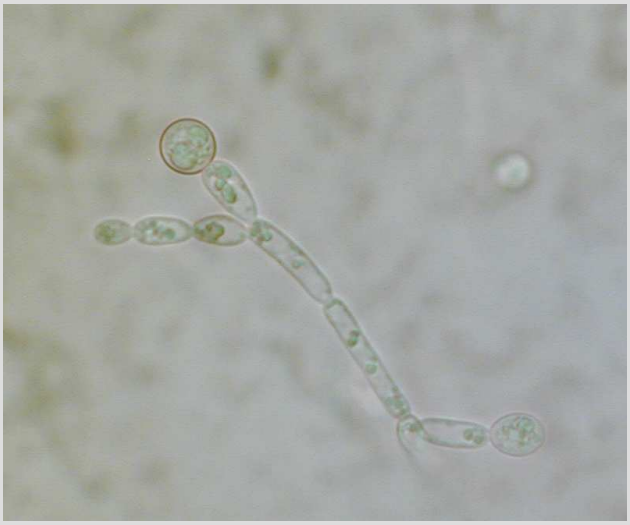
Nordic Society for Medical Mycology

6th Nordic Society for Medical Mycology Scientific Meeting



Programme and Abstracts

Fungal infections today: Diagnostic and treatment challenges

Copenhagen, Denmark, March 13, 2009

Introduction

Dear Friends and Colleagues,

It is with great pleasure we welcome you to the 6th Nordic Society for Medical Mycology scientific meeting. The meeting this time takes place at IDA Conference Centre at Kalvebod Brygge in the centre of Copenhagen.

This year we open the meeting focussing on *Aspergillus* and other mould infections as these pose increasing challenge due to their high mortality, their increasing numbers, the difficulties we face establishing the diagnosis and their emerging resistance. Next we turn to the more clinical aspect of the fungal infections – what are the current treatment and how do we monitor the patient and evaluate treatment response?

We are proud to welcome three European experts William Hope from the University of Manchester in the UK, Bart-Jan Kullberg from the Nijmegen University Centre for Infectious Diseases in the Netherlands and Georg Petrikkos from Laiko General Hospital in Athens in Greece as key-note speakers together with a distinguished faculty of speakers from the Nordic countries who are ready to share their knowledge in their area of expertise.

At the end of the meeting we hope that every participant has learned something new, has been refreshed on something old and has had the opportunity to meet other Nordic colleagues within the field of medical mycology.

On behalf of the NSMM board

Ditte Saunte
Treasurer for NSMM

Maiken Cavling Arendrup
President for NSMM

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This meeting would not have been possible but for the generous support of our sponsors. We gratefully acknowledge their contributions.

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Programme

Fungal infections today: Diagnostic and treatment challenges.

Opening Ceremony & Aspergillosis and other Mould infections

10:00 **Opening remarks and welcome**
Maiken Cavling Arendrup, president, NSMM.

10:15 **Aspergillosis: current status**
William Hope, MD, MBBS, FRACP, FRCPA, PhD, University of Manchester, UK

10:45 **Resistance in *Aspergillus*: An emerging problem?**
Maiken Cavling Arendrup, MD, PhD, Head of Unit of Mycology, Statens Serum Institut, DK

11:00 **News from the mycology lab.**
Malcolm Richardson, PhD, FIBiol, FRCPath, Associate Professor in Med Mycology, Dept of Bacteriology & Immunology, Haartman Institute, University of Helsinki, FI

11:25 Coffee break

Keynote Lectures

11:45 **When is failure failure? – Case presentation and discussion**
Bart-Jan Kullberg, MD, FIDSA, Professor of Med and Infect Dis, Head of the Division of Infect Dis, Nijmegen University Centre for Infect Dis., Nijmegen, NL

12:30 **Imported mycosis: An update**
Georg Petrikkos, Professor of Internal Med and Infect Dis, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, GR

13.00 Lunch

Update on treatment guidelines

14:00 **Candidiasis**
Ingvild Norøy, MD, PhD, Dept Clin Microbiol, Rigshospitalet, Oslo, NO

14:20 **Aspergillosis**
Juha Salonen, MD, PhD, Chief physician in Infect Dis, Päijät-Häme Central Hosp, Lahti, FI

