Getting things done

A few weeks ago the ECMM has moved its domicile to Basel, Switzerland. Many societies and organizations in Europe and beyond have done this in the past. We are now officially a non profit organization stationed in Switzerland. Our Fellow societies in this country are among others the FIFA, UEFA and European Society for Clinical Microbiology and Infectious Diseases. However, it remains a pity that our Swiss medical mycology colleagues were not able yet to erect a Swiss Society for Medical Mycology. We would like to have them among the national societies affiliated to the ECMM. Some of our current members countries do not have a national mycological society but are rather working groups from dermatological or microbiological societies. ECMM should try to stimulate and help erecting multidisciplinary societies for medical mycology in every European country.

At the recent ECMM Council Meeting several decisions were made regarding the new Executive Board and the venue of the 2010 ECMM educational meeting and the 2011 TIMM meeting. After 6 years of commitment to the Confederation, Prof. Emmanuel Rolfides and Prof. Martin Schaller resigned as General Secretary and Treasurer respectively. Six years is the maximum term for participating in the Executive Council and I would like to thank them both for their invaluable efforts and support to create the Confederation as it is now. The new executive committee was elected after a close race. Prof. George Petrikkos will serve as the new General Secretary and Prof. Cornelia Law-Flood as the new Treasurer. The Council gave me the green light to continue my term as President for another 3 years. The three of us will do our utmost best to fulfill the primary goal of the Confederation, organizing and promoting the science and all aspects of medical mycology in Europe and if necessary worldwide. Regarding the last objective we have been promoting medical mycology in Africa by supporting already three Pan African Medical Mycology (PAMMS) meetings. The next, ECMM and ISHAM sponsored, PAMMS III will take place in February 2009 in Nigeria and I suggest you to attend this meeting in this exciting continent, if possible. You can read more elsewhere in this newsletter. Our 2008 ECMM educational meeting was held during the International Union of Microbiological Societies gathering in Istanbul early August of this year. Two ECMM working groups (continued on page 4)

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ECMM Affiliated Societies
(Information provided by the member provided)
Mycology newsletter

Fusarium species cause a variety of infections in humans, including superficial, locally invasive, and disseminated infections. The clinical presentation largely depends on the immune status of the host and the fungal portal of entry. Superficial infections, such as keratitis and onychomycosis, are usually observed in immunocompetent individuals, whereas invasive and disseminated infections occur in immunocompromised patients and are mainly associated with prolonged and profound neutropenia or severe T-cell immunodeficiency.

Among the more than 50 Fusarium species identified, twelve have been described as causes of human infection. Fus. solani is the most frequently reported Fusarium species and is the cause of approximately 50% of the Fusarium infections; the next prevalent species, in order, are F. verticilloides (10%), F. verticilloides (10%), and F. moniliforme (now classified as F. verticilloides, 10%). In contrast with data from the literature, in Italy F. verticilloides resulted as the prevalent species (41%) followed by F. solani (25%). In particular, F. verticilloides was the most frequent species (57%) in deep-seated infections and F. solani is more common in superficial infections (46%).

Fusarium species are relatively resistant to most antifungal agents. Careful analysis, however, shows that different species have different patterns of susceptibility. The majority of F. solani isolates exhibited reduced susceptibility to azoles. (1,4,8)

The prognosis of fusariosis in immunocompromised hosts is poor and also the treatment of skin and nail infections is frustrating and failure of systemic and local treatment is common. The major purpose of this study is to understand the epidemiology of fusariosis in Europe, collecting information on the patients infected by Fusarium (risk factors, localization/extent of infection, diagnosis, antifungal treatment and outcome) and on the infecting isolates (identification by molecular methods, in vitro susceptibility to antifungal agents).

Cases of fusariosis, deep seated as well as superficial infections, for which the infecting isolate is available, should be recorded on a questionnaire and the isolate collected and characterized. The form and the corresponding isolates will be collected in the national coordinator laboratory and strains studied. The prospective study is planned to start on January 1st, 2009 and it will last for two years (2009-2010) retrospective data will be also collected. Investigators interested in participating to this study as national coordinator for their country are welcome.

Anna Maria Tortorano

REFERENCES

The new version of ECMM website is ready at http://www.ecmm.eu. Under the recommendations of ECMM website committee (M.C. Arendrup, S. Arikan, J. Brandão, J. Meis, E. Rolides, A.Y. Sergeev, M.A. Viviani), it was decided to maintain the initial site design proposed by Prof. F.C. Odds, but to extend it functionality. To do so, we have installed the famous European open-source framework, Drupal.

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The digital focus of our society, www.ecmm.eu, has undergone a major transformation. The ECMM Website committee, under the direction of Profs. Alexey Sergeev has prepared a new digital communication board for the ECMM members. I hope you will visit the website regularly to browse and gather information.

The year 2008 runs to an end. I wish you that you were able to achieve all your personal goals set for this year and are prepared for the changes that will take place in the new year. ECMM will fly into a new exciting new year of change and things to look forward to in 2009.

Jacques F. Meno
ECMM President

Join the new ECMM website!

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Jacques F. Meno
ECMM President

Survey of Infections due to Fusarium species in Europe


# Mycology newsletter - December 2008

## Patient Code: M

**Country of origin:**

**National Coordinator:**

**Centre:**

### Patient Information

<table>
<thead>
<tr>
<th>Field</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Patient code</td>
<td>M</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
</tr>
<tr>
<td>Birthdate</td>
<td>1/1/2000</td>
</tr>
<tr>
<td>Country of birth</td>
<td>Country of residence:</td>
</tr>
<tr>
<td>Ward of hospitalisation</td>
<td>Hematology, ID 596 Other, ophth, derm</td>
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<tr>
<td>Date of admission</td>
<td>1/1/2008</td>
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### Fungal Pathology

<table>
<thead>
<tr>
<th>Date of diagnosis</th>
<th>Disseminated infection</th>
<th>Localised infection</th>
<th>Colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Blood culture positive</td>
<td>Blood culture negative</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>Urine culture positive</td>
<td>Urine culture negative</td>
<td></td>
</tr>
<tr>
<td>Peritoneum</td>
<td>Peritoneum culture positive</td>
<td>Peritoneum culture negative</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Skin culture positive</td>
<td>Skin culture negative</td>
<td></td>
</tr>
<tr>
<td>Nails</td>
<td>Nails culture positive</td>
<td>Nails culture negative</td>
<td></td>
</tr>
<tr>
<td>Other, ophth, derm</td>
<td>Other, ophth, derm culture positive</td>
<td>Other, ophth, derm culture negative</td>
<td></td>
</tr>
</tbody>
</table>

### Underlying Disease/Factors

- Autoimmune disease, ophth, derm
- Lymphoma, ophth, derm
- Solid cancer, ophth, derm
- Haematological, blood transfusion
- Transplantation, autologous, allograft, mismatched, unrelated, unrelated, matched
- Haematological, myeloblastic, relapse, remission, relapse, remission
- Chronic obstructive pulmonary disease, ophth, derm
- Surgery, ophth, derm
- Solid organ transplant, ophth, derm
- Diabetes, type I, type II
- AIDS CD4 number/mm³
- Accidental trauma, ophth, derm
- Dialysis, home, hospitalised
- Illness in ICU, APACHE II score
- SAPS II score

### Treatment of Fungal Infection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Daily dose</th>
<th>From (dd/mm/yy)</th>
<th>To (dd/mm/yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td>Daily dose</td>
<td>From (dd/mm/yy)</td>
<td>To (dd/mm/yy)</td>
</tr>
<tr>
<td>Drug 2</td>
<td>Daily dose</td>
<td>From (dd/mm/yy)</td>
<td>To (dd/mm/yy)</td>
</tr>
<tr>
<td>Drug 3</td>
<td>Daily dose</td>
<td>From (dd/mm/yy)</td>
<td>To (dd/mm/yy)</td>
</tr>
<tr>
<td>Surgery, ophth, derm</td>
<td>Date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Corresponding Physician/Mycologist

<table>
<thead>
<tr>
<th>Name of mycologist</th>
<th>Phone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of mycologist</td>
<td>Phone</td>
<td>Email</td>
</tr>
</tbody>
</table>

