International Speakers' and Key- note Presentations

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David W Denning

Professor of Infectious Diseases in Global Health

David Denning is an internationally recognized clinician with expertise in fungal diseases. He manages the UK's National Aspergillosis Centre in Manchester, the world's only such center. David Denning has published more than 500 papers, books and book chapters and lectures worldwide. His writings have been cited over 40,000 times and he has successfully lead many major international collaborative science, diagnostic and treatment projects and clinical guidelines, with subsequent publication in Nature, the New England Journal of Medicine and the Lancet. He is the Founder of two University spinout biotechnology companies– F2G Ltd (antifungal drug discovery and development) and Myconostica Ltd (molecular diagnostic tests for fungi), now owned by Lab21.

David is Chairman of the Editorial Board of the Aspergillus Website (1998-) with over 1 million pages read per month. He has chaired the Scientific Committees of several international fungal infection meetings and co-chairs the alternate year Advances Against Aspergillosis meetings, attracting ~400 delegates from >120 countries.

The impact of aspergillosis across the world – much disease unseen

David W Denning
Professor of Infectious Diseases in Global Health
Director of the National Aspergillosis Centre, The University of Manchester and President of the Global Action Fund for Fungal Infections
Email: ddenning@manchester.ac.uk

Few estimates of the global burden of aspergillosis have been made. There are an estimated 4.8 million adults with allergic bronchopulmonary aspergillosis complicating asthma (193 million adults of 334 million asthmatics total). A very small number occur in children. Severe asthma with fungal sensitisation (SAFS) probably affects around 3% of mostly adult asthmatics, or ~6 million people. Of the 76,201 estimated CF patients worldwide (not including India), 37,714 were >18 years old and among these ABPA and *Aspergillus* bronchitis are estimated to affect 17,989 (47.7%) adults and some children and teenagers. No other estimate of *Aspergillus* bronchitis has been done, but it affects mostly patients with bronchiectasis. Using old UK data, 1.2 million patients with chronic pulmonary aspergillosis following pulmonary tuberculosis are estimated with perhaps a total of 3 million because of the high frequency of COPD worldwide. At least 250,000 cases of invasive aspergillosis occur annually, most not diagnosed.

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Paul E. Verweij

Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, the Netherlands

Paul Verweij is the professor of medical microbiology and consultant microbiologist at the Department of Medical Microbiology at Radboudumc in Netherlands.

His main research interests include diagnosis of invasive aspergillosis, resistance in molds, and clinical studies of new antifungal agents.

He has published several papers on the relationship between resistance to medical triazoles in the opportunistic fungus Aspergillus fumigatus and the use of azole fungicides for crop protection and material preservation.

Management strategies for invasive aspergillosis

Paul E. Verweij

Department of Medical Microbiology, Radboud University Medical Centre, and Centre of Expertise in Mycology Radboudumc/CWZ, Nijmegen, the Netherlands

Email: M.Verweij@awepa.org

Invasive aspergillosis is an opportunistic fungal infection that affects primarily immunocompromised patients. In the past decades the prognosis for these patients has improved due to better management of underlying diseases, better diagnostic tools and more effective antifungal agents. Before the mold-active antifungal azoles were introduced the mortality of invasive aspergillosis was 65% to 70%. The most recent trials using azole-based therapy and large surveillance studies indicate a mortality rate of less than 30%. Early studies indicated that empiric antifungal therapy was a good approach to patients with persistent fever unresponsive to broad-spectrum antibacterial therapy. In the absence of sensitive diagnostic tools, such a strategy reduced treatment delay, although many patients without invasive fungal disease received antifungal therapy. Nowadays better diagnostic tools are available including computed tomography and specific biomarkers. Some centers use a pre-emptive, diagnostic-driven, approach most commonly based on the monitoring of galactomannan antigen in serum of high-risk patients. This strategy enables a better selection of patients that require antifungal therapy. This strategy is logistically challenging involving many health-care workers and different medical specialties. Alternatively antifungal prophylaxis is a strategy that can be employed, which proved to be effective in certain patient groups with hematological malignancy. The incidence of invasive aspergillosis was reduced as well as the mortality.