14:40 **New therapeutical options: Inhalation, new compounds and combination**
Jens Schierbeck, MD, Chief physician in Intensive Care Unit, Odense Universitets Hospital, DK

15.00 **Muco-cutaneous infections**
Ditte Saunte, MD, PhD & Else Svejgaard, Dr.sci., Dept Dermatovenerology, Bispebjerg Univ. Hospital, DK

15:30 Coffee break

Free Papers

16:00 ***Aspergillus fumigatus* infection in a pt. with Wegener's granulomatosis (WG).**
Larsen L, & Rasmussen, N. Mould Lab, Danish Technological Inst. & Depf Otolaryngology, Rigshospitalet, DK

16:15 **Primary Cutaneous Zygomycosis: An Emerging Clinical Entity**
Chander J, Kaur J, Gulati N, Attri A and Mohan H. Dept Microbiology, Surgery and Pathology, Government Medical College Hospital, Chandigarh, India

Annual General Meeting for NSMM

17:00 General Assembly for members of the society

18:00 Farewell Dinner (25 €)

Abstracts

Aspergillosis and other Mould infections

Aspergillosis - Current status

William Hope, MD, MBBS, FRACP, FRCPA, PhD
Clinical Senior Lecturer and Honorary Consultant in Infectious Diseases,
University of Manchester, UK

Invasive fungal infections are leading causes of morbidity and mortality in immunocompromised patients. The epidemiology of these infections in profoundly immunocompromised patients is well described. *Aspergillus* spp. are the most frequent and medically important moulds. Increasingly, invasive aspergillosis is recognized outside classical risk groups, such as critically ill patients in the intensive care unit or patients receiving newer immunosuppressive agents such as TNFα antagonists. Chronic pulmonary aspergillosis complicates the course of patients with a wide range of underlying chronic respiratory conditions. Pre-existing pulmonary cavities are colonized by *Aspergillus* spp. There is usually a progressive increase in the size of cavities with time, but some patients develop a profound fibrotic reaction. Triazole resistance is increasingly seen, and probably results from the inability to achieve fungicidal concentrations within pulmonary cavities.

This talk will focus on recent advances in the pathogenesis, diagnosis and treatment of invasive aspergillosis. Challenges in the diagnosis of the more uncommon manifestations of invasive aspergillosis, including the non-neutropenic critically ill patient in the intensive care unit will be discussed. Some of the issues in the management of patients with chronic pulmonary aspergillosis, including the approach to treating patients with triazole resistance will be discussed.

Resistance in Aspergillus: An emerging problem?

Maiken Cavling Arendrup, MD, PhD, Head of Unit of Mycology,

Statens Serum Institut, DK

Susceptibility testing of conidia forming moulds has recently been standardised but no breakpoints have yet been established. Whilst the endpoint reading is straight forward for azoles and amphotericin B due to the growth versus no growth pattern of inhibition, the endpoint determination for the echinocandins is more difficult to determine due to significant trailing growth.

Recently, a number of reports have indicated that azole resistance is emerging in clinical *Aspergillus* isolates. Azoles act by blocking the ergosterol (an essential cell membrane component) biosynthetic pathway through binding to and inhibition of lanosterol 14-α demethylase enzyme encoded by the *erg11/cyp51*A gene. Azole resistance may be restricted to itraconazole or involving cross-resistance to other tri-azoles as well, and has been associated with a number of hot spots in the *cyp51*A gene with or without simultaneous tandem repeat in the *cyp51*A promoter region. The following specific mutation – resistance patterns have been characterised:

- Resistance to ITC and PSC associated with amino acid substitutions at Cyp51A glycine 54 (Gly 54).
- A pattern of resistance to ITC and high VRC, RVC, and PSC MICs (strains exhibiting this susceptibility profile harbor amino acid substitutions at methionine 220 [Met 220]).
- A pattern of azole cross-resistance associated with higher *cyp51A* expression produced by a tandem repeat (TR) of a 34-bp sequence in the *cyp51A* gene promoter in combination with an amino acid substitution at Cyp51A leucine 98 (TR-L98H).
- A triazole cross-resistance related to an amino acid change at Cyp51A glycine 138 to cysteine (G138C).

Noteworthy, azole resistance have been found not only in patients after long term treatment but also in *Aspergillus fumigatus* from azole naïve patients and in environmental *A. fumigatus* isolates in the Netherlands.

