Meet-The-Expert Sessions

M01

Multi-organ failure and antifungal treatment

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Critically ill patients with life threatening infections often experience multi-organ failure. These patients who are frequently hemodynamic unstable, require aggressive therapeutic interventions that will impact the pharmacokinetics of antifungal drugs. Vice versa, antifungal drugs are not without side-effects likely causing a further deterioration of specific organ functions. Applying effective (and safe) drug regimens for these patients with the selection of the most appropriate drug and to optimize the exposure of these drug, requires understanding of the pharmacokinetics.

In the treatment of fungal infections in hematology and ICU patients, the heterogeneous nature of patients combined with limited evidence on how to manage these patients often leads to a high variability of applied drug regimens and regular off-label drug use. Failure to anticipate and monitor for changes in the pharmacokinetics of a drug can contribute to clinical failures or adverse drug events.

In this session we will discuss the general principles of PK of antifungal drugs and how critical illness can influence the specific pharmacokinetic phases (absorption, distribution, metabolism and elimination).

We will start with current challenges in oral absorption of antifungal drugs, the differences in oral bioavailability and the impact of food-drug interactions. Next we will discuss if we can identify certain drug that might have a preferential profile for targeting certain organ systems (distribution) and the impact of a wide variety of factors that influence distribution of antifungal drugs such as protein binding.

With drug metabolism, we discuss the impact of hepatic enzyme activity on the pharmacokinetics. Finally, we review drug elimination and discuss the impact of renal function (kidney injury) and topics such as augmented renal clearance. The role of extracorporeal elimination techniques such as CVVH(D)(F) and ECMO on the pharmacokinetics of antifungal drugs will be touched upon.

For the purpose of this section, we will highlight relevant literature and characterize the impact of above mentioned factors on the PK profile and, where appropriate, provide general suggestions on how to adapt drug regimens to manage specific challenges. Finally recommendations will be made on the role of therapeutic drug monitoring to guide dosing in the setting of critical illness.

In short, the following will be addressed: (i) potential impact of critical illness on the pharmacokinetic (implications for absorption, distribution, metabolism and elimination; including hepatic and renal dysfunction, extracorporeal elimination techniques etc; (ii) choice of drug in the setting of critical illness and specific organ dysfunction (including safety related aspects); and (iii) the role of TDM for dosage adjustment to achieve optimal drug exposure for individual patients in the setting of organ dysfunction.

M02

Professional exposure to fungal pathogens - an update to exposure conditions and exposure measurement

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In many occupational settings an exposure to fungi occurs. Fungal exposure may occur for instance in the form of dermatocytes, yeasts or mold. Associated to the fungi themselves an exposure to cell wall components like ß(1 → 3)-D-glucans, to mycotoxins or to microbial volatile compounds can occur. Health hazards may differ across species because fungi may produce different allergens and mycotoxins, and some species can infect humans.

Occupational settings are often characterized by special exposure conditions with respect to duration, frequency and especially to the level of exposure resulting at least sometimes to high or very high fungal exposure. Because of these special conditions occupational settings are suitable for epidemiologic studies. However, the knowledge about occupational exposure to fungi and associated compounds like mycotoxins is still fragmentary and not well disseminated. An indication for a high fungal exposure is for instance the handling of dry natural products like grain, hay or herbal plants with a high specific surface and the tendency to release dust during handling. The fungal components often form the determinative part of such dusts and might be a vehicle to respiratory airways.

The authors will present results of exposure measurements of occupational settings and exposure conditions which are only rarely investigated.

For a sound risk assessment a profound exposure characterization is indispensable. However, each measurement technique has limitations. Thus it is necessary to be aware of which information can be achieved by the different measurement techniques. Very common is the use of cultivation based methods. But not for all fungi appropriate culture media are available and slow growing fungi can be overgrown. In the case of the search for distinct fungi the use methods like the real-time quantitative PCR (qPCR) amplification of genes from specific fungal species offers considerable advantages. Such methods can also help for the comprehensive characterization of the

Table 1 Comparison between fungal assessment through conventional and molecular methods.

