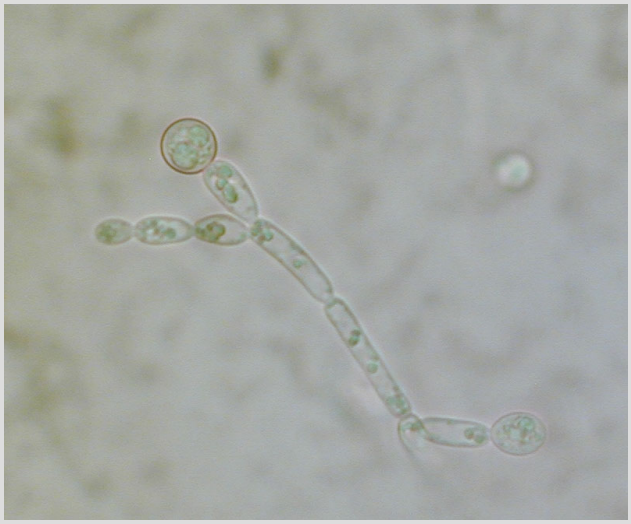
Nordic Society for Medical Mycology

2nd Scientific Meeting of the Nordic Society for Medical Mycology



Program and Abstracts

Proper Use of Antimycotics.

Børsen, Copenhagen, Denmark

April 1, 2005

Introduction

Dear Friends and Colleagues,

It is with great pleasure that we welcome you to the second scientific meeting of the Nordic Society for Medical Mycology. The meeting this time takes place at Børsen, the old stock exchange building build by King Christian the IVth, in Copenhagen, Denmark.

The scientific programme focus on the use of antifungals, and it has been our goal to cover as many aspects as possible regarding the treatment of fungal infections, i.e. susceptibility trends and epidemiology, aspergillosis, PK/PD, mono- and or combination therapy and the optimal choice of treatment in various patient categories. We are proud to welcome Georg Maschmeyer from Germany and Rod Hay from UK 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

Maiken Cavling Arendrup
President of NSMM

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Program
Proper use of antimycotics

Opening Ceremony and "Susceptibility and Resistance Epidemiology"
Chairmen: Maiken Cavling Arendrup and Per Sandven

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

10:10 **Trends in candidemia in and outside the Nordic countries**
Per Sandven

10.30 **Surveillance of fungemia in DK: species distribution and susceptibility**
Maiken Cavling Arendrup

10.45 **Epidemiology of dermatophyte infections.**
Ditte Marie Lindhardt Saunte

11:00 Coffee break

Keynote Lectures
Chairmen: Jan Faergemann and Maiken Arendrup

11.30 **Aspergillosis: Epidemiology – how big is the problem, and how to treat?**
Georg Maschmeyer, DE

12.15 **Antifungals available and ones being developed. Mono or combination therapy.**
Rod Hay, UK

13.00 Lunch

PK/PD parameters and their relevance for dosing
Chairmen: Ditte Marie Lindhardt Saunte and Lena Klingspor

14:00 **Pharmacokinetics of antimycotics for systemic use.**
Erik Eliasson, Huddinge

14:20 **Skin and mucosa pharmacokinetics of antimycotics for oral use**
Jan Faergemann

Optimal choice and dosing of antimycotics in various clinical situations
Chairmen: Per Sandven and Lena Klingspor

14.40 **Deep and/or organ infection (fungemia, hepato-splenic candidiasis, CNS infection, endophtalmitis etc.)**
Stig Frøland, Norway

15.00 **Superficial fungal infections (skin infection, mucositis, Madura foot etc.)**
Malcolm Richardsson, Finland

15.20 **Patients with renal and /or hepatic dysfunction**
Juha Salonen, Finland

15.40 **Paediatric patients**
Lena Klingspor

16:00 Coffee break

Free Papers
Chairmen: Malcolm Richardsson and Juha Salonen

16:30 **Yeast bloodstream infections in Sweden 2003**
Jakobson E, Skoog G, Hagblom P and Fernandez V, Sweden