---

**Outcome of Fusarium Infection**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Date of death (dd/mm/yy)</th>
<th>Date of cure (dd/mm/yy)</th>
</tr>
</thead>
</table>

---

**Mycology**

<table>
<thead>
<tr>
<th>Site</th>
<th>Direct microscopy</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>not done</td>
<td>done</td>
</tr>
<tr>
<td>Nasal secretion</td>
<td>done</td>
<td>not done</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>done</td>
<td>not done</td>
</tr>
<tr>
<td>Biopsy, ophth, derm</td>
<td>done</td>
<td>not done</td>
</tr>
<tr>
<td>Skin, ophth, derm</td>
<td>done</td>
<td>not done</td>
</tr>
<tr>
<td>Nasal secretion</td>
<td>done</td>
<td>not done</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>done</td>
<td>not done</td>
</tr>
</tbody>
</table>

---

**Ready for Fusarium (positive sample and date)**

- Blood culture positive
- Blood culture negative
- Urine culture positive
- Urine culture negative
- Peritoneum culture positive
- Peritoneum culture negative
- Other, ophth, derm culture positive
- Other, ophth, derm culture negative

---

**Histopathology**

- Biopsy, ophth, derm, sample(s) and date
- Autopsy, ophth, derm

---

**Fusarium isolates sent to the National/European Coordinator**

<table>
<thead>
<tr>
<th>Ref number</th>
<th>Identification</th>
<th>Collected from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref number</td>
<td>Identification</td>
<td>Collected from</td>
</tr>
<tr>
<td>Ref number</td>
<td>Identification</td>
<td>Collected from</td>
</tr>
</tbody>
</table>

---

**Working Groups**

- Epidemiology and clinical form
- Direct microscopy and culture
- Direct microscopy
- Culture
- Oral secretions
- Nasal secretions
- Bronchial secretions
- Pleural fluid
- Peritoneal fluid
- Biopsy, ophth, derm
- Skin, ophth, derm
- Nails, ophth, derm
- Other, ophth, derm
- Bone marrow transplant
- Other, ophth, derm
- Bone marrow transplant
- Brain death
- Bone marrow transplant
- Brain death
- Bone marrow transplant
- Brain death

---

**Note:**

- Presence of hyphae
- Presence of hyphae

---

**Epidemiological and clinical form**

- Patient weight: 70 kg
- Patient age: 45 years

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**Working Group**

- Euro Surveillance Working Group
ECMM Survey of Coccidioidomycosis in Europe

Background
Coccidioidomycosis is a disease endemic to parts of South-West USA (Arizona, California, Utah, New Mexico). Central and South America, caused by the dimorphic fungus Coccidioides immitis and C. posadasii, desert soil-dwelling ascomycetes. These fungi grow as a filamentous saprobe in the soil and as endosporulating spherules within the host. Inhalation of arthroconidia results in a symptomatic respiratory tract disease, usually mild and self-limited, in up to 40% of infected patients. But the disease can last months and in 1% of cases disseminates beyond the lung. CNS, lymph nodes, bone tissue and skin are primarily involved. Disseminated infections can be fatal or require lifelong therapy.

Coccidioidomycosis in Europe
While not endemic in Europe, cases of coccidioidomycosis occur in individuals who have lived or traveled in endemic areas. Reactivation of infections from several previous years may result from a failing immune system, for example occurs in some AIDS patients. Information of the general prevalence of this mycosis in Europe is not available.

Because the international tourism and the immigration from endemic countries are increasing, physicians in Europe need to become more familiar with the manifestations and with the approach to diagnosis. Travel history should always be sought in the evaluation of patients. Since few fungal elements can be present in biopsy, histology with special stains and the more sensitive culture examination should always be performed. In addition, to avoid risk of accidental exposure, laboratory workers should be informed of the clinical suspicion.

Objective of the survey
The objective of this survey is to discover the prevalence of coccidioidomycosis in Europe, where and how the infection was acquired, the group at risk, the fungal species responsible and the method by which the infection was diagnosed. The antifungal therapy and the outcome will also be analysed. This will lead to a better understanding of this imported mycosis and will enable a coordinated effort to target at risk populations and to standardize methods for the diagnosis and treatment of the disease.

Investigators interested in participating in the study as “national coordinator” for their country are requested to contact Prof. B. Dupont

Study period
Notification of new cases will start on 1 January 2009. Retrospective cases since 1983 will also be collected.

Collection of data and isolates
Notification of cases should be made using the epidemiological form for coccidioidomycosis reported on page 9. Data from the retrospective study should be compiled as soon as possible and send to the national coordinator. For the prospective study the information should be sent as the cases arise.

The isolate, if available, should be stored in the laboratory where it was identified. Please contact your national coordinator to know if molecular identification species is available before sending the isolates according to safety national rules. Postal regulations on the safe packaging of these dangerous pathogens need to be strictly followed.

Bertrand Dupont
Further information can be obtained from Prof. Bertrand Dupont (bertrand.dupont@nck.aphp.fr).
Dr. Shigeru Kohno, the Conference Chair and Dean, Nagasaki University School of Medicine, warmly welcomed the conference participants to Nagasaki and noted that this was the first time the ICCC was being held in Far East Asia. He then introduced John Perfect, who gave the Opening Address. Dr. Perfect cited the latest Center for Disease Control (USA) estimates that there are over 1,000,000 cases of cryptococcosis per year and, of those cases, approximately two thirds will die. He then went on to focus on why Cryptococcus is a “brainy” yeast – in other words, why it is neurotropic. Dr. Perfect and his laboratory have examined what the requirements are for *C. neoformans* to survive in the cerebrospinal fluid (CSF) with the hypothesis that certain gene products promote dissemination and survival in the brain. Of 1700 mutants that were tested, 19 could not grow in CSF. The nature of these mutations was being studied.

Dr. Perfect then informed the audience that the IDSA Practice Guidelines for the treatment of cryptococcosis were in the final stages of revision and should be published soon. He emphasized that amphotericin B plus 5-flucytosine remains the optimal choice for induction therapy of cryptococcal meningitis. Fluconazole is not as good, but if practical considerations dictate its use, it should be used at doses >800 mg/day. In patients found to be co-infected with HIV and *C. neoformans*, it remains uncertain when is the best time to start antiretroviral therapy. One must balance the risk of further complications of AIDS with the risk of an immune response inflammatory syndrome to the fungus. Finally, Dr. Perfect addressed the issue of management of elevated intracranial pressure with the opinion that those with pressure about 25 cm should have measures taken to relieve the elevated pressure, including repeated lumbar punctures and, if necessary, shunting.

**The Immune Response**

The Immune Response I session began with a presentation by Thomas Kozel (University of Nevada School of Medicine, Reno, USA) on the interaction of antibody and complement proteins with the cryptococcal capsule. Dr. Kozel emphasized that the capsule gets denser as it gets closer to the cell wall. There are differences *in vitro* versus inside the mouse as the capsule gets denser and has more O-acetylation when the fungus is *in vivo*. In addition, there are serotype-specific differences in the expression of O-acetylation groups in the fungus’ buds. Next, Christopher Mody (University of Calgary, Canada) presented the results of his research on the mechanisms by which NK cells inhibit and kill *C. neoformans*. He emphasized

From their humble beginnings of discovery as a human pathogen in the 1890s, *Cryptococcus neoformans* and *Cryptococcus gattii* have exploded onto clinical practice in this millenium. For instance, a recent outbreak of *C. gattii* infections from Vancouver Island to Northwest USA has demonstrated the ability of this encapsulated yeast to change its pathobiology and ecology. Even more impressive is that the CDC now estimates the global burden of HIV-associated cryptococcosis at 1 million cases per year with estimated deaths of 680,000 per year. When placed in number of estimated deaths from infectious diseases in Sub Saharan Africa excluding directly AIDS only malaria and diarrheal illnesses rank higher.

*John R. Perfect*
that perfors is required. While NK cells degranulation and lose per- forin when exposed to C. neoform- ans, the NK cells subsequently “re-arm” with more perforin. Anna Vecchiarelli (University of Perugia, Italy) then reviewed the immunosuppressive effects of the major capsular polysaccharide of C. neoformans, GXM. She then asked the question whether GXM could be used to treat autoimmune diseases. Beneficial effects were seen in an experimental model of collagen-induced arthritis.