Setting	Fungal species assessed by molecular biology	Molecular biology
Poultries	*A. flavus* complex (toxigenic strains)	4 (in 2 samples wasn't found by conventional methods)
	A. fumigatus complex	8 (in 7 samples wasn't found by conventional methods)
	S. chartarum	0
Waste water treatment plants (WWTP)	*A. flavus* complex (toxigenic strains)	0
	A. fumigatus complex	7 (in 6 samples wasn't found by conventional methods)
	S. chartarum	0
Waste management	*A. flavus* complex (toxigenic strains)	0
	A. fumigatus complex	15 (in 1 sample wasn't found by conventional methods)
	S. chartarum	0
Cork industries	*A. fumigatus* complex	0
	P. glabrum complex	10 (in 6 samples wasn't found by conventional methods)

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fungal diversity present at workplaces. For the latter objective the investigation of settled dust is recommended as settled dust usually acts like an integral of the airborne exposure over a longer period of time than conventional methods with air sampler do.

A study about fungal exposure in Portuguese occupational settings revealed that 64.2% of the sampling sites reveal different species in surfaces than the ones identified in air. That corroborates the importance of surface analysis to complement the mycological air characterization and it allows a more complete characterization regarding fungal contamination. In addition, only *A. fumigatus* complex was found through conventional methods and was not able to be detected by molecular tools in cork industry among several occupational settings previously assessed (Table 1).

M03

Fungal endocarditis

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Candida endocarditis is a very rare (<2% of all infective endocartitis cases) but devastating disease. Recent hospital mortality rates are still as high as 30–47%. Among *Candida* endocarditis, those affecting prosthetic valves are even more severe. Current ESCMID guidelines recommend antifungal treatment associated with early surgery for prosthetic valve endocarditis due to *Candida* (PVE-C). If surgery is not possible, life-long fluconazole may be prescribed, to suppress infection. These recommendations are based on the results of retrospective reviews of case series, case reports or small prospective series, and expert opinions, since prospective randomized studies are not possible in the field of this rare disease affecting very heterogenous populations.

The choice of the antifungal treatment may take into account the fungicidal properties of the molecules, and their activity against *Candida* biofilms. Liposomal amphotericin B formulations and echinocandins may thus confer an advantage, although no clinical data demonstrated their superiority. Early surgery is recommended on the basis of the high frequency of embolic complications associated with *Candida* endocarditis and the poor diffusion of antifungals through cardiac vegetations and around foreign bodies, but clinical data validating this recommendation are very scarce. In addition, patients are often poor surgical candidates. Results of the ESCAPE study analysing the long-term outcome of patients with PVE-C managed in Spain and France between 2005 and 2013, suggest that a prolonged suppressive antifungal therapy could improve the outcome of unoperated patients with PVE-C without major side effects.

M04

New diagnostic tools for *Pneumocystis jirovecii*

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In both the European Economic Area and the USA, *Pneumocystis jirovecii* pneumonia (PcP) is the most commonly diagnosed AIDS-indicative disease. The rising numbers of immunocompromised HIV-negative patients at risk of *P. jirovecii* infection (those receiving immunosuppressive therapies for malignancies, allogeneic bone marrow or solid organ transplantations or autoimmune diseases) are an emerging concern.

PcP is difficult to diagnose, in particular in HIV-negative patients owing to the nonspecific symptoms and signs associated. Since *P. jirovecii* is not cultivable, microscopic visualization of cysts or trophic forms in respiratory specimens based on cytochemical stainings or immunofluorescence stainings using monoclonal antibodies (IF/Mab) are the standard procedures to detect this fungus. Respiratory specimens obtained by invasive techniques (e.g. BAL) carry the risk of complications and are not easy to collect in children and patients with respiratory failure. Blood biomarkers could be a way to perform PcP diagnosis non-invasively. Several studies performed recently, explored the usefulness of candidate serum biomarkers, such as (1-3)-b-D-Glucan (BG), *Krebs von den Lungen*-6 antigen (KL-6), lactate dehydrogenase (LDH) or S-adenosyl Methionine (SAM), with the former presenting the most promising results. BG detection has a high sensitivity and a relatively high negative predictive value for diagnosis of PcP in immunocompromised HIV-positive and -negative patients, but a positive result may also indicate the presence of other invasive fungal infections.