16.45 **Position of the human pathogenic Basidiobolus and Conidiobolus in the fungal phylogeny**
Annette Bruun Jensen, Karsten Dromph and Jørgen Eilenberg, Denmark

Annual General Meeting for NSMM
17:30 General Assembly for members of the society

Abstracts

Susceptibility and Resistance Epidemiology

Trends in candidemia in and outside the Nordic countries

Per Sandven
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The increasing importance of invasive fungal infections has been recognized since the late 1980s and numerous reports on the incidence and species distribution of Candidemia in various hospitals have been published in recent years. Such studies are useful, but reflect only the situation in one particular hospital. Population based studies are needed to get a clear picture of the epidemiology of fungemia.

A few such studies have been published from the United States and also from Iceland and Finland. The results show quite a marked variation in the incidence in the different countries.

In Norway a prospective nationwide candidemia survey has been ongoing since 1991. The specific objectives of the study have been threefold: (1) to define the incidence of fungal bloodstream infections in Norway; (2) to identify the spectrum of pathogens causing yeast bloodstream infections; and (3) to obtain antifungal susceptibility data for Norwegian bloodstream isolates.

Yeast blood culture isolates in all microbiological laboratories in Norway (population 4.5 mill) have been recorded prospectively. Isolates have been sent to the national mycology reference laboratory for identification and susceptibility testing.

For the period 1991-2003 a total of 1400 candidemia episodes were diagnosed in Norway. The total number of yeast strains recovered was 1421 (21 patients with 2 species). The incidence of candidemia episodes per 100.000 inhabitants show an overall increase from approximately 2 episodes in the early 1990s (except 1991) to 3 episodes in 2001-2003. The average annual incidences vary markedly between the various age groups.

Results from recent candidemia studies in Sweden and Denmark will be presented at the present meeting.

Surveillance of fungemia in DK: species distribution and susceptibility

Maiken Cavling Arendrup
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There are few data on the epidemiology of fungemia in Denmark pertaining to one university hospital and one county demonstrating rates from <1% to 1.5% of BSI. In order to update knowledge on fungemia in Denmark we initiated a prospective semi-national surveillance study in 2003 in which six university departments of clinical microbiology participated in collecting all fungal BSI isolates for speciation and susceptibility testing. The aim was to present the first comprehensive data on fungemia in Denmark including distribution of species and range of susceptibility to major antifungal compounds based on a semi-national surveillance study initiated in 2003. The catchment area of the participating hospitals had a population of 2.8 million or 53% of the Danish population. Retrospective data of candidemia rates since 1992 were retrieved from the laboratory database systems and document a continuous increase over time.

During the first year of surveillance, a total of 307 episodes of fungemia were registered (annual rate: 11/100,000 population or 0.49/1000 hospital discharges). *Candida* species accounted for 97.4% of the fungal pathogens. *C. albicans* was the predominant species (63%) but the proportion varied from 57% to 72% among participating departments. *C. glabrata* was the second most frequent species (20%, range: 8% to 32%). *C. krusei* was a rare isolate (3%) and occurred only at two of the participating hospitals. For the 272 susceptibility tested isolates, MICs for amphotericin B and caspofungin were within limits expected for the species or genus. However, decreased azole susceptibility, defined as fluconazole MIC >8 µg/mL and/or itraconazole MIC>0.125 µg/mL was detected for 11 *Candida* isolates that neither was *C. glabrata* nor *C. krusei*. Including intrinsically resistant fungi we detected decreased susceptibility to fluconazole and/or itraconazole in 87 (32%) of current Danish blood stream fungal isolates. Retrospective data documented a continuous increase of candidemia cases since the early nineties.

The Danish semi-national surveillance programme has shown a continuous increase of fungemia in Denmark and a higher annual rate in 2003-2004 than in most other countries. The proportion of blood stream fungal isolates with reduced susceptibility to fluconazole and/or itraconazole was also notably high.

