DEVELOPMENTS IN INVASIVE FUNGAL DISEASE

More than 8500 infectious disease experts attended the 21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and 27th International Congress of Chemotherapy (ICC), which is the world’s largest conference on infectious diseases. Among the sessions on fungal disease, there was particular interest in a newly developed European guideline on diagnosis and management of *Candida* diseases.

**EFISG guideline on diagnosis and management of Candida diseases**

Delegates were given a preview of a *Candida* guideline prepared by the ESCMID fungal infection study group (EFISG). This first European guideline covers both diagnosis and management issues. The group’s aim is that it is adapted for local needs, said Andrew Ullmann (Johannes Gutenberg University, Mainz, Germany), who co-ordinated the development of the guideline.

One of the differences from the 2009 IDSA guideline on candidiasis management is the EFISG emphasis on use of an echinocandin for targeted treatment of candidaemia in intensive care unit (ICU) patients. EFISG says that all three echinocandins (anidulafungin, caspofungin and micafungin) have a strong recommendation (grade A recommendation, with level I evidence) while fluconazole has only marginal support (CI). Voriconazole and liposomal amphotericin B have moderate support (BI). The guideline says there is moderate support for simplifying therapy by stepping down to oral fluconazole after 10 days intravenous (IV) treatment, where possible. Combination therapy is not recommended.
For patients with haematological malignancies, EFISG strongly recommends (AII) caspofungin and micafungin for treating invasive disease/candidaemia in neutropenic patients (including haematopoietic stem cell transplant recipients). Anidulafungin has BII evidence. Combination therapy is again not recommended. For empirical treatment in these patients, only caspofungin and liposomal amphotericin B have AI evidence.

On the controversial issue of whether or not central venous catheters should be removed, EFISG says that for catheter-related bloodstream infection in ICU early catheter removal is not recommended in patients who are being treated with liposomal amphotericin or an echinocandin. For haematology/oncology patients, early catheter removal is seen as important, but with an option to retain the catheter in patients receiving treatment with an echinocandin.

The guideline also covers Candida infection in children and in patients with HIV infection/AIDS. Treatment costs were not considered in developing the EFISG guideline.

**Dealing with ocular candidiasis**

Diagnosis and treatment of ocular candidiasis can be a difficult area. Bart-Jan Kullberg (Radboud University, The Netherlands) noted that ocular lesions occur in around 16% of patients with candidaemias. These can have late presentation and so he suggested that a reasonable approach would be to undertake fundoscopy at day 10-14, before discontinuing antifungal therapy. Because the echinocandins have poor ocular penetration, he said he would switch to an azole in patients with eye lesions, an action that is also recommended by the new EFISG guidelines.

**Fungal infection in the Intensive Care Unit**

The management of invasive fungal infection in the ICU was discussed by Eckhard Müller (Herne, Germany). He highlighted the need to identify the patient population at high risk of fungal infection, to be familiar with local epidemiology to guide treatment, and to avoid delay in starting empirical treatment. He said that there were data to show that with every hour delay in initiating antifungal therapy, mortality increases by around 7.5%.
Dr Müller said that the incidence of invasive fungal infection in ICU is increasing. The large majority of fungal infections are Candida and a recent analysis of data from the EPIC II study showed that Candida bloodstream infection has a worse prognosis than bacterial sepsis.²

Noting EFISG’s recommendation of an echinocandin as first-choice therapy for Candida infection in the ICU, Dr Müller said that current data suggested little difference in clinical efficacy between anidulafungin, caspofungin and micafungin, but comparative clinical trials would be useful. At present, he said, caspofungin was still the ‘workhorse’ in the majority of ICUs in Europe.

Also discussing antifungal management strategies in the ICU, Thierry Calandra (Lausanne, Switzerland) highlighted the difficulty in early diagnosis of Candida infection. Risk factors include length of stay, antibiotic therapy, abdominal surgery, total parenteral nutrition, intravenous and urinary catheters, Candida colonisation in at least two sites, and immunosuppression. However these risk factors are not specific. He said that there are various prediction rules for invasive candidiasis in ICU and these can be helpful in “ruling out” invasive candidiasis. Serial β–glucan measurements may also help with early diagnosis.

New data reported at the congress included the results of the European/Canadian Invasive Candidiasis Intensive Care (ICE) study of anidulafungin for treatment of candidaemia and invasive candidiasis. This phase IIIb open-label study assessed intravenous anidulafungin followed by optional oral azole (voriconazole or fluconazole). Markus Ruhnke (Berlin, Germany) reported that cure or significant improvement was seen in 69.5% of patients.