In addition, PCR-based methods play an increasing role in the lab, initially developed to circumvent decreased sensitivity of microscopy in respiratory specimens and in HIV-negative patients. Real-time PCR is the only format adapted to diagnosis since the risk of contamination is minimal and quantification is possible. Quantitative results have been used for years to try to discriminate PcP (high fungal load) from carriage/colonization (low fungal load). However, these methodologies have limited use since intermediate fungal load are inconclusive. Combination with BG detection in serum helps but do not completely resolve the problem. With the ambition to bring a new concept for diagnosing infectious diseases, a new diagnostic PCR methodology based on the analysis of the expression of two genes could revolutionize PcP diagnosis.

M05

Infection control & fungi: what's hot and what's flop?

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Invasive Fungal Infections (IFI) caused by filamentous fungi such as *Aspergillus* sp. are feared diseases despite the recent evolution of therapeutic strategies. In order to avoid the exposure of the most at risk patients such as those undergoing neutropenic chemotherapy, or hematopoetic stem cell transplant recipients to fungal spores, air and water contol measures are usually implemented in hospitals. Their aim is to diminish the morbidity and mortality of these diseases, thereby reducing the need for associated healthcare (extension of hospital stay, prescription of complementary examinations and use of antifungal medication). During the session, we will analysed successively the methods used for air and water treatment, in normal situations but also during construction works in healthcare establishments, and how to monitor its efficacy.

M06

Meet the fungus - Rare fungal infections cases

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For the abstracts that will be discussed in this session, please see section 'poster sessions', corresponding abstract numbers: P102/P200/P122/P303.

M07

Genotyping fungal outbreaks and molecular epidemiology: the state of the art

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The processes driving infectious disease emergence and spread are reflected in their genetic diversity. Genotyping approaches are now an integral part of research in infectious disease epidemiology. Detailed individual- or species-level analyses of genetic diversity informs our understanding of disease transmission and the evolution and spread of antifungal resistance. Broader genomic analysis of microbial communities within the host is revealing important interactions between different fungal lineages, species and kingdoms, their response to interventions and their role in shaping the immune response to infection. This 'meet the expert' session will consider the scientific potential for high-throughput genotyping data in fungal disease epidemiology and the new opportunities offered by advances in genetic sequencing technology. We will consider the advantages and disadvantages of currently used genotyping techniques, the types of analyses that each platform supports, and the rapidly-developing opportunities that are afforded by new genotyping technologies. Our examples will be chosen to illustrate the spectrum of infectious fungi that impact humans and other animals.

M08

Non-dermatophytes moulds in dermatology

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Non-dermatophytes are sometimes seen as pathogens in onychomycosis and more rarely in skin infections.

The prevalence of non-dermatophytes (e.g. *Neoscytalidium*, *Scopulariopsis*, *Aspergillus* and *Fusarium*) as etiological agents of onychomycosis, varies in different studies depending on the definition of the diagnostic criteria used. It is often necessary to resample in order to confirm the diagnosis and exclude contamination. Secondary colonization of nail changes e.g. after trauma or nail alteration caused by diseases such as lichen planus or psoriasis is a challenge. The choice of systemic or topical antifungal treatment or a combination of antifungal treatment combined with chemical or mechanical nail avulsion is chosen based on the extent of nail changes in conjunction with the patient's other disorders and possible medication interactions. New treatment options such as photodynamic therapy and laser treatment are also available.

Skin infections caused by non-dermatophytes are rare in immune competent patients but may occasionally be inoculated by trauma. In immunosuppressive patients non-dermatophytes may disseminate by haematological spread to the skin secondary to a systemic infection.

This session will focus on the clinical presentation as well as the diagnostic and treatment challenges of non-dermatophytes in dermatology.

M09

ECMM external quality control programmes

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Participation in external quality assessment (EQA) plays a vital role in the quality management and improvement of services offered by clinical laboratories, thereby furthering the ultimate aim of ensuring a high standard of patient care. At its best EQA provides laboratory managers with an objective assessment of laboratory performance against recognised standards and provides a bench mark relative to peer performance in the same test. It can highlight issues with methodology or kit performance and is a marker for the efficacy of internal quality control (IQC). For commercially available kits it provides inter-laboratory performance evaluation and can be useful for post-marketing vigilance. In some areas it can be educational, occasionally challenging laboratories with results or organisms they may only encounter infrequently, although the bedrock of good EQA is to provide a test system for clinically relevant samples that mimic patient samples that are processed on a daily basis. In order to fulfil the remit EQA samples should be handled in the laboratory in exactly the same way as routine clinical samples. Failure of the intention of EQA occurs when samples are not handled in the same way but are marked out for special attention e.g. greater care with ensuring IQC is well in range, repeat testing of samples or calling more experienced colleagues to assist with an identification if that would not be normal laboratory practice for patient samples. This may of course result in excellent performance in EQA but will not help to highlight any issues thus helping to improve the overall performance of that laboratory. Of course a more generalised discussion or tutorial post result analysis and distribution is very beneficial for laboratories and wide discussion and dissemination of EQA results throughout the lab should be encouraged once the post analysis report is received.