Thanks to co-workers:

Kurt Fuursted, Bente Gahrn-Hansen, Irene Møller Jensen, Jenny Dahl Knudsen, Bettina Lundgren, Henrik C. Schønheyder, Michael Tvede.

Epidemiology of dermatophyte infections.

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Dermatophytes are keratinophilic fungi, which invade superficial skin, hair, and nails. They consist of three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*.

Classification of dermatophytoses is based upon the part of the body infected and their host preference.

Demographic factors such as age and gender vary in the different clinical diagnosis. For instance children are more susceptible to tinea capitis and adults are more susceptible to onychomycoses. Different diseases predispose to dermatophytoses: diabetes, HIV, psoriasis, atopic dermatitis, and cancer. Environmental factors also contribute: attending public bathing facilities, and smoking.

Endemic dermatophytes are restricted to one geographical area, while cosmopolitan dermatophytes are worldwide distributed. This is changing over time. *Trichophyton* (*T*) *violacum* and *T. tonsurans* used to represent approximately 45% of the dermatophyte infections in Denmark in the beginning of 1900. They disappeared in 1930 and are now beginning to cause infections in Denmark again. Is the aetiology changing? And which consequences do this have?

Keynote Lectures

Aspergillosis: Epidemiology – how big is the problem, and how to treat?

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Invasive aspergillosis (IA) has emerged as the main cause of death and a major cause of morbidity in patients with aggressive hematological malignancies as well as of allogeneic stem cell or organ transplant recipients. The spectrum of patients-at-risk has broadened by an increasing number of individuals undergoing invasive surgery and organ transplantation, and by the improvement of the prognosis of patients with cancer, leukemia, lymphoma or solid tumors.

The clinical outcome of IA is still dismal, although the armamentarium of highly effective antifungal agents has grown significantly over the past decade by the introduction of new third-generation azoles such as voriconazole or posaconazole and the availability of echinocandin antifungals such as caspofungin. In particular, patients with disseminated IA, CNS involvement, or those with IA in the context of persistent severe neutropenia may have a mortality rate of more than 70 per cent. Prevention and early empirical or pre-emptive intervention with systemic broad-spectrum antifungals may further improve treatment results. However, the sources of Aspergillus are ubiquituous, including hospital reconstruction and environmental dust or food and drinking water, so that prevention of hospital-acquired IA has to focus on a consequent avoidance of contaminated air. However, the time period during which patients with long-term immunosuppression are threatened by acquiring IA may exceed 180 days, and an effective prevention of inhalation of Aspergillus spores outside the hospital environment is an unresolved problem. Itraconazole long-term prophylaxis after allogeneic stem cell transplantation has been demonstrated to be more effective than fluconazole, however, it is not tolerated by approximately one third of patients.

In-hospital prevention of air contamination by uncontrolled reconstruction activities and other sources of contamination, in concert with very early empirical antifungal intervention in long-term neutropenic patients not responding to broad-spectrum antifungals, a prompt pre-emptive antifungal treatment in febrile neutropenic patients with lung infiltrates consistent with invasive pulmonary aspergillosis, and a consequent systemic antifungal therapy utilizing the recently licensed third-generation azole antifungals as well as the newly developed echinocandins will provide the chance of decreasing the number of IA as well as of increasing the clinical success rates of antifungal therapy in patients with probable or documented invasive Aspergillus infections. The choice of antifungal agents in individual patients will depend on the focus of infection, pre-existing organ dysfunction, and concomitant drug treatment. As a new therapeutic option, the combination of antifungals with different modes of action, e.g. of a polyen with an echinocandin or a third-generation azole with an echinocandin, appears attractive with respect to preclinical study results, however, properly designed prospective clinical trials on this subject are still lacking.

Antifungals available or in development – the potential for combination therapy

Rod J Hay
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The management of fungal skin disease has improved greatly over the past ten years and it is now possible to achieve cure rates of over 90% in many infections. Onychomycosis still remains a challenge as remission rates, while improved, are still less than 75% at long term follow up in many studies. In addition there are other problem areas such as infections due to pathogenic fungi which respond poorly to existing drugs such as those due to Scytalidium and, in HIV positive patients, treatment unresponsive oropharyngeal candidosis. Amongst the systemic fungal infections invasive candidosis and aspergillosis remain problematic although mortality figures have improved in the more recent surveys.

