opportunity. This biomarker tests positive when the clinical symptoms become first apparent and is, therefore, a valuable addition to conventional diagnostics. Moreover, 1-3-ß-D-glucan has a high negative predictive value and lack of detection and thus, it is clinically suitable for exclusion of invasive aspergillosis and candidiasis. 1-3-ß-D-glucan also test negative in viral or bacterial infections, as well as in infections with *cryptococcus neoformans* and *mucorales*.[24–27] According to Prof. Lass-Flörl, serological diagnosis of cryptococcosis offers reliable feasibility by detection of a capsular polysaccharide antigen. Prof. Prattes revised this statement by suggesting that diagnosis of invasive aspergillosis could be established through detection of galactomannan, a polysaccharide of cell membranes of *aspergillus spp*., using bronchoalveolar lavage or serum.

Prof. Willinger added that mass spectrometry (MALDI-TOF) and molecular biology techniques (PCR, filmarray, PNA-FISH, T2 magnetic resonance assay) were alternative methods for identification of the underlying pathogen, but also pointed out that although these methods are faster, they would detect only a limited spectrum of pathogens.[24]

Hence, the conclusion that combining different methods is essential for increasing the informative value of individual examinations and for ensuring a reliable diagnosis.

Antifungal Prophylaxis and Therapy

According to Prof. Hoenigl, the European and American guidelines consistently come up with strong recommendations for antifungal prophylaxis with posaconazole in patients with induction chemotherapy, prolonged neutropenia or graft versus host disease. The recommendations are mostly moderate when it comes to prophylaxis with posaconazole or alternatively voriconazole for patients with allogeneic stem-cell transplantation (up to engraftment).[20,28,29]

In Austria, echinocandins are the first and priority choice of treatment for critically ill patients with candida infections, whereby attention should be paid to increasing resistance to micafungin while maintaining sensitivity to anidulafungin.[21,30]

Any confirmed or suspected invasive aspergillosis should be treated with voriconazole or isavuconazole. Liposomal amphothericin B serves as a valuable alternative and more so for patients with extrapulmonary infestation (e.g. sinuses) or in the presence of potential drug interactions or impaired liver function. The duration of the therapy depends on the response, the immune reconstitution and the course of the microbiological findings, as the time span can range from weeks to months, as Dr. Schellongowski emphasizes.[20] Prof. Krause added that a switch from intravenous to oral therapy was possible with voriconazole, posaconazole and isavuconazole, although the bioavailability, the influence of food on resorption, the dosage interval and the need for TDM were different for each substance.[31]

The European Confederation of Medical Mycology (ECMM) together with other leading international specialists' societies, has published comprehensive guidelines for the treatment of mucormycoses and other rare mold and yeast infections as part of the "One World One Guideline" initiative. These guidelines strongly encourage the use of liposomal amphotericin B as a first-choice treatment in most clinical conditions.[32,33]

Therapeutic Drug Monitoring (TDM)

The quantification of plasma trough levels is essential for the successful therapy of mold with azoles. Itraconazole, voriconazole and oral formulations of posaconazole show large intra- and inter-individual fluctuations in plasma concentrations. Excessively low plasma levels have been regarded as a therapy and prophylaxis failure. In order to avoid overdoses and associated side effects, especially visual disturbances and liver toxicity, an individual adjustment of dosage is necessary.[28] In case where isavuconazole is used in routine clinical practice, TDM is only indicated in risk group patients (obese patients, dialysis, ECMO, cytosorber therapy).[34] According to Prof. Hoenigl, there is no need for routine TDM when using amphotericin B formulations, echinocandins and fluconazole.

Drug-Drug Interaction of Antifungal Drugs

Azole antimycotics have complex, substance specific pharmacokinetic properties with the possibility of drug-drug interaction. Knowledge on their individual metabolism and interactions with transport proteins is crucial for avoiding side effects and toxicity when used in combination with other drugs.[35]

The echinocandins caspofungin and micafungin are also metabolized by the liver, but according to Prof. Bellmann they have a lower risk for interacting with other drugs as compared to azoles. Anidulafungin undergoes slow, spontaneous degradation and is excreted in the bile and with faeces. Therefore, interactions with other drugs are not expected.

Regardless of its formulation (liposomal, colloidal, deoxycholate), amphotericin B is excreted unchanged in urine according to Prof. Bellmann.

Nephrotoxicity is a characteristic side effect of amphotericin B and is caused by vasoconstriction of afferent arterioles associated with a decrease in renal plasma flow. According to Prof. Bellmann, the risk for renal side effects is lowest for the liposomal formulation of amphotericin B. Furthermore, Bellmann states that the decay of the renal tubules is accompanied by the loss of potassium, magnesium and HCO3 and are linked to systemic vasoconstriction. That is why, synergistic interactions with other nephrotoxic substances are of special interest in the case of amphotericin B and flucytosine.[35]

Conclusions of the First Akademykotika 2021

The Akademykotika offered physicians, who are interested in infectious diseases, the opportunity to personally exchange experience with experts from all over Austria on different topics related of fungal infections and to collect hands-on knowledge for everyday clinical practice in intensive care units on most of the current topics such as CAPA. The event was definitely a success – a conclusion based on the feedback from all participants and speakers. The next edition of the Akademykotika for 2022 has already been planned!

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