Increasingly, bodies that provide accreditation of clinical laboratory performance are looking for participation in a range of EQA schemes that encompass the entire repertoire of tests undertaken by a laboratory. Whilst the range of tests available for mycology services has been expanding and now encompasses; identification and susceptibility testing of yeast and moulds, including dermatophytes; antibody testing for candidosis and aspergillosis; antigen testing for cryptococcosis; *Aspergillus*, *Candida* and *Pneumocystis* DNA detection; and a wide range of antifungal assays, there are some notable gaps. We will discuss the schemes that are available and discuss ways such as inter-laboratory exchanges that can be used to fill the gaps until standardised schemes are available for all the tests and services routinely conducted in mycology laboratories.

M10a

Are all potential human pathogenic Mucorales identical?

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Mucormycosis is an emerging infection due to several species belonging to Mucorales. Indeed, Mucorales represent a large group of fungi including very diverse species that can be found all over the world. Among the several hundreds of known species of Mucorales, more than 20 different species belonging to more than 10 genera can be responsible for infections in humans.

Although there have been relatively few studies to evaluate the specific characteristics of each species it is clear that they are very diverse in terms of genetics and biology, geographical distribution and epidemiology, antifungal susceptibility, predisposing factors of the patients, and clinical presentation of the diseases they are

causing. This diversity could have a direct impact on the performance of diagnostic tools and may have, in the future when more active drugs are available, an impact on the therapeutic strategies.

Recently, the taxonomy of Mucorales has been largely revised and molecular studies have shown the great diversity among the genera and even among species belonging to a given genus. One the practical consequences of these large genetic variations is that a single DNA target (ITS region) can be easily used for a precise molecular identification of almost all the pathogenic species.

Although Mucorales seems to be worldwide distributed, the frequency of the species is related to the geographical area. For example, species belonging to *Saksenaea* or *Apophysomyces* are more often recovered in tropical countries and *Lichtheimia* species seems more frequent in Europe than in North America.

They are also difference between species for their antifungal susceptibility. Some species such as *Cunninghamella* spp. are less susceptible to amphotericin B than others and variable susceptibilities to posaconazole have also been reported among Mucorales. The clinical impact of these differences are nevertheless currently largely unknown.

The underlying conditions of the patients with Mucormycosis and the clinical presentation of the disease is also dependent on the species. Some species such as *Saksenaea* and *Apophysomyces* are mainly responsible of post-traumatic cutaneaous/subcutaneous infections in immunocompetent patients. In contrast, *Rhizopus* species are more often responsible for rhino-cerebral infections in diabetic patients.

Overall, the group of human pathogenic Mucorales, which is often considered as a homogeneous group of fungi, is in fact constituted by a series of very diverse species.

M10b

Are all potential human pathogenic Mucorales identical?

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Species of *Rhizopus, Mucor* and *Lichtheimia* are the most common members of the order *Mucorales* that cause mucormycosis, accounting for 70–80% of all cases. In contrast, species of *Cunninghamella, Apophysomyces, Saksenaea, Rhizomucor, Cokeromyces, Actinomucor and Syncephalastrum* individually responsible for <1–5% of reported cases of mucormycosis. Clinical presentation, host predilection, and outcomes seem to vary as a function of the degree and type of immune dysfunction, geoclimatic locale and species of Mucorales. Epidemiology, clinical presentations and outcome of unusual Mucorales are less well studied and there is particular need for improving clinical and laboratory diagnosis. New active antifungal drugs and new treatment strategies to improve the outcome especially for *C. bertholletiae* and *R. pusillus* are urgently required. Clinical Infectious Diseasescid.oxfordjournals.org

M11

Rare fungal infections cases

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For the abstracts that will be discussed in this session, please see section 'poster sessions', corresponding abstract numbers: P109/P296/P148.