The choice of management strategy depends on many local factors, including the prevalence of invasive aspergillosis, the level of diagnostic support and the availability of antifungal agents. Furthermore, the local epidemiology is important. Recently azole resistance has emerged in many countries which challenges the management strategies used and requires new approaches both for early diagnosis as well as for primary therapy.

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Sülyha Hilmioğlu Polat

Department of Medical Microbiology
Faculty of Medicine, Ege University, Izmir, Turkey

Sülyha Hilmioğlu Polat, MD, is a Professor of Medical Microbiology in the Faculty of Medicine, Ege University, Izmir, Turkey.

She received her MD and Clinical Microbiology and Infectious Diseases specialist degree from the same university.

Her topic of interest is the laboratory diagnosis of fungal infections. She is one of the founder members of Turkish Society of Medical Mycology and at present she is the general secretary of the society.

Probable invasive aspergillosis and gastrointestinal mucormycosis: A case report

Süleyha Hilmioğlu-polat

Department of Medical Microbiology, Faculty of Medicine, Ege University, Izmir, Turkey

Email: uleyha56@gmail.com

Invasive aspergillosis (IA) is a life threatening opportunistic infection that usually affects immunocompromised patients. The majority of the cases are caused by *Aspergillus fumigatus*, followedby *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*. IA most commonly involves the respiratory tract, lung, and sinus; however, other organs may be also infected as a result of the hematogenous spread. Gastrointestinal (GI) aspergillosis, which is associated with high mortality, is a rare form of extra-pulmonary aspergillosis, which is most often described in the setting of disseminated disease. GI involvement is also rarely seen in mucormycosis and most reported cases are associated with malignant haematological diseases.

Herein, we present the case of a child with acute lymphoblastic leukaemia who simultaneously developed probable invasive aspergillosis and was diagnosed with GI mucormycosis by histopathologic examination. The patient referred to the Pediatric Intensive Care Unit of Ege University due to clinical deterioration and severe lower gastrointestinal system bleeding. Main symptoms were abdominal distension and rectal bleeding. The patient was diagnosed to suffer from IA owing to the strongly positive result of galactomannan test (4.73), the growth of *A. flavus* in sputum and tracheal aspirate, the radiological findings, and especially the lung involvement. Urgent surgical intervention played a key role in controlling the disease. However, it was surprising that the histological findings were consistent with mucormycosis since *Mucor* was not detected in the previous microbiological examinations.This raises questions about the actual diagnosis: Was it only IA, co-infection or breakthrough infection under voriconazole therapy?

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Macit Ilkit

Professor of Microbiology in the Faculty of Medicine at the University of Çukurova, Adana, Turkey

Macit Ilkit is a Professor of Microbiology in the Faculty of Medicine at the University of Çukurova, Adana, Turkey and serves as director of the Division of Medical Mycology.

He graduated from the same faculty and defended his Ph. D. in 1995. He has been actively involved in dermatophytes and dermatophytosis research, with an interest in epidemiology and diagnosis.

He was also one of the founders of the Society of Medical Mycology in Turkey, which was established in December 2011.

Currently, he serves as an Associate Editor/Editorial Board member for the internationally peer-reviewed journals Mycopathologia, Biomed Research International Infectious Diseases, and Medical Mycology.

Aspergillus flavus keratitis: Experience of a tertiary eye clinic in Turkey

Macit Ilkit

Division of Mycology, Department of Microbiology, School of Medicine, University of Çukurova, Adana, Turkey

Email:Macitilkit@gmail.com

Mycotic keratitis is a challenging condition in ophthalmological practice, and for those suffering from this condition treatment options are limited and many cases require surgery to maintain corneal integrity. Overall, the *Aspergillus* and *Fusarium* genera are the most common causes of filamentous mycotic keratitis worldwide. In the *Aspergillus* genus, following *Aspergillus fumigatus*, *Aspergillus flavus* (section *Flavi*) is the second most common opportunistic pathogen causing systemic infections and is the leading cause of superficial infections in humans.