Resistance to caspofungin has been described in clinical *Candida* isolates, and recently, breakthrough infections with *A. fumigatus* isolates with elevated MECs have been reported. Some of these have mutations in the *FKS*1 gene encoding a subunit of the β-1,3-D-glucan synthase enzyme involved in the cell wall synthesis, a mechanism that has been detected in clinical *Candida* isolates with reduced susceptibility to caspofungin. Yet other resistant mutants had wild type gene sequence, function, level and caspofungin susceptibility of the glucan synthase enzyme itself. In a recently published case the echinocandin resistance was linked to an over-expression of the glucan enzyme.

Taken together recent data indicate a growing need for routine susceptibility testing of clinical *A. fumigatus* isolates for guidance of treatment and the need for surveillance of susceptibility epidemiology of *Aspergillus* isolates in order to monitor changes in the susceptibility pattern of *Aspergillus* in general.

What's new in the Mycology Lab?

Malcolm Richardson,
University of Helsinki, and Helsinki University Central Hospital,
Finland.

Serious infections are being reported with an ever-increasing array of fungal pathogens. It is now clear that there are no non-pathogenic fungi; virtually any fungus can cause a lethal mycosis in an immunocompromised host. It is absolutely essential that mycology laboratories provide a wide array of diagnostic capabilities for the early detection of opportunistic fungal infections. Successful diagnosis and management of such infections in the compromised patient are highly dependent on a team approach involving clinicians, mycologists and pathologists. Although culture and histopathology remain the primary means of diagnosing fungal infections, there continues to be a need for more rapid, non-culture methods for diagnosis. Tests for detection of antibodies, rapid detection of specific fungal antigens, secondary metabolites, and fungal species-specific RNA or DNA sequences have the potential to yield rapid diagnostic information that can guide the early and appropriate use of antifungal therapy. Although a great deal of progress has been made in these areas, the true impact on the diagnosis and outcome of invasive fungal infections has yet to be realized.

Many commercial kits are now having an enormous impact on the capabilities of diagnostic mycology laboratories. Direct nucleic acid probes and amplification-based molecular approaches provides more rapid and objective identification of yeasts and moulds compared with traditional phenotypic methods. These chemiluminescent-labeled DNA probes (Accuprobe, Gen-Probe) specific for target fungal rRNA and are commercially available. Standard molecular analysis of filamentous fungi is done by sequencing rDNA Internal Transcribed Spacers (ITS), supplemented with data from more variable gene regions, such as introns in the β-tubulin gene. Subsequently a comparison with sequences deposited in GenBank is undertaken in view of species identification. However, GenBank depositions are poorly supervised and for less common fungi this system is far from adequate. It is essential to use dedicated, validated databases.

Many commercial ELISA techniques are now available which detect anti-Aspergillus and anti-Candida antibodies in an effort to diagnose infections caused by these organisms, for example, a new anti-Candida antibody (antienolase and intracellular antigens) detection ELISA-based kit (Syscan 3) has been evaluated. However, it is clear that the diagnosis of invasive disease cannot be made by a single test for antibody alone.

Although tests to detect fungal antigens or secondary metabolites have been widely available for 30 years and some have been standardized, issues still remain concerning the sensitivity and specificity of the various tests in certain patient populations. Currently, mycology laboratories use an array of tests for various fungal cell wall components such as α- and β-mannan, β-1,3-glucan, and galactomannan. New test formats for invasive aspergillosis are becoming available. A monoclonal antibody that binds to an antigen of *Aspergillus* secreted during active growth has been used to develop an immunochromatic lateral-flow device for the rapid (15-min) detection of *Aspergillus* antigens in human serum. The test is highly specific.

Despite an enormous amount of effort over the past 20 years molecular methods are used in only about 5% of laboratories providing diagnostic services in medical mycology. It has not been demonstrated convincingly that PCR can compensate for the limitations of culture and histopathology in the rapid diagnosis of invasive fungal infection and produce a definite impact on invasive fungal infection-related mortality.

Strain typing as a routine clinical laboratory procedure is becoming more familiar to mycologists. Typing *Aspergillus* and *Candida* strains on the basis of DNA sequences at multiple loci has greatly advanced study of the epidemiology and evolutionary phylogenetics of fungal pathogens and will become more routinely used. We have used this technique to type strains isolated over many years from APECED patients where the sequences of bases in PCR fragments of seven housekeeping genes (*AAT1a, ACC1, ADP1, MPI1b, SYA1, VPS13,* and *ZWF1b*) were determined. This typing approach showed strain maintenance with microevolution in APECED patients suffering from chronic mucocutaneous candidosis.