The antifungal drugs currently used for the treatment of fungal diseases belong to two large families, the polyenes and the azoles; in addition there are a number of other medications. The largest family of antifungals in common use is the azole family, comprises the imidazoles and the triazoles. Developmental work amongst azoles has focussed on new molecules, drug combinations and prediction of the likely outcome of therapy. Clinical trial experience with the newer triazoles - voriconazole, posaconazole and ravuconazole - is limited at present as the drugs are comparatively new and some information is based on anecdotal evidence of efficacy. However their main targets are systemic infections including both aspergillosis and systemic candidosis. There are no new allylamines and work here has concentrated on the use of drug combinations and their potential role in deep fungal infections. Cell wall antagonists such as caspofungin, an echinocandin that blocks glucan synthase have etablished efficacy in deep candida infections. The polyene antifungals, while having considerable importance for the management of systemic infections, have not been developed further apart from in lipid associated formulations.

Combinations of antifungals have mainly been applied to systemic infections with combinations of flucytosine and amphotericin B, azole combinations and sequential amphotericin B and azoles being explored. They have not been widely applied in superficial infections although there have been attempts to combine surgery with drug therapy or chemical nail plate ablation with chemotherapy in nail disease. In onychomycosis recent work has shown that the combination of either itraconazole or terbinafine with topically applied amorolfine produce higher remission rates than with the oral compound alone. The other areas in which antifungals have been used in combination are in drug resistant candidosis and non-dermatophyte onychomycosis. Preliminary studies in chronic mucocutaneous candidosis suggest that the benefits of combining azole with allylamine therapy are not sustained even though there is evidence of in vitro synergy. In Scytalidium nail plate infections the use of combined itraconazole and terbinafine has not improved cure rates. It would be important to support further development of the use of combination therapy by in vitro studies. There is, for instance, evidence of additive effects and, in some cases, synergy between amorolfine and a range of other antifungals against dermatophytes.

PK/PD parameters and their relevance for dosing

Pharmacokinetics of antimycotics for systemic use.

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Systemic treatment with antimycotic drugs is complicated by considerable variation among patients in drug disposition and susceptibility to adverse drug reactions. In part, this relates to underlying diseases that are associated with impaired drug clearance or require poly-pharmacy that give rise to unfavourable drug-drug interactions.

The systemic antimycotics in use today differ significantly in their chemical properties and route of elimination. While flucytosine and fluconazole completely depend on elimination by glomerular filtration in unchanged form; ketoconazole, itraconazole and voriconazole instead undergo extensive hepatic metabolism. All azole antifungals strongly interact with the hepatic cytochrome P450 system (CYP), which may lead to significant interactions with many other drugs that are subject to CYP-metabolism. The elimination of amphotericin B and caspofungin is not as well characterised, but drug-drug interactions appear to be less of a clinical problem.

Therapeutic drug monitoring (TDM) is recommended for flucytosine, itraconazole and voriconazole. For the latter two substances, there is a striking inter-subject variability between dose and plasma concentration, which relates to differences in the expression and activity of relevant CYP enzymes. The hepatic biotransformation of itraconazole is mainly dependent on CYP3A4, whereas voriconazole is metabolised by CYP2C19 and CYP2C9, together with CYP3A4. For both CYP2C-enzymes, there exist genetic variants that code for a slow metaboliser phenotype in which drug accumulation is a potential problem.

Further studies are motivated to clarify whether TDM and/or CYP genotyping might help to reduce the risk of liver toxicity from voriconazole, since this adverse effect appears to be concentration-dependent.

Skin and mucosa pharmacokinetics of antimycotics for oral use

Jan Faergemann
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Details of skin and mucosa distribution of oral antifungal drugs should provide the basis for a more rational, pharmacodynamic-oriented approach to antifungal therapy than the use of traditional blood levels.