The session concluded with two presentations selected from the submitted abstracts. First, Mark Krookenberger (University of Sydney, Australia) presented data on a new rat model of C. gat- tii pulmonary infection and con- trasted it to what is known about rat models of C. neoformans. Fi- nally, Simon Johnston (University of Birmingham, UK) presented intriguing data that Cryptococcus can escape from macrophages without killing the host cell by a process termed reverse phagocy- tosis or vomocytosis.

Kazuyoshi Kawamoto (Tokoh University Graduate School of Medicine, Japan) opened the Im- mune Response II session by ex- amining selected aspects of the in- nat immune response to C. neoformans. He presented data that the beta-glucan receptor, dectin-1, was dispensable for immunity to C. neoformans, C. gattii and C. africana. He found cytokine production follow- ing stimulation of dendritic cells with C. neoformans DNA. Next, Stuart Levitz (University of Massa- chusetts Medical School, Worcester, USA) discussed immune re- sponses to mannoproteins. These immunodominant proteins are heavily mannosylated by both N- linkages and O-linkages. Dr. Levitz presented data suggesting that mannoproteins are poor stimula- tors of cytokine production by den- dritic cells. However, combining mannoproteins with TLR ligands synergestically boosted cytokine production. Dr. Levitz speculated that this combination could make a good vaccine.

Type I interferons are known to play a critical role in viral infec- tions, but their contribution to host defenses against the mycoses has received scant attention. Therefore, Giuseppe Teti (Uni- versity of Messina, Italy) looked at the role of type I interferons in cryptococcosis. Mice deficient in either IFN-beta or the INFal- fa/beta receptor had reduced sur- vival in a pulmonary challenge model. Small, but significant, amounts of INFalpha were pro- duced by macrophages after cryptococcal stimulation.

Two speakers selected from the submitted abstracts finished the session. Kirsten Nielsen (Universi- ty of Minnesota, Minneapolis, USA) examined the role of pheromone signaling during the vi- vo infection. In a co-infection model, she studied dissemination of a and alfa strains that had dis- rupted pheromone signaling. The a cells were increased in size and had decreased central nervous sys- tem penetration. Finally, Hansong Ma (University of Birmingham, UK) presented data positively cor- relating virulence of C. neoformans and C. gattii with the capacity to proliferate intracellularly in macrophages. Interestingly, strains isolated from the Vancouver Island outbreak were amongst the most rapid intracellular replicators.

West Meets East

A report of the epidemiology and clinical manifestations of cryptococcosis in the Far East, Europe, the United States and Australia

Africa remain HIV-associated. Though the incidence in Thailand has declined since the introduction of HAART, cryptococcosis is still the third commonest opportunistic infection in HIV-infected patients. In South Africa, despite the roll-out of antiretroviral therapy programs, many patients with HIV present late with low CD4 counts, hence the inci- dence of cryptococcosis appears little changed. In C. neoformans, HIV-associated cryptococco- sis has more than halved in the US and France since the advent of high- ly active antiretroviral therapy. In contrast, the overwhelming majority of cases in Thailand and South Africa are estimated to be the infectious propag- ulum. Dr. Botts characterized their surface composition. He found evi- dence for a thin layer of GXM as well as partially exposed beta-glu- canes and mannans. The session con- cluded with a presentation from Wozniak (University of Massachusetts Medical School, Worcester, USA) examining intra- cellular events following phagocy- tosis of C. neoformans by dendritic cells. C. neoformans traffics to com- partments containing endosomes and lysosomes. Moreover, crude lysosomal extracts from dendritic cells potently killed the fungus in a dose-dependent manner.
tion is now of particular importance (but not haematopoietic stem cell transplantation). In the US, cryptococcosis is the third commonest invasive fungal infection in recipients of solid organ transplants, often presenting more than 12 months post-solid organ transplantation.

C. neoformans serotype A is the predominant pathogen in all countries. In Australia, where infection due to C. gattii is endemic and affects apparently healthy individuals, approximately half of the cases in this group are still caused by C. neoformans, whereas in other countries reporting C. gattii infection, the proportion of cases in HIV-negative individuals is lower. Notably, data from British Columbia, Canada, which is the site of the most recent outbreak of cryptococcosis due to C. gattii, were not presented in this session. In France, serotype D causes a significant minority of cases compared with serotype A but is infrequent outside of Europe.

A number of presenters noted that cirrhosis/chronic liver disease, diabetes mellitus and/or end-stage renal disease were present in a significant number of non-AIDS-associated cases, though in the absence of case control or prospective studies, it was not always clear that these constituted independent risk factors for cryptococcosis. Nevertheless, several speakers spoke to their clinical impression that outcomes are significantly worse in patients with cirrhosis, due largely to poor tolerance of the best therapeutic regimens in this group. More work to elucidate optimal therapy is required.

There was a consistent finding that abnormal mental status at presentation is associated with a worse outcome regardless of therapy. It was of interest to hear that 22% of patients in Shanghai present with optical disease, significantly higher than in Western countries represented. A similarly high rate of papillodema/optic neuritis was reported from Papua New Guinea prior to the AIDS epidemic and was attributed to a typically late presentation of illness. Other statistically significant poor prognostic markers in CNS diseases included underlying cirrhosis and high CSF protein (Korea) and CSF cryptococcal antigen >512, infection with serotype A rather than D and failure to receive 5-flucytosine as part of the induction antifungal therapy (France).

Several delegates raised the possibility that differences in epidemiology, clinical features and response may result from individual genetic and/or ethnic genotypic differences. There was general agreement that further investigation of host determinants is warranted.

### Approaches to Induction Therapy

The development of induction therapy for cerebral cryptococcosis varies depending on the availability of drugs in different countries. In those where amphotericin B and 5-flucytosine are available, this combination was generally considered to be the treatment of choice. In organ transplant recipients in the US, liposomal AMB is preferred to conventional AMB because of the high risk of renal failure in this group. In Thailand, where 5-flucytosine is not available and most cases are associated with AIDS, an initial 2-week course of AMB is followed by 400 mg/d of fluconazole for 8 weeks and then maintenance fluconazole therapy is used. The high prevalence of cryptococcosis and HIV co-infection in Thailand is the rationale for the unique recommendation that primary prophylaxis be given. Itraconazole, which is also effective against another problematic opportunistic fungus in Northern Thailand, Penicillium marneffei, is recommended for those with a CD4 lymphocyte count <100.

Two speakers, Zhu Yuanjie and Tania Sorrell, emphasized the prolonged time that more than one of CSF glucose, leukocyte count, India Ink stain and cryptococcal antigen titre remain positive, even with successful therapy. It can be concluded that a better means of monitoring the therapeutic response to allow individual optimization of therapeutic regimens is needed.

### Gene Regulation

Two sessions on gene regulation and signaling highlighted the complexities of the signaling pathways in Cryptococcus neoformans. For example, a host-specific signal like elevated temperature leads to a myriad of responses including altered shape, size and volume. Andrew Alspaugh (Duke University School of Medicine, USA) presented nice data demonstrating that the differential localization of Ras1, either to the cell surface or to endomembranes, may represent a mechanism by which C. neoformans Ras1 can specifically activate distinct signaling pathways in response to different upstream signals. Ping Wang (Louisiana State University Health Sciences Center, New Orleans, USA) showed that Crg2, a regulator of G protein signaling in C. neoformans functions as a multi-regulatory protein that controls mating distinctively from Crg1 and also inhibits Gpa1-AMP-dependent signaling. Among the repertoire of responses to different stresses is a calcium-mediated signaling pathway that promotes survival of C. neoformans to ergosterol biosynthesis inhibitors. Angie Gelli (University of California, USA) presented evidence demonstrating that the calcium channel Cch1-Mid1, a central mediator of this pathway is activated by the calcium signaling inhibitors that could function to promote fungicidal activity of ergosterol inhibitors such as azoles. Interestingly and perhaps not surprisingly some signaling pathways may operate differently in C. gattii compared with C. neoformans. In work presented by Jim Kronstad (University of British Columbia, Canada) where he discussed the use of combined transcriptional profiling by serial analysis of gene expression (SAGE) and DNA microarray analysis in understanding the role of iron as a regulator of virulence factor expression and as a central nutrient during infection. DNA microarrays were also used to study the mechanism of heteroresistance in C. neoformans. In work presented by June Kwon-Chung (NI-AID, NIH, Bethesda, USA), transcriptome comparisons between H99 and clones resistant to fluconazole revealed several hundred genes that were upregulated in the resistant subpopulations. Many of the differentially regulated genes were located on chromosome A and L, and central signaling pathways were duplicated in resistant clones. Heteroresistance appears to be independent of Hog1 signaling, unlike the cellular response to other types of stresses.