It is essential that medical mycology laboratories harness and modify all available test formats already used routinely in clinical bacteriology and virology, and endeavour to design new approaches to detect and identify fungal pathogens.

Keynote Lectures

Responses to Therapy and Study Outcomes in Invasive Fungal Diseases: When is failure failure?

Bart-Jan Kullberg, MD, FIDSA,
Professor of Med and Infect Dis,
Head of the Division of Infect Dis,
Nijmegen University Centre for Infect Dis., Nijmegen, NL

The European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) have published authoritative consensus criteria on definitions of invasive mycoses for clinical research. However, little has been published on criteria for evaluating therapeutic responses, both in clinical practice and in randomized trials. There is an important need for generating consensus definitions of outcomes of invasive mycoses that will form a standard for evaluating treatment success and failure in clinical trials.

Although specific criteria for therapeutic success vary among the major invasive mycoses, global response requires survival and a positive effect on fungal disease. With certain invasive mycoses (e.g., candidemia), cure is the goal of therapy. The term 'documented clearance' is more appropriate than 'sterilization' since the yield of cultures can be variable, especially while receiving antifungals. In cryptococcosis, a response early after start of therapy may be termed 'successful control of disease', leaving the correct implication that cure may not have been achieved. Indeed, the best proof of cure for these fungal diseases is absence of relapse after cessation of therapy. The observation period to meet this high standard may require years and would be impractical for therapeutic trials.

Evaluation of response to therapy in invasive mould disease is difficult. Some of the clinical and radiological manifestations of invasive aspergillosis may not necessarily indicate clinical deterioration, but merely result from neutrophil recovery. Examples of hemoptysis, increasing volume of lesions on CT-scan and progressive cavitation have been documented during neutrophil recovery and have been incorrectly equated with fungal disease progression. There is inadequate knowledge about the course of serum galactomannan assays during response to treatment, although serial GM measurements are considered to be a highly promising therapeutic marker.

The primary analysis of trials on antifungal therapy should include all patients in the intent-to-treat (ITT) or modified intent-to-treat (MITT) groups. Completion of the assigned treatment regimen is generally a requirement for a successful outcome. However, it is also reasonable to make provision for 'success with modification' as was done in the trial comparing voriconazole with amphotericin B therapy for invasive aspergillosis. This trial, in effect, evaluated two different treatment strategies rather than two different drugs.

Imported mycosis: an update

George L Petrikkos
Professor of Internal Medicine and Infectious Diseases
National Kapodistrian University of Athens
Greece

In the era of increasing world traveling, climate changes, immigration and HIV infection, the diagnosis of rare infections imported to Europe from endemic areas is becoming more probable.

The most common imported fungal infections are histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and penicilliosis marneffei. They usually present with pulmonary manifestations often indistinguishable from tuberculosis or sarcoidosis, and disseminated disease in the immunocompromised infecting almost all organs

Histoplasmosis

Is caused by *Histoplasma capsulatum* and has been reported form all continents.It is endemic in North, Central and South America, Africa, India and Southeast Asia. *H. capsulatum* grows in soil and material contaminated with bat or bird droppings. Infection occurs by breathing the spores and outdoor activities like cave exploration increase the risk. More than 95% of healthy remain asymptomatic. When a high inoculum of spores is inhaled, 50 – 100% of patients develop acute pulmonary histoplasmosis, a “flu-like” illness. Disseminated disease occurs in the immunocompromised and the extremes of age. Before the HAART era, the prevalence in HIV infected was up to 30% in the endemic areas.

In the last survey of the ECMM Histoplasmosis working group (Ashbee et al., Med Mycol. 2008 Feb;46(1):57-65), 118 cases of histoplasmosis were reported in Europe in a period of 5 years (Jan 96 – Dec 99). Fifty four additional cases were reported from various European countries during 1998 – 2008 (PubMed query). Most of the patients were immunocompromised and had traveled to endemic areas, except 8 cases reported from Italy, Germany and Turkey which appear to be autochthonous.

Notable observations during the survey were the reactivation of the disease up to 50 years after the initial infection and transmission of the infection by a transplanted liver.