M12a

Indoor fungal exposure and disease: an overview

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Indoor dampness increases the risk of indoor fungal growth. A complex interaction between occupant behavours and the built environment are thought to affect indoor fungal concentrations and species diversity, which are believed to increase the risk of having asthma, exacerbation of asthma symptoms, or both, and contribute to allergic bronchopulmonary and chronic pulmonary aspergillosis. Mould spores and metabolites can be inhaled via the air and cause allergic and irritating reactions and/or complex symptoms in humans. In rare cases some mould species, for example, Aspergillus fumigatus, can cause infections in high risk groups. There is sufficient epidemiological evidence that damp and mouldy buildings increase the risk of respiratory symptoms, respiratory infections and exacerbations of asthma symptoms of the occupants. In addition, there is some evidence for increased risk of development of allergic rhinitis and asthma. Furthermore, there is clinical evidence for rare symptoms like allergic alveolitis, chronic rhinosinusitis and allergic sinusitis. Toxicological studies in vivo and in vitro demonstrate that microorganisms can cause short-term irritation (including spores, cell components, such as hyphal fragments and metabolites) from damp buildings. Numerous scientific and clinical studies have demonstrated that exposure to common environmental moulds in the built environment, such as, Aspergillus, Penicillium, Cladosporium, Ulocladium, Acremonium, Epicoccum, Trichoderma, Alternaria, and Wallemia species might represent a respiratory health risk to atopic and immunocompromised patients, and patients with other respiratory problems, living in homes with increased fungal concentrations. Many of these surveys do not provide sufficient detail to assess whether these fungi exacerbated asthma symptoms or potential health outcomes resulting from increased exposure to known allergenic or pathogenic fungal species (ie, fungi only identified to the genus level, for example: Aspergillus fumigatus instead of Aspergillus/Penicillium) present in higher concentrations at the time of sampling. Development of molecular tools enables us to more reliably quantify fungal species present indoors.

M12b

Indoor molds and chronic rhinosinusitis: could we improve detection of fungal spores from the sinuses and prevent fungal chronic rhinosinusitis (FRS) or invasive infections?

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Fungi are ubiquitous, found mainly in air, dust, soil, plants and decaying organic material but degree of fungal exposure appears to vary based on environmental conditions. Moisture in buildings becomes a critical factor for fungal proliferation and dissemination. Nutrients and moisture increase fungal adherence to dust particles which may be inhaled and deposited on the sinus mucosa, whose warm, moist environment is ideal for further fungal proliferation. The literature shows increasing appearance of noninvasive fungal inflammations of upper respiratory tract in immunocompetent patients (allergic and nonallergic) and invasive fungal infections (IFI) in immunocompromised patients as fungi could persist in sinuses as 'hidden-killers'.

Chronic rhinosinusitis (CRS) is inflammatory disease of the nasal and paranasal sinus mucosa with symptoms persisting longer than 3 months. CRS is one of the most common chronic diseases worldwide (prevalence in USA 14.1%). Several recent studies revealed the role of fungi in the pathogenesis of CRS but it is still controversial. It seems that different environmental/geographical conditions, fungal

species, patient's predisposition and risk factors are crucial in developing fungal CRS (FRS).

There is a great interest related to indoor fungi and upper respiratory tract diseases but the main problem is 'evidence based diagnosis'confirmed by mycology examination. Traditional methods for fungal detection, such as nasal swab, show low sensitivity and specificity, while the sampling of sinus mucine and tissue is complex and invasive. It results in the needs for developing and standardizing protocols for representative samples selection and proceeding in order to improve detection of fungi from the sinuses.