**Treatment strategies for haematological patients**

Management of fungal infection in haematology patients remains challenging. Discussing the pros and cons of the empirical and pre-emptive approaches, Johan Maertens (Leuven, Belgium) said that empirical treatment (a fever-driven approach) was a strategy developed in an era of lack of diagnostic tests and limited drug treatments. It remains the standard in many centres, especially those that do not have funding for diagnostic testing. The 2009 ECIL-3 guidelines³ consider there to be moderate evidence to support this strategy, but there are also disadvantages, including overtreatment of a high number of patients with non-fungal fever, high cost, and the risk of missing cases of fungal infection in the absence of
fever, for example, in patients taking steroids. However, the strategy may “buy time” if diagnostic facilities are not available.

The alternative pre-emptive (or diagnostic-driven approach) uses biological markers, combined with imaging, to direct therapy. The aim here is to identify and treat all patients who are likely to have invasive fungal disease (IFD) and to adopt a “wait and see” policy for those unlikely to have IFD. Dr Maertens acknowledged that this approach is not yet fully established and is not yet recommended by ECIL. He said that more data are needed to help in deciding between the two treatment approaches and noted that a new phase III study of empirical vs. pre-emptive antifungal therapy in patients with haematological malignancies (the EORTC 65091-06093 study) is expected to begin later this year.

One of the interesting aspects at ECCMID was the reporting of “real life” experience of use of antifungal agents. Ullmann reported how his Mainz hospital had switched from using fluconazole to posaconazole, for antifungal prophylaxis in the early phase of allogeneic haematopoietic stem cell transplantation (HSCT). There is now two-year clinical experience of use of the new regimen, in 88 neutropenic patients. He drew attention to a correlation between patient outcome and compliance with prophylaxis. Over the first 100 days after HSCT, there were statistically significant differences in presence of pulmonary infiltrates and in mortality between patients who complied fully with prophylaxis (defined as receiving prophylaxis for 70 days) and those who were not compliant (and received prophylaxis for less than 70 days). Incidence of possible, probable or proven IFD was also lower in the compliant group (13.6% vs. 24.1%) but because of the low numbers this was not statistically significant. Ullmann suggested that a prospective trial of prophylaxis in this patient group would now be useful.

Anna Candoni and colleagues (Rome, Italy) reported their experience of prophylaxis with posaconazole in 55 unselected patients with acute myeloid leukaemia. Compared with a historical control group who received fluconazole/itraconazole prophylaxis, there was a significantly lower incidence of breakthrough IFD with posaconazole (4% vs. 16%, P=0.02).

Candoni also reported data from the Seifem-Combo study of antifungal combination therapy in IFD in Italian haematology centres. This observational study included 84 patients (81% of whom had Aspergillus infection). The main antifungal combinations used were caspofungin
plus voriconazole and caspofungin plus liposomal amphotericin B. Overall response rate was 73%, and recovery of neutropenia during therapy predicted better outcome.

**Update on epidemiology and antimicrobial susceptibility testing**

In a presentation on clinical breakpoints, Michael Pfaller, from the University of Iowa, USA, outlined the new Clinical and Laboratory Standards Institute (CLSI) echinocandin breakpoints for *Candida*. These are species specific and have a three-step classification: susceptible, intermediate and resistant. In discussion, Professor Pfaller was asked what was meant by the “intermediate” echinocandin MIC. Surely isolates were either wild-type and would respond, or carried an *Fks* mutation and would not respond? He said that in this case “intermediate” probably served primarily as a buffer zone. Intermediate strains were more likely to have mutations than the wild-type population. There was not yet enough data to know whether intermediate strains would respond to therapy.

In some European countries, the prevalence of azole-resistant *Aspergillus* strains may now be 5-10%, said Kullberg. He suggested that in such countries (the UK, The Netherlands, Belgium and Denmark) there is now some concern about using voriconazole alone as first choice for invasive aspergillosis with unknown susceptibility. It might be necessary to switch back to liposomal amphotericin B as primary therapy.

The clinical relevance of rare invasive fungal diseases is increasing steadily, according to the latest data from the FUNGISCOPE international case registry on patients with rare fungal infection which was reported by Maria Vehreschild *et al.* (Cologne, Germany). The registry now has data on over 200 infections, with *Zygomycetes* the most common registered pathogens. For 53% of patients, a favourable outcome (complete or partial response to treatment) was recorded.

**References**


3. 3rd European Conference on Infections in Leukemia (ECIL-3); 2009 Antifungal therapy in leukemia patients. Available at: http://www.ichs.org