The golden standard for laboratory diagnosis is culture from blood, bone marrow or tissues. Urine antigen test is a rapid, highly sensitive test in disseminated disease and a newly developed Real-Time PCR seems promising.

Evidence based guidelines for the management of patients with histoplasmosis have been prepared by an Expert Panel of the Infectious Diseases Society of America (Wheat et al, CID 2007;45:807-25).

Coccidioidomycosis

Coccidioidomycosis is caused by the dimorphic fungi of the genus *Coccidioides* (*C. immitis and C. posadasii)*, which are endemic in desert regions of the southwestern United States, and Central and South America. Outbreaks occur following dust storms, earthquakes, and earth excavation where dispersion for arthroconidia is favored.

Due to protean manifestations primary infection is frequently unrecognized. However, disseminated infection can occur. Meningitis is the most lethal complication of coccidioidomycosis and thus is crucial to recognize.

About 60% of infections are asymptomatic, when symptoms are present it is usually a self-limited influenza-like illness. Cutaneous manifestations of primary coccidioidal infection include erythema nodosum and erythema multiforme. The most significant of risk factors is major suppression of cellular immunity, as in HIV infection, organ transplantation, or high dose glucocorticoid administration.

Only 5 cases have been reported in Europe from 1998 – 2008, although an increase in incidence has been reported in the USA for reasons not fully understood.

Most routine laboratory findings are unremarkable, with eosinophilia in approximately one quarter of patients.

Isolation of *Coccidioides* species in culture definitively establishes the diagnosis, even in patients with relatively mild pneumonia. Direct examination of the smear with KOH preparation or calcofluor white staining is helpful. Serologic testing is helpful for making the diagnosis and for monitoring patients on therapy.

Treatment should be given to patients with, or at high risk for, the more severe forms of the disease and evidence-based guidelines have been issued by an Expert Panel of the Infectious Diseases Society of America. (Galgiani et al, CID 2005;41: 1217-23).

Paracoccidioidomycosis

Paracoccidioidomycosis is endemic in South America and is caused by *Paracoccioidis brasiliensis*. In Europe the disease is very rare and only 11 cases have been reported in the literature since 1979, as infections in travelers to Latin America.

The diagnosis can be carried out by direct examination of samples revealing the presence of budding yeasts, as well as culture at 25^{o}C and 37^{o}C.

Antifungals like the sulfamethoxazole-trimethoprime combination, amphotericin B, but especially azole derivatives are used in the therapeutic management of patients.

Penicilliosis marneffei

Penicillium marneffei is the only dimorphic penicillium and is endemic in Southeast Asia in the Guangxi province of China, Hong Kong, and Taiwan. The first natural human infection was reported in 1973. Humans and bamboo rats are the only known animal hosts. Disseminated *P. marneffei* infection develops in immunocompromised individuals, especially those with HIV infection and those with acquired cellular immune deficits (hematologic malignancies, transplant patients, and those treated with steroids or cytotoxic agents). *P. marneffei* is the third most common opportunistic infection in HIV-infected patients in Southeast Asia, following cryptococcosis and extrapulmonary tuberculosis. The CD4 count at the time of diagnosis is usually <50 cells/µl.

In Europe, 14 cases have been reported since 1993, all in HIV patients.

The most common clinical signs and symptoms of disseminated disease include fever, weight loss, painful non-productive cough, skin lesions, hepatosplenomegaly, and generalized lymphadenopathy. Cases of pericarditis, pleurisy, osteomyelitis, and arthritis due to *P. marneffei* have also been reported. Anemia is the most common laboratory finding.

Definitive diagnosis is made by culture of the fungus from blood, skin biopsy, bone marrow, or lymph nodes.

For the patient with mild to moderate infection, antifungal therapy with itraconazole is recommended. For the patient with severe disseminated disease, suggested therapy is with amphotericin B followed by itraconazole.

Blastomycosis

Blastomycosis is a systemic pyogranulomatous infection, primarily involving the lungs, which arises after inhalation of the conidia of *Blastomyces dermatitidis*.

Most cases of blastomycosis have been reported in North America. Endemic areas include the southeastern and south-central states bordering the Mississippi and Ohio River basins, the mid-western states and Canadian provinces bordering the Great Lakes, and a small area in New York and Canada along the St. Lawrence River. Recent reports show increase in incidence in some of these regions. Outside of North America, blastomycosis has been reported most frequently in Africa with occasional cases identified in Mexico, Central and South America, India, and the Middle East.