We focused on: (i) CRS patients and developing of personalized approach for prediction of FRS and (ii) standardization of diagnostic protocols which could improve detection of fungi from the sinuses. During 2014th we done clinical and mycological examinations on 157 CRS patients: 43 with nasal polyps (NP) underwent surgery and 112 without surgery. According to obtained data 10 '*major*' CRS criteria were selected as key FRS predictors ('FRS_{index}'). We developed two types of sampling procedures that shown high sensitivity and specificity for fungal detection from the sinuses: (i) NP tissue obtained by surgery and proceeded to single cell suspension (SCS) and (ii) sinus mucine obtained after nasal cavum pretreatment in aim to remove nasal microbiome followed by induction of sino-nasal secretion (ISNS) and concomitant sampling by lavage and aspiration ($ISNS_{comb}$ method). SCS and $ISNS_{comb}$ methods significantly enhance detection of relevant fungi from the sinuses, compared to nasal swab methods or pathohistology. The highest positive fungal findings we found out in group of patients with: recalcitrant NP (42%), CRS without surgery (25%) and NP (23%). $ISNS_{comb}$ method showed the highest sensitivity and specificity (89%, 96%; respectively) and PPV and NPV (94%, 93%; respectively), according to developed FRS_{index}. Based on these data we showed prevalence of CRS in Serbia 13.8% and prevalence of FRS 2.8%. Out of 43 patients with NP 10 had positive fungal finding: *A. flavus, A. niger* and *Alternaria alternata*. Out of 112 patients without surgery 28 had positive fungal finding: *Aspergillus (A. fumigatus, A. flavus, A. niger), Penicillium, Cladosporium, Rhizopus, Alternaria* and *Fusarium*. In home air samples from 71 we revealed 224 indoor molds: *Aspergillus* (*A. flavus, A. nidulans, A. versicolor, A. glaucus, A. fumigatus, A. niger, A. terreus), Penicillium, Curvularia, Fusarium, Rhizopus, Alternaria, Chrysosporium* and *Ulocladium*. The most abound indoor molds were *A. niger* (62/224) and *Penicillium* (29/224).

In conclusion We could improve detection of fungi from the sinuses by developing and standardizing of reproducible, sensitive and cost-effective methods for FRS diagnosis. It could be strongly important for immunocompromised patients for preventing life-treating IFI with timely detection of indoor molds in sinuses, as 'hidden-killers'.

M13

Sand serves as a reservoir for potentially pathogenic microorganisms

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Recent studies suggest that sand can serve as a vehicle for exposure of humans to potential pathogenic microorganisms at beach sites, sandboxes and recreational areas. Recreational water quality, worldwide, focuses on monitoring bacterial indicators of possible faecal contamination by pathogens that cause Gastro-intestinal illness. The most recent bathing water directive in Europe hints on recreational water surrounding areas as a possible contamination source in itself. Yet, it leaves behind a clear message that sand is a relevant source of microorganisms, despite WHO's recommendation of sand monitoring in 2003; especially in regions where beach users stay mainly on the sand due to low temperatures of the water. This recommendation has been backed up recently by an epidemiological study conducted by Heaney *et al.* (2012) and the information collected during a 5 year beach sand monitoring program of the whole of the coast of Portugal (Sabino *et al.* 2011).

Given the diversity of microbes found in sand, studies are urgently needed to identify the most significant aetiologic agent of disease that may be conveyed through sand, and to relate microbial measurements to human health risk. Currently monitoring in sandboxes is limited to measurements of *Toxocara* eggs, although other microbes have been documented. A newly emerging group of fungi of concern include the black yeast-like fungi and in non-coastal settings, Cryptococcus gattii has been gaining significance already given to endemic and fungi resistant to antimicrobials, especially in Children and immune-impared individuals. Sampling for microorganisms in sand should therefore be considered for inclusion in regulatory programs aimed at protecting recreational users from infectious disease (Solo-Gabriel *et al.* in press).

Overall, we recommend environmental studies to support the link between fungi exposure in sand and human health impacts, and also to review existing sand analysis to make sure that other potential pathogens are cover.

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M14

Oral candidosis and cancer, a relation?

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In this session we will summarise and discuss the current knowledge on the role of *Candida* yeasts in the development of cancer. In addition, cases where a link between chronic candidosis and malignant transformation can be hypothesised will be presented.