Herein, we investigated four cases of mycotic keratitis caused by *Aspergillus flavus* to determine the predisposing factors, clinical presentations, and success of the therapeutic approach during July 2014-May 2015 at Çukurova University Hospital, Adana, Turkey. For all the cases, topical voriconazole was the first choice of treatment. Surgical procedures were required to control infection in three of the four cases, including intrastromal voriconazole injection for two cases and keratoplasty for one.

Predisposing factors included trauma (2 cases, 50%), contact lens wearing (1 case, 25%), and previous ocular surgery (1 case, 25%). The clinical presentations also differed, which consisted of well-limited ulcer (1 case), ulcer with an irregular feathery margin (1 case), and ulcer with satellite lesions (2 cases). The mean duration between the time of presentation and definitive diagnosis by culture was 14 days (range of duration: 8-25 days). We observed that *A. flavus* keratitis can be present with different underlying factors and clinical features. A combination of antifungal therapy and supportive surgical intervention may resolve the infection caused by *A. flavus* in the cornea.

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Willem JG Melchers

Associate Professor in Molecular Microbiology
Head of Department Medical Microbiology Laboratory,
Radboud University Medical Centre Nijmegen

Scientific Memberships:

- Netherlands Society of Medical Microbiology
- American Society for Microbiology
- Netherlands Society for Biochemistry and Molecular Biology
- European Group of Rapid Viral Diagnosis

Management:

- Head Clinical Laboratory Medical Microbiology (Chef de Laboratoire), Department of Medical Microbiology
- CEO NovioGendix Holding BV
- Head section Molecular Microbiology & Diagnostics, Department of Medical Microbiology
- Board Member Management Team Department of Medical Microbiology
- Board Member (Treasurer) Netherlands Society for Medical Microbiology (2006-2010)
- Chairman Member Concilium Molecular Medical Microbiologists (MMM) (2009-)
- Chairman Seminar Committee Graduate School Institute of Cellular Signaling (1999-2005)
- Chairman Research Committee Department of Medical Microbiology (1996-2006)
- Chairman Professional Committee Medical Microbiological Researchers (BBC) (1998-2008)
- Board Member Research Council Nijmegen Center for Molecular Life Sciences (2000-2005)
- Board Member National Committee for Medical-Biological Research Netherlands (NijmegenbUniversity-delegate) (2004-2008)
- Board Member Foundation Luis Pasteur (2000-2009)
- Educator Medical Microbiological Researchers (UMC Nijmegen) (2008-)
- Member NCMLS Research Committee - Grant-assessment (1999-2006)
- Member Dutch Working Group Molecular Diagnostics of Infectious Diseases (1999-)

The force awakens: multidrug resistance in *Aspergillus fumigates*

Willem JG Melchers

Department of Medical Microbiology, Radboud University Medical Center*, Nijmegen, the Netherlands*

Email: w.melchers@mmb.umcn.nl

The mould *Aspergillus fumigatus* can cause a spectrum of diseases in humans, ranging from allergic conditions to life-threatening invasive diseases in immunocompromised patients. The triazoles, itraconazole, voriconazole and posaconazole are the main drugs used for the management of Aspergillus diseases. Although until recently *A. fumigatus* was considered uniformly susceptible to medical triazoles, there are increasing reports of acquired resistance, most frequently due to single nucleotide polymorphisms in the Cyp51A-gene. In the Netherlands azole resistance was first reported in 1998 and since then the frequency has increased dramatically. Recently it was shown that azole resistance in *A. fumigatus* is endemic in the Netherlands and that patients with azole-resistant invasive aspergillosis have a probability of 88% of dying within 12 weeks of diagnosis. A highly dominant resistance mechanism was found (TR_{34}/L98H) which was present in over 90% of clinical resistant isolates. Resistance was observed in patients without previous azole exposure and TR_{34}/L98H was found in environmental *A. fumigatus* isolates. It was hypothesized that resistance may have emerged through exposure to 14α-demethylase inhibitors (DMIs). Thirty-one DMIs, that have been authorized for use in the Netherlands between 1970 and 2005, were investigated for the presence of cross-resistance to medical triazoles. Furthermore, CYP51-protein homology modeling and molecule alignment studies were performed to identify similarity in molecule structure and docking modes. Five triazole DMIs, propiconazole, bromuconazole, tebuconazole, epoxiconazole and difenoconazole, showed very similar molecule structures to the medical triazoles and adopted similar poses while docking the protein. These DMIs also showed the greatest cross-resistance and, importantly, were authorized for use between 1990 and 1996, directly preceding the recovery of the first clinical TR_{34}/L98H isolate in 1998. Through microsatellite genotyping of TR_{34}/L98H isolates we were able to calculate that the first isolate would have arisen in 1997, confirming the results of the abovementioned experiments. Azole-resistant *A. fumigatus* isolates appear to remain virulent and are capable of causing invasive disease in patients at risk. The efficacy of azole compounds against azole-resistant isolates, with different resistance mechanisms, has been investigated in experimental models of invasive aspergillosis. These indicate that the minimal inhibitory concentration (MIC) has major impact on the efficacy of the azole. This indicates that the rapid diagnosis and identification of mutations related to resistance may influence the individual patient management and the success rate of treatment. This seems even the more important as recently a second resistance mechanism TR46/Y121F/T289A has emerged in the Netherlands, following a similar pattern to that of TR34/L98H. In this presentation an overview will be presented on the development and emerging of azole resistance in *A. fumigates*. Furthermore some new directions for future research into azole resistance will be discussed.