It is very rare in Europe. Our knowledge of the epidemiology of blastomycosis remains incomplete because of the lack of well-characterized antigens for skin testing or for sero-epidemiologic studies.

Blastomycosis of the lung can be asymptomatic or manifest as acute or chronic pneumonia. Haematogenous dissemination frequently occurs. Extra-pulmonary disease of the skin, bones, and genitourinary system is common and almost any organ can be infected.

For therapy, evidence based guidelines have been issued by an Expert Panel of the Infectious Diseases Society of America. (Chapman et al, CID 2008; 46: 1801-12). Amphotericine B formulations or itraconazole are the drugs of choice according to the severity of the disease.

Given the rarity of imported systemic mycoses, differential diagnosis may be extremely difficult. More awareness of these otherwise curable diseases could facilitate diagnosis. Early initiation of therapy could prevent considerable morbidity and mortality

Update on treatment guidelines

An update on the treatment of candidiasis - in a Nordic setting

Ingvild Nordøy MD, PhD,
Rikshospitalet,
Oslo
Norway

Two factors are essential in deciding what therapy to use for an infection: first, the knowledge of the epidemiologic characteristics in your setting. Second, the knowledge of host factors in the patient you are treating.

In the Nordic countries, with the exception of Denmark, the incidence of candidaemia is still quite low. From recent publications, the incidence is increasing, but we lack knowledge of a correlation to an increase in certain patient populations (e.g. transplant recipients etc.). *C. albicans* is still the most common *Candida* species encountered. In certain populations, *C. parapsilosis* (newborn) and *C. glabrata* (the elderly) are the most common non-albicans species. Only a few small studies have been made on candidaemia in specific patient populations. Problems of resistance that are not of innate nature are rare.

Treatment strategies for candidaemia are the following: targeted, preemptive, empiric and prophylactic. These strategies are considered, in a Nordic setting, with the newly published IDSA guidelines for the management of *Candida* infections and with guidelines published by several European authors. For targeted and empiric therapy fluconazole or echinocandins are considered the recommended treatment options in the non-neutropenic patient, while echinocandins or lipidformulated amphotericin B are the options in the neutropenic patient. Lipidformulated amphotericin B, fluconazole or voriconalzole are alternative treatment options. Prophylaxis may not be warranted as the incidence of candidaemia in all settings in our countries is low.

Aspergillosis

Juha Salonen MD, PhD

Chief physician in Infect Dis, Päijät-Häme Central Hosp, Lahti,

FI

No Abstract Submitted.
A pdf copy of the presentation is available at www.nsmm.nu

New therapeutical options: Inhalation, new compounds and combination.

Jens Schierbeck, MD, Chief physician in Intensive Care Unit,
Odense University Hospital, DK.
Clinical Associate Professor, University of Southern Denmark.

Administration of nebulised drugs achieves high local concentration, avoiding undesirable systemic effects and drug interactions. Prophylaxis with aerosolised lipid-based Amphotericin B seems to have several advantages over amphotericin B deoxycholate: it can be administered at much longer intervals and is equally effective and better tolerated. Prophylactic use of aerosolized amphotericin B in patients undergoing heart or lung transplantation has demonstrated no serious adverse effects, and lead to a significant reduction in the rate of pulmonary mycosis. Although several studies have been published using aerosolised Amphotericin B, data remain inconclusive owing a lack of standardisation of administration procedures and dosing. Furthermore the method of drug delivery has not been explored in treatment of established fungal lung disease.