Cancer is one of the leading causes of death worldwide. There is a strong link between chronic inflammation and many types of cancers, and suppression or dysregulation of the immune system increases the risk for their developoment. Oral candidosis is common in patients with malignancies whereby the presence of *Candida* has logically been assumed to reflect the opportunistic nature of the yeast rather than its role in the development of a malignant lesion. Our group has focused its research on the biofilm-associated chronic oral-oesophageal candidosis, which has been shown to be potentially carcinogenic *in vivo*. The most important etiological factors of upper digestive tract cancers are alcohol consumption and smoking. Certain dietary and genetic factors as well as poor oral hygiene can also contribute to the increased risk. All these factors lead to increased exposure of the upper digestive tract mucosa to mutagenic acetaldehyde (ACH). ACH is the first metabolite of ethanol metabolism and fermentation. It binds to DNA and forms DNA adducts, causes point mutations, DNA crosslinking and interferes with the synthesis and repair of DNA, and is classified as a Group 1 carcinogen by WHO. We have shown that most *Candida* spp. can produce mutagenic levels of ACH, especially when grown in hypoxic/anaerobic conditions and as

biofilms. Therefore, in addition to inducing pro-inflammatory pathways *Candida* has the potential to induce carcinogenesis also by producing mutagenic by-products. These findings provide an explanation for the carcinogenicity of chronic oral-oesophageal candidosis, and indicate that *Candida* can be the cause for the development of a cancerous lesion in addition to being a secondary coloniser.

M15

Candida pneumonia in ICU?

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Candida species are frequently found in tracheal aspirate specimens even in healthy patients. After 48 hours of intubation and ventilation more than 20% of patients are colonized with *Candida* species at the tracheobronchial site. This proportion increases with the duration of ventilation. Studies analyzing bronchoalveolar lavage fluid (BALF) cultures from critically ill patients found up to 8% positivity for *Candida*, the majority of which were thought to be colonization or inconclusive and less than 5% classified as ventilator-associated pneumonia (VAP) by the treating physician. Although antifungal treatment is scarcely initiated, none of these patients appear to develop systemic candidiasis. Treatment of all patients with BALF analysis positive for *Candida* would result in excessive use of antifungal agents with risk of rapid development of drug resistance. Sheer presence of *Candida* in the BALF obviously does not prove a pathogenetic role of this microorganism in the development of pneumonia. Moreover, the radiological morphology of *Candida* lesions is diverse. Bronchopneumonia, abscesses, granulomas, intracavitary membranous exudates have all been described on X-ray and on high resolution chest tomography. The real incidence of *Candida* pneumonia is thus notoriously difficult to determine. The most reliable method would be lung histology and proof of an association between *Candida* lung invasion and local inflammation. The patients clinical condition, high oxygen dependency and thrombocytopenia, commonly present, often exclude the possibility of pulmonary biopsies. Therefore, most reports of *Candida* pneumonia are based on isolation of *Candida* from sputum aspirates or BALF in the absence of other causative pathogens. Studies in critically ill, ventilated and non-neutropenic patients with quantitative cultures from tracheal aspirate and BALF failed to discriminate presence from absence of *Candida* pneumonia established by autopsy findings. It was even suggested that there is no evidence for the existence for such clinical entity at all. Taking into account the high number of patients colonized with *Candida* species in the tracheal tract it seems a convincing conclusion that colonization alone does not lead to pulmonary infection. Furthermore, *Candida* species are at most a very rare cause of pneumonia. But to rule out the existence of *Candida* pneumonia as a clinical entity at all may be premature. An interesting question would be whether those *Candida* species colonizing the tracheobronchial tree are merely innocent bystanders? It has been shown that mechanically ventilated patients colonized with *Candida* species were more at risk to develop *Pseudomonas aeruginosa* VAP and in those patients who received antifungal treatment the incidence of VAP was reduced. Furthermore, colonization with *Candida* species is an independent risk factor for increased morbidity and mortality in ICU patients. But whether colonization with *Candida* has a causative role or is merely a marker for poor outcome is unclear.

An increasing number of immunocompromized patients due to immunosuppressive therapy, malignancies and infections are treated in ICU who are at risk to develop *Candida* pneumonia. Moreover, there are genetic associations that determine the susceptibility for *Candida* infections. Therefore, *Candida* as the causative microorganism of pneumonia in ICU patients should be considered in differential diagnosis. *Candida* pneumonia is a rare entity. But there is evidence that the condition can occur under certain clinical circumstances: (i) immunosuppression by cancer, sepsis, drugs, malnutrition, (ii) risk factors for increased *Candida* load as diabetes mellitus, nicotine and alcohol abuse, aspiration of gastric fluids, diverticulum of the esophagus, (iii) broad spectrum antibiotic treatment. Quantitative cultures of BALF appears the diagnostic approach of choice in absence of histology.