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Emmanuel Roilides

Professor of Pediatrics – Infectious Diseases
Head, Infectious Diseases Unit and Research Laboratory,
University of Thessaloniki, Greece

Dr. Emmanuel Roilides holds doctoral degrees in Medicine (MD) and Microbiology (PhD) from Athens University (AU) School of Medicine, and Board Certifications in Pediatrics and Pediatric Infectious Diseases from the Greek Ministry of Health. Following extensive training at the NIH, he was recruited to Aristotle University School of Medicine, where he rose to become Professor of Pediatrics, Chief of Pediatric Infectious Diseases, and Founding Director of the Infectious Diseases Research Laboratory. The author or co-author of >450 publications, Emmanuel has made fundamental, extensive, and enduring advances in four key areas: innate host defenses against Candida spp., Aspergillus spp., and emerging fungal pathogens; epidemiology and treatment of pediatric mycoses; mentoring postdoctoral research fellows in pediatric infectious diseases; and fulfillment of key leadership positions in scientific societies. As a recipient of numerous grants and research awards, he has built the leading laboratory of innate host defenses and pediatric mycology in Greece and one of the premier programs in EU. Emmanuel has served in key leadership positions in the European Confederation for Medical Mycology, European Society for Pediatric Infectious Diseases, and International Immunocompromised Host Society. He is a Fellow of the Infectious Diseases Society of America, serves on editorial boards of six biomedical journals, and reviewer for >50 journals. He has trained >25 post-doctoral fellows with dissertations.

Aspergillosis in pediatric patients

Emmanuel Roilides
Aristotle University, Thessaloniki, Greece
Email: roilides@med.auth.gr

Aspergillus species may cause a broad spectrum of conditions in immunocompetent or immunodeficient children, ranging from transient asymptomatic colonization, pulmonary hypersensitivity reactions, colonization of airway cavities, and life-threatening tissue invasive infection. Invasive aspergillosis usually occurs in patients with predisposing immune qualitative or quantitative deficiency most importantly prolonged neutropenia, chronic granulomatous disease (CGD) or conticosteroid therapy. The most common site of invasive aspergillosis is the lung, with dissemination particularly to the central nervous system occurring in approximately 30% of cases. *Aspergillus fumigatus* and *A. flavus* are the most frequent species, whereas *A. nidulans* is isolated more frequently in patients with CGD. As in adults, cornerstones for successful management of invasive aspergillosis include the prompt initiation of appropriate antifungal therapy, reversal of the patient's underlying deficiency in host defenses if exists and is feasible, and, in select circumstances, surgical interventions.

Tissue culture and histopathology remain the most significant diagnostic modalities of aspergillosis. In addition, non-culture methods such as determination of galactomannan in serum, BAL or CSF as well as DNA detection are methods that have variable diagnostic utility in pediatric patients especially when non-*Aspergillus* filamentous fungi are considered.