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Epidemiology, Molecular Typing, Population Genetics

A number of presentations illustrated the recent advances made in the fields of taxonomy, epidemiology, molecular typing and population genetics. In a summarizing presentation Teun Boekhout (CBS Fungal Biodiversity Centre, Utrecht, The Netherlands) described the presence of six monophyletic lineages present within the Cryptococcus neoformans species complex that may represent separate species. Based on nuclear genes these lineages were found to be genetically isolated. Although recombination has been observed to be present in C. gattii in some mitochondrial genes. Moreover, interspecific C. neoformans x C. gattii hybrids were discussed. Dee Carlin (University of Sydney, Australia) addressed the issue of sexual recombination in C. neoformans. Most Cryptococcus populations show a highly unbalanced mating type ratio, yet the infectious agent is thought to be a sexually generated basidiospore. Interestingly, recombining populations were observed to occur by analyzing small clusters of isolates occurring on phylogenograms based on AFLP analysis. C. neoformans isolates belonging to the VNI and VNNI genetic types isolated from small animals in the Sydney region showed recombination. Apparently, recombination occurs in the environment in both C. neoformans var. grubii and C. gattii. Ancestral Southern African, where they occupy a specific ecological niche, especially related to the mopane (Colophospermum mopane) tree. VNI isolates, in contrast, seem to be imported in Africa by migration of humans and/or birds (especially pigeons). Different subpopulations of VNB are geographically isolated, they show recombination within the environment, and hybridization occurs between strains of VNI and VNB. Finally, Wieland Meyer (University of Sydney, Australia) showed his results of an ongoing effort to study the global molecular epidemiology of the C. neoformans species complex. Using PCR-fingerprinting and MLST eight major molecular types were observed, including two subtypes in C. grubii and the serotype AD hybrids. In addition, evidence was presented that the high and low virulent genotypes VGII-A and VGII-B also occur in South America, and that these may be ancestral to the Australasian populations as well as the population causing the Vancouver Island outbreak.

Teun Boekhout

Anastasia Litvintseva

Molecular Typing, Population Genetics

Virulence Factors

During the last two decades we have learned much about the pathogenesis of cryptococcosis and yet the understanding of the molecular mechanisms of pathogenicity of Cryptococcus neoformans in the contest of the status of the host immune response is only very recently taken under consideration. There is now a consensus that the virulence factors of C. neoformans are not static components of its pathogenic fitness but rather fungal features that change dynamically during the infection perhaps according to the host environment in which the fungus is located.

The session on “Virulence factors”, have shed light on possible mechanisms by which this fungus adapting to host environments.

Interesting, this process may also favor the survival of the fungus within macrophages during the latent infection. Bettina Fries (Albert-Einstein College of Medicine, USA) talked about the phenotypic switching of C. neoformans and its contribution to virulence. During infection, this fungus can undergo reversible switching from a smooth parent to a mucoid variant. Interestingly, the mucoid is more virulent than the smooth variant. Dr. Fries identified two genes (ALL1 and ALL2) that are downregulated in the mucoid variant and, thus, deletion of these genes significantly enhanced virulence.

Teun Boekhout

Massimo Cogliati and Wieland Meyer

Teun Boekhout

Anastasia Litvintseva

Maurizio Del Poeta

Molecular Typing, Population Genetics

Anastasia Litvintseva

Teun Boekhout

Teun Boekhout

Reiko Ikeda

Anastasia Litvintseva

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The studies presented at the Tissue Tropism session explored different mechanisms by which cryptococci are able to persist in the lung, and to gain access to the brain and spread throughout the CNS. One of the most striking findings was the identification of a novel mechanism involving the interaction of HA with CD44 molecules to achieve firm adhesion between the organism and the host’s endothelial cell. Furthermore, the interaction of HA with CD44 triggered signaling pathways that lead to phosphorylation of protein kinase alpha, downstream recruitment of beta-actin to the endothelial membrane rafts and their rearrangement. Dr. Yong proposed that C. neoformans exploits this pathway, to transverse across the endothelium in a “zipper like” fashion following firm adhesion to the endothelial cell surface.

References
Sex, Mating, and Evolution
Kirsten Nielsen

This session contained talks about micro evolutionary events, sexual reproduction in Cryptococcus and related species, and sexual infections often display gross chromosomal rearrangements. Translocations, duplications, inversions, and deletions could provide a selective advantage, but would likely lead to sterility. Changes in subtelomeric regions would allow subtle changes that are tolerated during sexual development. Examination of sub-telomeric regions revealed genes associated with niche adaptation. The Fraser lab has characterized one of these regions on the right arm of chromosome 3 that contains many hexose transporters. They observed amplification of the arsenic transporter gene ARR3 with 3-18 copies of the gene. Arsenic is a toxic metalloid that is pumped out of cells by ARR3. Analysis of arsenic resistance revealed that strains with increased ARR3 gene copy number had higher resistance. Joe Heitman (Duke University Medical Center, Durham, USA) presented a fascinating talk on the structure and evolution of the mating type locus in Cryptococcus and closely related species. Cryptococcus is a member of the basidiomycete phylum. Most basidiomycetes have a tetrapolar mating system with two unlinked loci. Yet Cryptococcus has a bipolar mating system with only a single locus. Analysis of this locus suggests it was generated by fusion of two loci. To better understand the mechanism of the evolution of the MAT locus, the Heitman lab has cloned and analyzed the mating loci from other closely related species. By characterizing the mating loci in C. amylolentus they have been able to identify strains of opposite mating type and characterized mating for this species. In addition, Dr. Heitman also presented additional data supporting the prevalence of same-sex mating in the environment and showed that it may be linked to a specific Si2 alpha phenotype. Emilia Krzel from Christina Hull’s lab (University of Wisconsin-Madison, USA) presented an elegant study to characterize gene expression during sexual development using microarray analysis. They identified early, intermediate, and late genes and also found spatial differences in expression of many genes known to be involved in mating. For example, pheromone gene expression was up-regulated early in the mating process and then repressed later in sexual development. They also identified a class of unknown genes which were involved in dikaryotic growth. There were also a few talks in other sessions which relate to sex, mating, and evolution. Dee Carter (University of Sydney, Australia) described population genetic studies which show evidence of recombination and same-sex mating in limited geographic or temporal ranges suggesting that sex and spore production are probably common in the pathogenic Cryptococcus species but may be masked by clonal expansion. Kirsten Nielsen (University of Minnesota, Minneapolis, USA) showed confluence with both mating types blocks central nervous system penetration by one of the sexes in a pheromone dependent manner. The pheromone signaling results in giant cell production which may alter host cell interactions to affect virulence. Finally, Michael Botts, from the Hull lab, showed that spores are more resistant to environmental stresses. Electron microscopy revealed that the spore coat contains capsule which plays a role in proper sexual development and spore dispersion. These studies underscore the importance of sex and evolution in many aspects of Cryptococcus biology and virulence.

First Session

Robert Larsen, from the University of Southern California, discussed a new method of susceptibility testing for Cryptococcus neoformans and attempts to correlate results with clinical outcomes. The fundamental approach to his method, which has not been validated in clinical trials, is based on the concept that quantitative cultures are a useful tool in assessing mycologic response, and that susceptibility testing should be linked to quantitative cultures providing more of a “quantitative rather than a simple ‘susceptible or resistant’ result. Dr. Larsen has not been able to correlate these data with clinical outcome, but his hypothesis is that the current method of susceptibility testing is somewhat flawed, and that relationship between susceptibility data and clinical outcome should be further explored.