Fluconazole is a broad spectrum, orally active triazole derivative. Skin pharmacokinetic results show that fluconazole reach the stratum corneum both through a direct diffusion and through sweat. Very high concentrations are obtained in the stratum corneum within hours after oral administration (23.4 µg/g), and fluconazole remains in the stratum corneum for a long time after stop of therapy. High concentrations (8.54 µg/g) have also been found in nails after weekly medication with 150 mg in the treatment of onychomycosis of the toenails. Oral fluconazole reach the oral mucosa rapidly and in high concentrations.

Itraconazole is another orally active triazole derivative. It is lipophilic and found in lower concentrations in stratum corneum than both fluconazole and terbinafine. However, the levels in nails (0.93 µg/g) are comparable to terbinafine (0.39 µg/g) and it is also found there for several months after stop of therapy. This is the rationale for pulse therapy one week per month for 3 to 4 months in onychomycosis. Itraconazole has been found in high concentrations in vaginal mucosa and it was still detected 3 days after twice daily treatment once.

Terbinafine, an orally active allylamine is orally active especially against dermatophytes. It is lipophilic and delivered to the stratum corneum through direct diffusion and in very high concentrations in sebum (56 µg/g). It remains in the stratum corneum and especially in nails for a long time after stop of treatment. This is important in treatment and terbinafine is effective in the treatment of onychomycosis of toenails caused by dermatophytes after a dose of 250 mg once daily for 3 month.

The concentration of oral antifungal drugs in the target organ should always be compared to the Minimal Inhibitory Concentration (MIC) of the drug against the fungi relevant in diseases. Terbinafine has very low MIC's against dermatophytes of 0.001 to 0.01 µg/ml compared to fluconazole with MIC's over 1 µg/ml against dermatophytes and itraconazole with MIC's of 0.1 µg/ml against many dermatophytes.

Optimal choice and dosing of antimycotics in various clinical situations

Deep and/or organ infection (fungemia, hepato-splenic candidiasis, CNS infection, endophtalmitis etc.)

Stig Frøland
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Abstract not available.

Optimal choice and dosing of antimycotics in various clinical situations: superficial fungal infections.

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Superficial fungal infections are chronic and recurring conditions. Tinea capitis is a scalp infection, primarily affecting prepubescent children. Ringworm infections, such as tinea corporis and tinea cruris, involve the glabrous skin. Tinea nigra is a rare mycotic infection that may be related to travel abroad. Piedra, black or white, is limited to the hair shaft without involvement of the adjacent skin. Pityriasis versicolor and seborrhoeic dermatitis are dermatoses associated with yeasts of the genus Malassezia that affect the lipid-rich areas of the body. Tinea pedis, an infection of the feet and toes, is one of the most common forms of dermatophytosis. Onychomycosis is a fungal infection affecting the nail bed and nail plate; it may be chronic and can be difficult to treat. In instances where the superficial fungal infection is severe or chronic, an oral antifungal agent should be considered. Terbinafine, itraconazole and fluconazole that are effective in the treatment of superficial mycoses.

Yeast infections of the mucous membranes include oral and vaginal candidosis, caused by various species of Candida. It is imperative to identify the causal organism to species level before formulating a treatment plan. In many situations where the infection is recurrent antifungal susceptibility test is of great value. Fluconazole and itraconazole are useful drugs for these infections.

A range of subcutaneous fungal infections (diseases of implantation) are caused by environmental fungal, primarily in tropical regions of the world. Chronic diseases such as chromoblastomycosis, eumycetoma and sporotrichosis respond to itraconazole and fluconazole. A definitive diagnosis and hence optimal treatment of these infections is achieved by direct microscopy and culture.