Options for first-line antifungal treatment of invasive aspergillosis in patients 2 years or older consist of voriconazole and liposomal amphotericin B; for children younger than 2 years, voriconazole is not indicated, and liposomal amphotericin B is the only option with an existing pediatric dosage and safety profile.

Primary chemoprophylaxis of invasive aspergillosis may be indicated in high-risk populations with incidence rates of approximately 10% or higher. These may include patients with acute leukemia, patients with bone marrow failure syndromes, and those following allogeneic hematopoietic stem cell transplantation, particularly when immunosuppression is augmented for graft-versus-host disease. In addition, patients with primary immunodeficiency CGD should be on antifungal prophylaxis with either itraconazole or posaconazole.

Except for patients with hematological malignancies and those with CGD, other pediatric patients at risk of aspergillosis, such as patients with solid organ transplant (mainly lung or liver), premature neonates, and those with cystic fibrosis are treated with specific considerations if aspergillosis occurs.

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Seyedmojtaba Seyedmousavi

Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH), Bethesda, MD, USA.

Amir (Seyedmojtaba) Seyedmousavi is a Ph.D. Medical/Molecular Mycologist and Research Scientist in Medical Microbiology & Infectious Diseases. His current research, at the lab of Dr. Kwon-Chung at the National Institutes of Health, Bethesda, Maryland, focuses on molecular mycology, pathobiology, and immunology of chronic and invasive aspergillosis caused by multi-resistant cryptic species of *Aspergillus.*

Amir was born in Khomam, a small City in Rasht County, Gilan Province, North of Iran on the 21st September 1977. After finishing high school (1995) in "Biology and Natural Sciences" in his hometown, he completed his undergraduate studies at the University of Tehran, Iran in 2002, followed by a Ph.D (Cum Laude) in Mycology in 2006, under the supervision of Prof. S.J Hashemi and Prof. A.R. Khosravi. He was also appointed as Lecturer and Assistant Professor of Medical Mycology in Iran between 2002 to 2009.

He then moved to Netherlands and did his first postdoctoral research (2009-2010) in molecular mycology, taxonomy and phylogeny of melanized fungi in the lab of Prof. Sybren de Hoog at the CBS-KNAW Fungal Biodiversity Centre, Utrecht, the Netherlands.

Between 2010 to 2016, he also completed his postdoctoral training programs subject *Aspergillus fumigatus*, molecular epidemiology of Antifungal-resistance and preclinical Pharmacokinetics and Pharmacodynamics (PK/PD) strategies to treat invasive fungal infections at the Departments of Medical Microbiology, RadboudUMC, Nijmegen, and ErasmusUMC, Rotterdam, the Netherlands, under supervision of Prof. Paul Verweij, Prof. Johan Mouton and Dr. Willem Melchers. In 2014 Amir also succeeded with honor in a second Ph.D examination, subject Medical Mycology and PK/PD, at the Radboud University Medical Center, Nijmegen, The Netherlands.

He teaches internationally on a number of basic and advanced postgraduate courses/workshops on various aspects of Medical and Veterinary Mycology.

Since 2014, he serves as an Editor of Medical Mycology journal, published by Oxford University Press on behalf of International Society for Human and Animal Mycology (ISHAM) (http://mmy.oxfordjournals.org/)

He is also Ambassador of Science (Science Diplomat) to IRAN at American Society for Microbiology (www.asm.org).

Pharmacokinetics and pharmacodynamic (PK/PD) strategies for treatment of patients underlying azoleresistant aspergillosis: from the genotype to the bedside

Seyedmojtaba Seyedmousavi

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), BG 10 RM 11C106, 10 CENTER DR, 9000
Rockville Pike, Bethesda, MD 20892, United States of America
Email: Seyedmousavi@nih.gov , Seyedmousavi@gmail.com

Azole resistance is an emerging problem in *Aspergillus fumigatus*, and is associated with a high probability of treatment failure.

An azole resistance mechanism typically decreases the activity of multiple azole compounds, depending on the mutation. Here we discuss the relation between resistance genotype and phenotype, and further discuss our preclinical and translational modeling experience applying pharmacokinetic and pharmacodynamic (PK/PD) principles on currently available systemic antifungals to optimize treatment of patients underlying azolesusceptible and azole–resistant aspergillosis.

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