Li-Ping Zhu, from Fudan University in Shanghai, reported a retrospective 11-year survey of non-HIV infected patients who have been diagnosed with cryptococcal meningitis. During this 11-year period spanning the years 1997 through 2007, 154 cases of non-HIV-associated cryptococcal meningitis were diagnosed at this institution. Surprisingly, only 27% of patients had significant underlying conditions. Out of 72 cases who underwent CD4 lymphocyte testing, only 25% were found to have counts >200 cells/mm3. Most patients received initial therapy with amphotericin B with or without 5-flucytosine. Despite this, up to 20% mortality at the end of antifungal therapy (10 weeks). About 60% of these deaths were attributable to cryptococcal meningitis. The authors note that clinical manifestations in immunocompromised patients were less severe than their “normal” counterparts, suggesting that therapy was significantly higher in immunocompromised patients than other patients (P = 0.046). The mortality was similar for immunocompromised and normal patients. Dr. Zhu’s interesting findings regarding the incidence of non-HIV-associated cryptococcal meningitis is increasing in China and that treatment outcomes tend to be better among immunocompromised compared to otherwise normal individuals.

Peter Pappas, from the University of Alabama at Birmingham, discussed cryptococcosis among transplant recipients. Most of Dr. Pappas’ discussion focused on the results of TRANSNET, a prospective surveillance program among 25 US transplant centers, which was conducted between 2001 and 2006. During that time, 98 cases of transplant-associated cryptococcosis were identified. Dr. Pappas underscored the importance of this infection among solid organ transplant recipients and indicated that three-month mortality for this disorder was approximately 25%, among the lowest of the invasive fungal infections in this vulnerable population. He emphasized that cryptococcosis remains an important complication in the late post-transplant period in solid organ transplant recipients. Tania Sorrell, from the University of Sydney, discussed cryptococcal phospholipase B as a potential antifungal drug target. Cryptococcal phospholipase B1 facilitates invasion of the lungs and is essential for hematogenous dissemination of infection. Using structure-activity relationship analysis, the author attempted to correlate antifungal activity of several compounds through inhibition of phospholipase B1. Interestingly, miltefosine, an anti-protozoan agent with broad-spectrum fungicidal activity, inhibited phospholipase B1 activity, but only at concentrations greater than six times the MIC, suggesting that phospholipase B inhibition is not its primary role in antifungal activity. Other compounds demonstrated significant antifungal activity, but this was restricted to yeasts. The most promising of these compounds was miltefosine.

Kirsten Nielsen

Clinical Sessions

Robert Larsen

Second Session

John Bennett (NIAMD, Bethesda, USA) opened the session by providing a historical overview of clinical trials in cryptococcal meningitis (CM), and outlining key gaps in our understanding of optimal therapy post diagnosis of CM, as well as better definitions and guidelines for management of cryptococcal immune reconsti-
Special report

Previous studies have shown a relationship between baseline CSF opening pressure and outcome in cryptococcal meningitis. Tihana Bicanic (St George’s University of London, UK) presented findings from three studies of HIV-associated CM from Thailand and South Africa (n=163), showing that aggressive management of raised CSF opening pressure using repeated lumbar punctures over the first 2 weeks of treatment resulted in no significant differences in mortality at 2 and 10 weeks between patient groups categorized according to baseline opening pressure (<20, 20-30, >30cm H2O). Opening pressure correlated with fungal burden, both at baseline and day 14 of treatment.

Tom Harrison (St George’s University of London, UK) concentrated on important issues in the treatment of CM in developing countries. In phase II studies, rates of clearance or early fungicidal activity have been shown to be a suitable marker of treatment response. Pooled data from studies in Thailand, Uganda and South Africa (n=262) demonstrate that a poor rate of clearance is independently associated with mortality at 2 and 10 weeks. In places without facilities to administer amphotericin B, studies of the best oral treatment regimen have shown that a comparison dose alone with a combination of oral fluconazole given for 14 days, followed by maintenance fluconazole. All three arms were well tolerated. At day 14, successful outcome (composite clinical/mycological endpoint) was seen in 41%, 27% and 54% of patients in the 3 arms respectively. There was a trend towards better outcomes in the combination arms at 6 and 10 weeks. The results should be validated in a phase III trial.

The ensuing discussion focused on the need for collaborative international efforts and mobilization of political will and funding to address the above questions, probably in the form of a Phase III trial including both developed and developing countries, coupled with primary prevention in the form of antigen screening and targeted primary fluconazole prophylaxis.

Tihana Bicanic

Eddie Byrnes representing the Heitman laboratory from Duke University opened the session with a discussion on the variation within the Cryptococcus neoformans var. grubii type strain H99. Gaining insights into C. neoformans var. grubii virulence mechanisms and genomic architecture through a detailed analysis of parasaged H99 isolates. Since the “birth” of isolate H99 on February 14th, 1978 many things have happened. The isolate lost virulence through lab passage (possibly multiple independent times), was parasaged through a rabbit to increase virulence, and distributed globally to many labs. Some version of this isolate was used to sequence the genome, construct a congeneric strain pair (KN99a/alfa), construct large-scale mutant libraries (Madhani/Lodge), and most recently used to construct a tiling array. This has been the major type strain for type A, and has been used in countless publications over the last 2 decades. Acknowledging and understanding the differences between these parasaged isolates, and increasing awareness of isolate choice for experiments is important for many future studies. To examine differences in phenotype and genotype, we are conducting classical genetic experiments with mating and artificial diploid construction, comparative genomic hybridizations with NimbleGen (Heitman and Kronstad), cDNA microarray studies in YPD, CSF, and L-DOPA media (Perfect and Heitman), murine virulence experiments (Lodge), and whole genome sequencing of several variants with single and paired end Solexa sequencing (Dietrich). It is our goal that this focus will allow a greater understanding of genetic, and possibly epigenetic determinants of virulence, and mating.

Kim Gerik from the Lodge laboratory at Saint Louis University described progress by the microarray consortium. Arrays with C. neoformans var. neoformans genes have been available through the Washington University Genome Center since 2005. Many of the probes also hybridize to var. grubii genes. Now that the annotations for the var. grubii strain H99 have been updated, the arrays are currently being augmented with probes specific for H99, as well as mating type loci genes, and additional var. neoformans probes. The probes are ready for printing, and a new .gal file generated by Steve Giles in Christina Hull’s laboratory is available. The Broad will be releasing a new annotation of H99 soon.

Tom Harrison
John Bennett

Congress report

Jennifer Lodge

Eddie Byrnes

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Teun Boekhout from Utrecht University, provided AFLP and MLST evidence for six distinct molecular types (VN1/VN2, VNIV, VGI, VGI, VGI, and VGI) that likely represent cryptocistic species within the C. neoformans/C. gattii species complex. This evidence is being marshaled to support a proposal that C. neoformans var. neoformans and C. neoformans var. grubii be recognized as distinct species rather than simply as varieties, and similar proposals should be forthcoming assigning four species within C. gattii (VGI, VGI, VGI, and VGI). Genomic sequences are currently available for VNI (H99), VNIV (JEC21 and B3501A), VGI (WM276) and VGI (R265) and representatives of each other lineage (expect the VGI and VGI lineages) should be advanced for sequencing. In addition, in select lineages it will likely be advantageous to sequence other isolates, such as for the VGI and VGI lineages. In addition, closely related nonpathogenic species such as Cryptococcus amylolentus, recently discovered to have a novel teleomorphic form (Filobasidiella amyloenta), should also be sequenced for comparisons. This robust genomic database would considerably advance the field.

Fred Dietrich from Duke University discussed Solexa, the next generation of DNA sequencing. Sequences obtained from Solexa sequencing can be problematic to assemble since the sequence reads are so short. He described an approach that he is applying to the fungal pathogen of cotton, Ashbya gossypii, which utilizes paired end reads and improves assembly.

Sarah Brown from the Lodge laboratory at Saint Louis University described a proteomic approach to examining the response to oxidative stress in Cryptococcus. There were very few changes in the Cryptococcus proteome induced by exposure to oxidative stress compared to the response to nitrosative stress.