Key references

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Patients with renal and /or hepatic dysfunction

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Amphotericin B (AmB) has been the gold standard in the treatment of invasive fungal infections for several decades. It has a broad antifungal spectrum covering most of the pathogenic yeasts and molds, but unfortunately its use is complicated by considerable nephrotoxicity. The nephrotoxicity of AmB is partly mediated through toxic effect on renal tubular cells and partly through vasoconstriction causing reduced glomerular filtration. The acute renal failure caused by AmB is often a factor which prevents use of effective doses in treatment of invasive fungal infections in critically ill patients. Although salt loading can be used as a prophylactic measure, the renal failure is sometimes irreversible and necessitates hemodialysis. Both the duration of AmB treatment and the baseline creatinine level predict the likelihood of nephrotoxicity.

New antifungal agents have been developed mainly to overcome the toxic effects of AmB. Three new lipid formulations of AmB (liposomal AmB, ABLC and ABCD) have clearly been shown to be less nephrotoxic than conventional AmB. However, there is little information of use of these agents in severe renal dysfunction and at least careful monitoring of renal function during the antifungal therapy is indicated in these patients. Impaired renal function necessitates dose reduction when Fluconazole, a triazole agent, is used. Voriconazole, another triazole, should not be administered intravenously to patients with moderate or severe renal insufficiency, since accumulation of the intravenous vehicle, sulfobutylether-β-cyclodextrin, occurs. If use of Voriconazole is indicated to these patients, intravenous formulation should be replaced with oral Voriconazole. Intravenous formulation should be used only when careful assessment of the benefit/risk to the patient justifies it. In such case serum creatinine levels should be closely monitored.

Caspofungin is the only new antifungal agent, which dosage need not to be adjusted in patients with severe renal dysfunction. With a low nephrotoxic potential and parenteral route of administration it is clearly the optimal choice for critically ill patients with imminent septic shock and anuria. Caspofungin is not dialyzable and supplementary doses are not necessary following hemodialysis. The high protein binding of Caspofungin indicates that it is not filtered in hemofiltration.

Hepatic route is the primary way of elimination for both Voriconazole and Caspofungin. Both drugs have been associated with transient abnormalities in liver function tests and infrequent cases of more severe hepatic toxicity. The maintenance dose of Voriconazole should be halved in patients with mild or moderate hepatic dysfunction (Child-Pugh Class A or B). A reduced daily dose of Caspofungin (35 mg) is recommended after the initial 70 mg loading dose in patients with moderate hepatic insufficiency (Child-Pugh Class B). There are no studies on use of Voriconazole or Caspofungin in patients with severe hepatic dysfunction and they should be used only if the benefit outweights the potential risks. New AmB lipid formulations accumulate in the reticuloendothelial system and may cause elevations in liver enzymes, as well. Although most of these laboratory abnormalities have been mild and transient, these agents should be used with certain caution in critically ill patients receiving other concomitant hepatotoxic medications. In these patients liver function tests should be monitored during the antifungal therapy.

Paediatric patients

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Invasive fungal infections have evolved into important causes of morbidity and mortality in neonates, infants and children with severe underlying diseases.The fungal pathogens causing infections in pediatric patient are mainly due to Candida or Aspergillus species .Other opportunistic yeasts such as Malassezia species, Cr. neoformans and moulds such as Fusarium may also cause invasive disease. The incidence in children,for invasive candidosids ranges from 8-10% in high risk leukaemia /BMT and 8-28% in infants< 1000g, and the incidence for invasive aspergillosis in hematological malignancies/BMT, ranges from 4.5%-10% with a crude mortality of 40% -94%.

The clinical signs are often unspecific and diagnosis of these infections are difficult. Responses to treatment depends on early diagnosis and restoration of host defenses.

The pediatric age groups shows important differences in host biology, including specific anatomic, physiologic, and immunologic aspects. Risk factors vary with age and underlying disease.

The options for treatment has for decades been limited to amphotericn B with or without flucytosine .

However, during the last years there has been a development of less toxic formulation of amphotericin B, the antifungal triazoles and the novel class of echinocandins.

The optimal choice of antifungal treatment and dosing in the pediatric patient must be guided by the underlying diease, the fungal species causing infection, the site of infection , the age of the patient, toxicity and interactions with other drugs.