Invasive fungal infections are associated with significant morbidity and mortality among immunocompromised patients. Combination antifungal therapy as a concept appears attractive as a life-saving measure, since it offers the possibility of an extended anti-fungal spectrum, of synergy or at least additive effect, and perhaps even reduced dosing with potential reduction in toxicity.
Combination therapy could be an alternative with improved efficacy to monotherapy for patients with invasive infections that are difficult to treat, such as those due to multi-resistant species and for those who fail to respond to standard treatment. In the recent published IDSA guidelines "Clinical practice guidelines for the management of candidiasis" an antifungal combination therapy is only mentioned in the context of Candida endophthalmitis and meningitis because the combination of Amphotericin B and flucytosine results in an in vitro synergism and a high CSF flucytosine concentration[1].
Clinical randomised studies on invasive Candida infection are few and not encouraging. In the largest study on 219 nonneutropenic patients Rex and co-workers demonstrated that the combination of fluconazole plus Amphotericin B was not antagonistic compared with fluconazole alone, but the combination trended toward improved success and more rapid clearance from the bloodstream[2].
For patients with progressive aspergillosis despite monotherapy, the addition of a second agent, such as an echinocandin, may be reasonable. In the context of invasive aspergillosis the clinical evidence comes from relatively small retrospective case series or prospective open-label studies, including studies with caspofungin-voriconazole combination. Results concerning potential relevant synergy do not permit definite conclusions.
In a newly published paper van de Sande et al compared voricinazole, anidulafungin and combination therapy in advanced invasive pulmonary aspergillosis in transiently neutropenic rats. Combining both agents did not significantly improve therapeutic outcome.

1) Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD; Infectious Diseases Society of America. Clin Infect Dis 2009;48(5):503-35.

2) A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S, Brass C, Vazquez JA, Chapman SW, Horowitz HW, Zervos M, McKinsey D, Lee J, Babinchak T, Bradsher RW, Cleary JD, Cohen DM, Danziger L, Goldman M, Goodman J, Hilton E, Hyslop NE, Kett DH, Lutz J, Rubin RH, Scheld WM, Schuster M, Simmons B, Stein DK, Washburn RG, Mautner L, Chu TC, Panzer H, Rosenstein RB, Booth J; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis 2003;36(10):1221-8.

3) Combination therapy of advanced invasive pulmonary aspergillosis in transiently neutropenic rats using human pharmacokinetic equivalent doses of voriconazole and anidulafungin. van de Sande WW, Mathot RA, Ten Kate MT, van Vianen W, Tavakol M, Rijnders BJ, Bakker-Woudenberg IA. Antimicrob Agents Chemother 2009 Feb 23. [Epub ahead of print]

Update on treatment guidelines Muco-cutaneous infections

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Muco-cutaneous infections comprise infections caused by dermatophytes, some non-dermatophyte moulds, and yeast, primarily *Candida albicans* and *Malassezia* species. Superficial mycoses are frequent and usually easily treated. Thus topical antimycotic preparations containing terbinafine, azoles, and ciclopirox are all effective in most cases of localized dermatophytosis and intertriginous *Candida* infections likewise respond well to topical treatment with azoles or ciclopirox. However, some patient groups constitute pronounced therapeutic challenges. The focus will be on these:

1. Tinea capitis. In DK the dermatophytes causing tinea capitis are *Microsporum canis, M. audouinii, Trichophyton mentagrophytes, T. verrucosum, T. violaceum,* and *T. tonsurans.* Infections with zoophilic species usually respond well to standard treatment with terbinafine, and so do infections with anthropophilic species, which, however, may cause difficult manageable epidemics. Further, therapeutic failures have been observed in some infections caused by *Microsporum* species. Systemic therapy with griseofulvine, terbinafine or azoles is always indicated in tinea capitis and combination with a topical drug is often recommended. Guidelines will be given.
2. Onychomycosis. The cause of onychomycosis is mainly dermatophytes i.e. *Trichophyton rubrum* and *T. mentagrophytes.* In a few percent non-dermatophyte moulds or yeast act as the pathogen. The clinical picture varies from superficial infection to involvement of the entire nail with matrix and nail bed. Standard treatment is systemic with terbinafine or itraconazole eventually combined with a topical antimytotic and removal of infected nail tissue with a file or surgery. Non-dermatophyte molds such as *Fusarium, Scopulariopsis brevicaulis, Aspergillus* and *Scytalidium* may also cause very refractory nail infections clinically indistinguishable from dermatophytosis. Systemic treatment is often unsatisfactory. Avulsion of infected nail tissue combined with a topical antimycotic drug may be useful.
3. Vulvovaginal Candidosis is most often an uncomplicated acute disease (VVC) and experienced by most adult women one or more times during life. It is caused by *Candida albicans* and treatment with fluconazole systemically for one day is nearly always effective. Topical azoles are likewise effective. However, a small group of patients develop a recurrent or complicated course (RVVC) where non-albicans species are involved. Antimycotic therapy has to be directed according to the resistance pattern of the isolated microorganism and to be maintained for weeks to months.
4. *Malassezia* related disorders. Pityriasis versicolor is an infection with *Malassezia,* where the fungus is present in the lesions as yeast and hyphae. In other disorders such as seboroic dermatitis, head-and-neck dermatitis, and *Malassezia* folliculitis only yeast cells are observed. In the first and second the fungus is responsible for an inflammatory reaction (eczema), in the latter the yeast is occluded in the follicle causing a local inflammation (folliculitis). Azoles, topical and systemic, are effective in all varieties of *Malassezia* related disorders. Guidelines will be given.