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Overall there was excellent progress reported on gene deletions, analysis of strains with differences in phenotypes, and availability of microarrays (http://genome.wustl.edu/activity/ma/cneoformans/). C. neoformans deletion strains sets (UCSF or SLU) are available through the Fungal Genetics Stock Center (http://www.fgsc.net/) at low cost. There was discussion regarding the pressing need for a central database to house genomic, annotation, microarray, gene deletion, proteomic and other related data.

Jennifer Lodge
towards pathogenicity' Alessandro Pasquallotto (Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil) gave on summary on the clinical syndromes due to A. fumigatus and A. flavus. He stated that most of the information available about Aspergillus infections has been originated from A. fumigatus, the most frequent species in the genus. A. flavus is however particularly prevalent in regions of the world with dry and hot climate such as the Middle East and Sudan. Interestingly, A. flavus seems more virulent and more resistant to antifungal drugs than most of the other Aspergillus species, which has been demonstrated both in vitro and in animal models. He suggested that aflatoxin does not seem to be a major factor in the pathogenesis of A. flavus infections. A. flavus isoflavones produce aflatoxin B1, the most toxic and potent hepatocarcinogenic natural compound ever characterized. A. flavus is a common eutropho etiology of fungal sinusitis and infections, but not fungal pneumonia. Only chronic cavitary pulmonary aspergillosis has rarely been associated with A. flavus. Although A. fumigatus is responsible for the vast majority of cases of allergic bronchopulmonary aspergillosis (ABPA), A. flavus has also been implicated in multicellular community helps to colonize the substratum and resist external aggressions. Biofilms formed by the pathogenic yeasts Candida and Cryptococcus neoformans on medical devices show an increase in the number of cells and increase in the number of biofilms. Filamentous fungi are also forming biofilms. Recently many keratitis with contact lens increase were attributed to biofilm formation of Fusarium species. Extracellular material surrounding the Aspergillus fumigatus mycelium has been seen during growth in infected tissues or in vitro under static conditions. This matrix is composed of galactomannan, melanin and other elements specific to in vivo or in vitro conditions. In vitro afl1As.3 glucans, antigens and hydrophobins are present in ECM whereas in vivo, these components are only cell wall components.
Invasive Fungal Infections in the Intensive Care

Chairs: J. Meris, L. Klingspor

The heterogeneous population of severely ill patients admitted to an intensive care unit (ICU) shares a high susceptibility to nosocomial fungal infections. A symposium entitled “Invasive fungal infections in the intensive care” was organised by ECMM at the IUMS 2008 held in Istanbul last August. This symposium, chaired by Jacques Meis and Lena Klingspor, broached different topics: infections caused by Candida and by filamentous fungi, risk factors and prophylaxis, and antifungal therapy. The abstract results of the ECMM survey on deep-seated Candida infections in ICU surgical patients were reported by Lena Klingspor, convenor of the Working Group.

An overview on yeast and mould infections in ICU patients was presented by Anna Maria Tortorano and Setvap Arikan, respectively.

The gastrointestinal insults that may arise as a consequence of ICU management procedures are responsible for the vulnerability of these patients to haematogenous dissemination of Candida species, such as C. albicans, C. glabrata, C. tropicalis, that form part of their commensal flora of the gastrointestinal tract. The alteration of the skin barrier, as in the presence of IV lines, favours the acquisition of yeasts such as C. parapsilosis, colonizing the patient’s skin or the hands of the healthcare workers. In addition, the vascular catheters, as well as other implantable devices, may be hemogenous seeded by Candida, such as C. albicans, C. glabrata etc., coming from distant local infection. Formation of biofilm on implanted biomaterials increases resistance to antifungal agents, protects Candida from host defences, and causes failure of devices.

Infections caused by filamentous fungi, such as aspergillosis, fusariosis, zygomycosis, are now increasingly recognized to occur with increasing frequency in patients other than those with immunosuppression (HIV patients). Prof Samonis reviewed the available evidence against these “new” threats. Combinations of antifungal agents are under investigation, but conclusions have not yet been drawn. Prof Samonis concluded that the patient in ICU is often too sick for anything to work and the outcome of the fungal infection highly depends on an early diagnosis and on the recovery of the immune function of the patient.

Lena Klingspor, closed the symposium reporting the results of the first 18 months of the ECMM survey. A total of 420 episodes of deep Candida infection (76% blood-stream infections) were reported from the participating countries, that is 169 from Italy, 88 from Austria, 69 from Greece, 39 from Sweden and 10-29 from UK, Finland and Czech Republic. Most of the patients (46%) underwent an abdominal surgery and 17% a thoracic intervention. A solid organ transplant was performed in 2.7% of the cases. A total of 78 (19%) patients died during the inter-ventions. A solid tumour was the underlying disease in 34% of the patients, that is 15% of the episodes, followed by C. glabrata (15%), C. parapsilosis (13%), C. tropicalis (6%). C. krusei was reported as cause of infection in 11 cases (3%) and C. lusitaniae and C. dubliniensis in 8 episodes each. Overall crude mortality of the day 30 was 31%, highest in C. glabrata (40.5%), C. krusei (46%) and C. lusitaniae (30%) infections. A total of 11% of the patients was under systemic antifungal prophylaxis when Candida infection was diagnosed. The management of the infection consists of fluconazole in 52% of the episodes, caspofungin and liposomal amphotericin B in 21% and 16%, respectively. Prof Samonis reviewed the classic les-sons on the characteristics of the typical surgical patient in ICU affected with deep fungal infections, as well as echinocandins, cover both Candida and Aspergillus. Unfortunately, while treatment options are increasing, new fungal threats, such as Fusarium and zygomycetes, have emerged. Amphotericin B compounds and possibly posaconazole are indicated against these “new” threats. Combinations of antifungal agents are under investigation, but conclusions have not yet been drawn.
Zygomycosis

Chairs: G. Petrikkos, E. Tümbay

G eorge Petrikkos (Athens University, Greece) presented the current epidemiology of zygomycosis in Europe, showing the data from the ECMM Working Group on Zygomycosis. Fifteen countries submitted 230 cases (Italy 60, Greece 36, Germany 35, Switzerland 22, France 21, Belgium 16, Austria 12, Spain 9, Russia 6, Norway 5, Finland 2, Czech Republic 2, Turkey 2, Netherlands 1 and UK 1). Israel also submitted cases but they will be included in 2008.

The mean age of the patients was 50 years and 60% were male. The main underlying diseases were hematologic malignancies (45%), bone marrow transplantation (10%), trauma (17%), diabetes (9%), other malignancies (5%) and solid organ transplantation (4%). The main sites of infection were the lungs (29%), rhinocerebral (14%), the sinuses (13%), soft tissues (25%) and disseminated (15%). Statistical analysis showed correlation between hematological malignancy and pulmonary disease, as well as between diabetes and rhinocerebral disease. Zygomycosis was proven in 114 cases and probable in 116. Various methods of diagnosis were used including histology, culture, direct microscopy and molecular methods. The isolated fungi were mainly Rhizopus sp (24%), Mucor sp (22%) and Absidia sp (14%).

Mortality was 44.7%. On multi-variate analysis, the factors found to be related to the outcome were age, previous administration of cyclosporin, trauma as an underlying factor, treatment with amphoterin B and surgical treatment. The pathogenesis and host defenses against Zygomycetes were analyzed by Emmanuel Rolides (University of Thessaloniki, Greece). He pointed out that although the pathogenesis of zygomycosis has not been fully understood yet, many interesting aspects of it have been studied, including the role of monocytes and neutrophils, various pro- and anti-inflammatory cytokines etc. He concluded that the genetic mapping of important Zygomycetes will help in revealing pathogenesis of zygomycete infections and help creating more and better diagnostic and therapeutic targets.

Eric Dannaoui (Institut Pasteur, Paris, France) talked about conventional and molecular diagnostic methods. He pointed out that morphological-based identification of fungi can be erroneous in >20% of cases. He presented data showing that sequencing of ITS region is a reliable method for accurate identification of Zygomycetes and he also talked about the use of PCR testing on histology specimens.