To improve outcome in the pediatric patients a high degree of awarness and knowledge of invasive fungal infections, and better diagnostic tools are of outmost importance .

The management of invasive infections in pediatric patients must rely on the rational use and early institution of available antifungal agents.

Free Papers

Yeast bloodstream infections in Sweden 2003

Jakobson E[1], Skoog G[2], Hagblom P[1] and Fernandez V[1]. The Swedish Reference Group for Antifungal Agents.*

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In a nationwide survey of yeast causing bloodstream infections, the distribution of species and the susceptibility to antifungals were retrospectively evaluated in a total of 219 isolates from 214 patients. *Candida albicans* was the cause of infection in 65% of the patients, 23% were due to *C. glabrata* and 6.4% to *C. parapsilosis*. Prevalence of *C. glabrata* increased with increasing patient age from 0 to 30%, whereas *C. parapsilosis* was more commonly found in newborns. A majority of the patients underwent surgery (36%), resided in a general medicine ward (21%) or in an intensive care unit (18%). *C.* non-*albicans* species were more frequently isolated from patients in infectious disease clinics (50%). In vitro susceptibility testing revealed that 98% of the isolates were susceptible to amphotericin B, 96% to flucytosine, 87% to fluconazole and 73% to itraconazole. Three of the isolates displayed elevated MIC values for voriconazole. Resistance or reduced susceptibility to azoles was more common among isolates of *C. glabrata*, which is the species associated with highest mortality in candidaemia. In conclusion, the frequency of *C. albicans* and its susceptibility to azoles remains constant while *C. glabrata* emerges as a more common cause of bloodstream infections. This change in epidemiology could in part be explained by the extensive use of the drug fluconazole for the prophylaxis and treatment of *Candida* infections since the early 1990s.

Position of the human pathogenic Basidiobolus and Conidiobolus in the fungal phylogeny

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Background
Closely related organisms share more characteristics and might react more similarly to medical treatment that distantly related organisms. Therefore it is important that evolution, the phylogeny is reflected in modern systematic. In some groups of organisms, for example the "lower" fungi, only relative simple morphological characters available, and thus the chytrids are grouped together due to the presence of motile spores, whereas zygomyzetes are grouped together because of their coenocytic mycelium and simple sexual conjugation resulting in formations of zygospores. The genera Basidiobolus and Conidiobolus contain vertebrate (including human) pathogens and have traditionally been placed in Entomophthorales (zygomycetes), basically because both genera have actively dischargeable conidia. Their ecology (lifestyle) is however quite different and Basidiobolus posses, in contrast to Conidiobolus, remnants of the flagellum, which suggest a closer link to the chytrids. The correct position of human pathogenic species is obviously important.

Materials and Methods
DNA sequences from a variety of fungi of the nuclear subunit ribosomal DNA (nSSU rDNA and nLSU rDNA), the DNA dependent RNA polymerase II largest subunit (RPB1) and the b-tubulin were used to make phylogenetic analyses to elucidate the history of fungi in particular Conidiobolus and Basisidiobolus. In addition literature was consulted on clinical cases of these fungi as well as literature on the ecology and biology of these fungi.

Results
All the molecular analysis supported the polyphyletic relationship between Basidiobolus and Conidiobolus. A look at the reported symptoms and clinical manifestation of infections by Conidiobolus or Basidiobolus in humans shows a distinct pattern. Basidiolous mostly causes chronic infection of subcutaneous tissue of the body and more rarely involves infection of gastrointestinal tract, whereas Conidiobolus typically cause a chronic, indolent infection of the face.

Discussion
Molecular analyses, the etiological and some of the morphological characteristics showed that Conidiobolus and Basisidiobolus belong to separate orders, Entomophthorales and Basisiobolales respectively, and are only distantly related. Hence a differentiation of treatment strategies of mycosis caused by these two groups of fungi, which until now has been uniform, might be considered. We also discuss how these facts should be reflected in the clinical nomenclature.