Free Papers

Aspergillus fumigatus infection in a pt. with Wegener's granulomatosis (WG).

Larsen L, & Rasmussen, N
Danish Technological Instititute, Mould lab. & Rigshospitalet, Dpt. of Otolaryngology
Denmark

Backgound.

Pulmonary infections with *A. fumigatus* may mimic pulmonary manifestations of WG. This may lead to potentially fatal therapy.

Materials and Methods.

30 years old woman admitted with WG featuring symptoms from the nose, sinuses, ears and lungs was initially treated succcessfully with prednisolone and methotrexate. After 11 months switched to cyclophosphamide due to relapse with pulmonary infiltrates. These were then present to a variable degree for one year before samples obtained from endoscopy showed *A. fumigatus.* Treatment with itraconazole slowly healed the pulmonary infiltrates and immunotherapy could then be tapered slowly. The patient has now survived 10 years but is still on immunosuppressive therapy.
Dust from home and summerhouse were analysed for contamination with *A. fumigatus* conidia.
From each dust sample 30 mg was inoculated to V8 agar (+ antibiotics) and incubated at 26℃ and 37°C, respectively. After growth the microfungi were identified microscopically.

Results.

Dust from home revealed contamination with *A. fumigatus,* whereas in dust from summerhouse there was no such contamination.

Discussion.

Contamination of the home- dust with this mould originated possibly from a wall of straw that was torn down during a renovation of the house. "It had been very dusty" and the conidia from *A. fumigatus* were spread all over the house and were still present in the dust years after. The patient got the infection shortly after this renovation and was continuously exposed with *A. fumigatus* at home. This risk was not present in the summerhouse. This mould has its natural habitat in dust, straw, hay and wood chips, but is not normally found in mouldy houses.

We hypothesize that the persistent pulmonary infiltrates were due to *A. fumigatus* and continuing immunosuppressive treatment without antifungal treatment could have been fatal.

Primary Cutaneous Zygomycosis: An Emerging Clinical Entity

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Background: Zygomycosis is an extremely invasive fungal infection with high mortality rate. Various zygomycotic infections are becoming increasingly common and survival of patients remains pitiable. In most of patients, diabetes mellitus is underlying background but in primary cutaneous zygomycosis presentation may be without any such factor. **Objectives**: To raise clinical awareness of this emerging infection and to emphasize importance of early diagnosis and treatment of such condition.

Patients: All patients diagnosed with primary cutaneous zygomycosis at our tertiary care hospital between November 2001 and September 2008 are being reviewed. They presented with diagnosis of necrotizing fasciitis. **Methods:** Detailed history of each patient was taken, clinical presentation, site of involvement, underlying illness and risk factor, if any were noted. The diagnosis was established by direct microscopic evidence of broad, aseptate or sparsely septate ribbon-like hyphae with right angle branching in KOH wet mount and histopathological examination of stained sections with H&E, PAS and GMS stainings. Fungal cultures were put up for isolation and species identification. Outcome of medical and/or surgical therapy was analysed.

Results: Out of nine patients reviewed, underlying illness i.e. diabetes mellitus was present only in one. Commonest risk factor was found to be injection abscess. *Apophysomyces elegans* was isolated in four cases, *Saksenaea vasiformis* in one and *Absidia corymbifera* in one. The fungal culture turned out to be sterile in three cases despite direct findings being positive. Mortality rate was very high. Only four patients responded well to medical and/or surgical treatment.

Discussion: There is a need for high index of clinical suspicion and an early biopsy of affected site so that benefits of prompt diagnosis and therapy may be achieved. The key to survival is an early diagnosis, correction of underlying disease state and prompt antifungal therapy combined with extensive surgical debridement.