Grit Walther (CBS Fungal Bio-diversity Center, Utrecht, The Netherlands) presented the ongoing study of his group, the aim of which is to achieve a reliable diagnosis of mucormycosis by ITS bar-coding of the Mucorales. In order to further cover the diversity of the Mucorales species, the group is in the process of generating ITS bar-codes for all species of the Mucorales present in the CBS collection. These sequences will be used to set up a database for an accurate and rapid routine identification of Mucorales species that will be made publicly available through the CBS website. This set of ITS DNA barcode database will not only improve the reliability of the species recognition, it will also facilitate the detection of unknown pathogenic species and the search for a potential correlation between species and underlying diseases.

The pharmacology of antifungal agents against zygomycosis was presented by Andreas Groll (Children’s University Hospital, Munich, Germany). He also presented the current epidemiology of zygomycosis in transplant recipients (M. Cuenda-Estralla), and hospital acquired zygomycosis illustrated by a recent outbreak in Athens (G. Antoniadou).

Session 2 explored risk factors and pathogenesis. Lectures included: zygomycosis and trauma (Anna Skaida), deferoxamine vs. Deferasirox: what is the role of iron (A. Symeonidis); zygomycosis and neutropenia (Livio Pagano). He talked about the traditional view of zygomycosis and diabetes (Olivier Lortholary), and considering the apparent increase in cases of zygomycosis in the setting of voriconazole prophylaxis, a very timely lecture entitled: Is voricona-zole a risk factor? (J. Parada).

The clinical presentation and diagnosis of zygomycosis was covered in session 3 with lectures on the clinical presentation in adults (George Samonis), methods of diagnosis (Cornelia Lass-Flörl), molecular methods of diagnosis (Eric Dannaoui), and susceptibility testing: in vitro – in vivo correla-tions (Juan Rodríguez Tudela).

The second days programme concluded with a session on treatment. The challenges in the management of zygomycosis was presented by George Daikos and L. Vrana. The use of liposomal amphotericin B (AmBisome) was re-viewed by Georgios Petrikos. Oliver Corredy posed the question: posaconazole: an alternative or an add-on choice? Andreas Groll presented the current thinking on the use of fenolamine, a potential adjunctive method of manage-ment and the session was conclude-
High-risk groups for Aspergillus infection
IFI is six times more common in patients undergoing HSCT than those who have autologous grafts, and the risk is also raised in patients who have umbilical cord blood transplants, according to data presented at the congress.

Aspergillus
High-risk groups for IFI

Dr Raiola concluded that IA is associated with high mortality, especially in patients whose immune system does not recover after HSCT.

Guidelines updates

Empirical versus pre-emptive antifungal therapy?

Pre-emptive antifungal therapy is a cost-effective alternative to empirical therapy in patients who are neutropenic for relatively short periods (under 15 days), but further refinement of diagnostic techniques is needed before it can be recommend ed for high-risk patients who are likely to have a low neutrophil count for more prolonged periods.

This was the conclusion of Catherine Cordonnier, Hôpital Henri Mondor, Paris, France, at the end of a presentation during which 38% of the audience said that they used pre-emptive treatment in allogeneic HSCT patients and 34% said they used the empirical approach.

Professor Cordonnier’s advice was based on the PREV-ERT VERT study, which compared empirical and pre-emptive treatment in 293 patients with haematological malignancies and an expected period of neutropenia of 10+ days during their treatment. All were screened twice weekly for galactomannan antigen.

Seventeen patients in the study had an IFI, 2 (2%) in the empirical group and 15 (9%) in those receiving pre-emptive therapy (p=0.02), though the overall survival rate was comparable (p=0.12). Further investigation revealed that there was no difference in infection rate between the two treatment approaches when neutropenia was short. But the longer the period of neutropenia, the greater was the risk of infection with pre-emptive therapy.

Professor Cordonnier therefore recommended that future pre-emptive strategies should include more refined techniques - imaging tools or biological markers - to increase diagnosis during hospital stay, diagnostic tests, blood products, antifungal and other therapies. Against this background, he analysed the cost per quality-adjusted life year (QALY) of using posaconazole for antifungal prophylaxis, in line with the ECIL2 and IDSA guidelines.

But, as some 5000 delegates at the recent 34th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT) congress heard, putting key European and US guidelines into practice falls well within internationally accepted cost-effectiveness thresholds, according to new data, presented by Helmut Ostermann from the University of Munich Hospital, Germany.

Aspergillosis mortality was also higher in allogeneic than autologous transplant patients - 77% and 14% respectively - with candidaemia associated with the prolonged immunosuppression that accompanies HSCT.

Pre-emptive antifungal therapy?

Pre-emptive antifungal therapy is a cost-effective alternative to empirical therapy in patients who are neutropenic for relatively short periods (57% and 44% respectively).

Data from a retrospective analysis of 306 patients undergoing HSCT concluded Johanna Zaske, from the PREV-ERT VERT study, which compared empirical and pre-emptive treatment in 293 patients with haematological malignancies and an expected period of neutropenia of 10+ days during their treatment. All were screened twice weekly for galactomannan antigen.

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The 4th Congress on Trends in Medical Mycology (TIMM-4) will be held in Athens, Greece from the 18th till the 21st of October 2009. TIMM mycological international meetings are jointly organized by the European Confederation of Medical Mycology (ECMM) and by the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG). TIMM have taken place in Athens as one of the most important places among the meetings in the field of fungal infections globally, and has become a forum in which investigators and clinicians from all over the world exchange results and opinions on medical practice. Well-known speakers discuss the most important advances in basic science and clinical research in mycology. The executive committee in collaboration with the national and international scientific committees works hardly in order to prepare an excellent scientific program and make the participation to the congress a long-lasting memory. The meeting is designed for infectious disease specialists, haematologists, oncologists, transplant physicians, microbiologists, immunologists, dermatologists, intensivists and other health workers with interest in medical mycology.

The preparation for the meeting is going very well. The program of the Congress has come close to finalization and experts on the field are invited to give lectures on a wide range of educational topics brought by the most expert mycologists. There will be two innovations in this meeting compared to the previous TIMM’s. First, in addition to the well-established Drouhet Lecture that has been given for the best abstracts and posters. This is expected to attract more high-quality presentations to the congress. The venue for the TIMM-4 is in Athens, Greece. Athens is the most important classical city in Greece, the birthplace of democracy, science and philosophy. Athens is full of historical and cultural treasures throughout the downtown area and the surrounding region. Acropolis with Parthenon, many other classical monuments and a number of beautiful Byzantine churches as well as excellent museums make the visitors’ experience unforgettable. Greece will undoubtedly give an irresistible background for this exciting scientific forum, providing not only a beautiful setting for a high powered meeting, but also a flavour of the Greek taste of life to all congress participants.

The meeting venue, Athens Hilton (www.hilton.com), is located at the heart of the Greek capital, a few kilometers away from Acropolis and Athens historic town. Detailed information about the program will be published in January 2009 in the 2nd announcement of the congress and on the congress website www.timm2009.org. Abstract deadline is 1 June 2009 and for more information contact the congress secretariat Congress Care info@congresscare.com. Phone: 31-73-690-1415 or www.congresscare.com.

The TIMM-4 in Athens will once again offer excellent science and medicine in a superb venue. We look forward to greeting you in Greece and discuss new developments in medical mycology!

Emmanuel Roilides and George Petrikkos on behalf of TIMM-4 Executive Committee

ISHAM 2009:
The 17th Congress in Tokio

ISHAM has become one of the most active international organizations in medical mycology, and its congress is an event that you may not miss. The congress, held in Tokyo, 25-29 May, 2009 is very reasonably priced: this is a great chance to visit Japan! Registration for ISHAM2009 is now open. For accommodation, see online hotel online booking. There is a wide range of options between deluxe and budget. The organizers have put together an excellent densely informative program covering all aspects of modern medical mycology. More than 50 symposia and sessions are planned with distinguished speakers on themes in medical, veterinary and indoor mycology with a focus on animal and human health. More than 80 chairpersons have been confirmed for the majority of the Scientific Sessions and speaker selection is progressing well; a list of chairpersons and speakers will be available soon. The extremely wide range of experts will stimulate and expand the scope of your research.

A significant amount of attention will be devoted to posters, so that all participants will have ample opportunity to present their work. Every day there will be viewing as well as oral poster sessions in a poster forum, held in addition to the regular poster exhibitions. Poster presenters in the PF will have 5 minutes of oral presentation, may show 5 slides, and may receive 1 question. Case reports are particularly welcome. In addition, twelve poster prizes will be given to posters of highest research quality. The ISHAM congress will host a meeting for ISHAM-affiliated organizations. The meeting is open to anyone volunteering to stimulate medical mycology in all its aspects. Major theme is the promote networking and providing facilities for joint research. The agenda is posted on the ISHAM website, www.ISHAM.org.

Each day several luncheon and evening seminars are scheduled, and every evening a pleasant and interesting activity will be organized. Keynote lectures can be found on the ISHAM website. In addition, several ISHAM Working Groups will hold their meetings.

Mycologists under 35 and having a great career in mind become ISHAM member and get their money back when participating ISHAM2009. Young members present in Tokyo will receive an extra gift worth $ 100.

Important dates:

Call for Papers: On-line Abstract Submission for Poster Presentations is open now.
Early registration deadline at low fee: February 19, 2009.
ISHAM 2009 is one of the top international congresses, an optimum arena to present your latest research. Please join us in Tokyo and take advantage of this marvellous opportunity to enjoy intensive science, international contacts, and warm Japanese hospitality!

Hideoki Ogawa, Congress President
Sybren de Hoog, ISHAM President

The first meeting of the ISHAM Working Group on Filamentous fungi and chronic respiratory infections in cystic fibrosis will be organized in Angers University, Angers, France, on 7 and 8 June, 2009. Aim is to focus attention on the much overlooked respiratory infections caused by filamentous fungi in patients with cystic fibrosis.

Beside bacteria which remain the major causative agents of respiratory infections in the context of cystic fibrosis (CF), several filamentous fungi may also colonize the respiratory tract of these patients. This fungal colonization of the airways, facilitated by the frequent and prolonged cures of antibiotics and by the use of corticosteroids, may also lead to true respiratory infections whose frequency regularly increases along with the development of lung transplantation and the increase in life expectancy. Apart from Aspergillus fumigatus, numerous other species are reported increasing, such as Scedosporium apiospermum, A. terreus, Exophiala dermatitidis and S. prolificans, some of them being poorly susceptible to current antifungals and therefore difficult to treat. However, the prevalence of these fungi in the context of CF is certainly underestimated and their clinical significance still remains to be defined. Large scale multicenter studies should be designed in order to define the real prevalence of these species and the clinical significance of their recovery from respiratory secretions, but also to highlight possible geographic variations in their prevalence and to improve the biological diagnosis of airway colonization/infection. Additionally, numerous questions arise from the colonization of the airways by these filamentous fungi, and basic research on the ecology of these fungi, their biochemistry, and their pathogenic mechanisms should be promoted to define prophylactic measures or to develop more effective antifungal drugs.

The Workshop will be open to anyone who wishes to contribute to the study of chronic respiratory infections caused by filamentous fungi in patients with CF. It will be asked to each attendant to give a short presentation of his or her lab and of the work(s) that has been done in the past few years in our research field. Presentation of scientific projects in this area with search of partners is also encouraged. But a large part of this meeting will also be dedicated to discussions in order to plan future developments and collaborative studies. The number of participants is limited to 50 and there will be no fee.

Jean-Philippe Bouchara

Previous meetings

Successful 1st meeting (“Medical Mycology: The African Perspective”) was held at the Hartenbos Beach Resort near Mossel Bay in the Western Cape, South Africa on 25 January 2005. The Pan African Medical Mycology Society (PAMMS) was inaugurated during this meeting and a steering committee consisting of Hester Vismer (Cape Town, South Africa), Ieoma Enweani (Ekpoma, Nigeria) and El Sheikh Mahgoub (Khartoum, Sudan) was elected to look after PAMMS during its first few years.

The 2nd meeting was also held in CTICC, Cape Town, South Africa between May 6-8, 2007. During this meeting PAMMS Council members were elected viz Hester Vismer (Cape Town) President, Ieoma Enweani (Nnewi, Nigeria) Vice President, John Rheeder (South Africa) Secretary, Alf Botha (South Africa), Abdalla Ahmed (Saudi Arabia), and Ahmad Moharram (Egypt) as members. Membership of the PAMMS is free, as the Africa Fund for Fungal Biodiversity and Mycotic Infections, initiated by Sybren de Hoog and Jacques Meis of the Netherlands, will cover the initial costs of the Society.

Conference Announcement

It is a pleasure to invite you to attend the 3rd meeting of the PAMMS in Abuja to be held at the National Center for Women Development (NCWD) located in the Central Business District. The conference will provide medical mycologists from Africa with a unique opportunity to present their latest research findings, to foster collaboration and to establish long-term relations between scientists from Africa and abroad. A PAMMS General Meeting will be held to discuss various updates on Medical Mycology Studies. Invited speakers from the African continent and speakers from outside Africa, working on topics concerning African fungi will participate in the meeting.

Poster presentations will also form an important part of the programme.

In addition to the stimulating scientific programme planned for PAMMS 2009, Abuja is the current capital of Nigeria and is situated at the heart of Nigeria. It has a diverse culture with tourist attractions and hospitable people.

Organising Committee

Ieoma Enweani (Chairperson); Grace Ayanbimpe (Treasurer); Members: Lydia Abia-Bassey, Emeka Nweze, Harish Gugnani, Afe Ekundayo, Dennis Agbonlahor, Francisca Okungbowa, Onyechere Allison.

Scientific Committee

Hester Vismer (South Africa), David Katerere (Cape Town), Jacques Meis (Netherlands), Sybren de Hoog (Netherlands), El Sheikh Mahgoub (Sudan), Abdalla Ahmed (Saudi Arabia), Ieoma Enweani (Nigeria), John Rheeder (South Africa).

Important Contacts and Addresses

All information regarding the PAMMS 2009 conference is also available at the following website: http://www.cbs.knaw.nl/meetings

Enquiries

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Reduced toxicity through unique liposomal delivery of amphotericin B5

ABBREVIATED PRESCRIBING INFORMATION

Presentation: A sterile lyophilised product for intravenous infusion. Each vial contains 50 mg of amphotericin B, encapsulated in liposomes. Indications: The treatment of severe systemic and/or deep mycoses where toxicity (particularly nephrotoxicity) precludes the use of conventional amphotericin B.

Dosage & Administration: AmBisome must be administered to the specific requirements of each patient. The recommended dose for the treatment of Aspergillosis, in adults, is 1 mg/kg/day for 3 – 4 weeks has been typical. Dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient. Reduced toxicity through unique liposomal delivery of amphotericin B.

Reduce the risk of infusion-related reactions: Infusion-related reactions are rare, administration of a test dose is still advisable. If these reactions are severe, AmBisome should be administered at a lower rate (e.g. 2 mg/ml over a 30 – 60 minute period).

Contra-Indications: There are no specific dosage recommendations or precautions for elderly patients. AmBisome and data suggest no dose adjustment is required, however administration should be avoided during the haemodialysis procedure.

Use in pregnancy: AmBisome should be administered by infusion over a 30 – 60 minute period. The recommended dose is 1.0 – 3.0 g of amphotericin B over 3 – 4 weeks has been typical. Convulsion, thrombocytopenia, hypomagnesaemia, hypocalcaemia, hyperglycaemia, hyponatraemia, tachycardia and hypotension are rare, administration of a test dose is still advisable. If these reactions are severe, AmBisome should be administered at a lower rate (e.g. 2 mg/ml over a 30 – 60 minute period).

Overdosage: In two double-blind, comparative studies, AmBisome treated patients experienced a significantly lower incidence of infusion-related reactions, as compared to patients with either conventional amphotericin B or amphotericin B lipid-complex. Treatment necessary for resolution of mycoses. However, cumulative dose of 1.0 – 3.0 g of amphotericin B over

References:

Date of preparation: August 2006. AmBisome is a trademark.