

**14th International Symposium on Infections
In the Immunocompromised Host
Crans-Montana, Switzerland,
July 2-5, 2006
Report by Vicki Madden, Medical Writer**

Introduction

More than 450 clinicians and researchers attended the symposium organised by the International Immunocompromised Host Society (ICHS) in Crans-Montana, Switzerland, to hear about recent developments in clinical research that affect the care of immunocompromised patients. Important topics presented at the meeting included the management of infections in solid organ and stem cell transplant recipients, the management of cancer and haematological malignancies and the care of patients during surgery and in intensive care units. Delegates also heard details of the new *European Guidelines on Antimicrobial Therapy in Patients with Acute Leukemia*, presented by members of the organisation committee of the 1st European Conference on Infections in Leukemia (ECIL), held in autumn 2005.

Increased use of invasive monitoring and continual advances in medicine has resulted in a large population of immunocompromised patients who are vulnerable to invasive fungal infections (IFIs). This group includes hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant recipients and people with leukemia and other haematological malignancies where effective antifungal therapy has become an essential part of their management.

The major fungal pathogens, which account for around 70% of all IFIs, are caused by *Aspergillus* species and *Candida* species, but delegates heard that this spectrum is changing as *Fusarium*, *Zygomycetes* and other moulds emerge as important pathogens. Response rates vary according to the fungal infection, but typically only 50% of patients with invasive aspergillosis (IA) and 60-70% with invasive candidiasis respond to first line antifungal therapy.

Mortality rates remain high and improving patient outcome depends on a number of factors including: improving organ function in the host; antifungal prophylaxis; early diagnosis and effective antifungal therapies.

IFIs are extremely difficult to diagnose early enough to prevent a fungal infection taking hold in a patient who is immunocompromised. For this reason, the meeting's many oral sessions and symposia focused on advances in diagnostic tests and when to employ prophylactic or pre-emptive treatment.

This report focuses specifically on the treatment options and strategies for caring for patients who are at risk of developing an invasive fungal infection.

European Conference on Infections in Leukemia (ECIL) guidelines

The new ECIL guidelines provide clinicians with evidence-based recommendations to help prevent and treat life-threatening bacterial and fungal infections in leukemic patients. Six topics were addressed including:

- Fluoroquinolone antibacterial prophylaxis
- Aminoglycosides for antibacterial prophylaxis
- Glycopeptides for antibacterial prophylaxis
- Empirical antifungal therapy
- Antifungal prophylaxis
- Antifungal therapy

Four organisations participated in the development of the ECIL guidelines:

- The European Organisation for Research and Treatment in Cancer (EORTC) Infectious Diseases Group – www.eortc.be
- The European Group for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party – www.ebmt.org
- The Supportive Care Group of the European Leukemia Net (ELN) – www.leukemia-net.org
- The Immunocompromised Host Society (ICHS) – www.ichs.org

ECIL organisation committee member Professor Per Ljungman, Stockholm, Sweden, explained that in order to reach consensus, six working groups reviewed data from the literature in order to answer specific 'closed' questions on the prevention and treatment of bacterial and fungal infections in neutropenic patients. Once consensus was reached and the guidelines finalised, each proposal was scored according to the Centers for Disease Control and Prevention (CDC) grading scheme. Each proposal was allocated two scores based on the level of evidence (I, II, III) and the level of recommendation (A- 'strongly recommended'; through to E 'never recommended').

Data available after the 1st ECIL conference held in Juan-les-Pins, France, from 30 September to 1st October 2005 were admitted, but recommendations based on these data were given a provisional recommendation pending update in 2007, noted Professor Ljungman. This ruling, although based on unpublished data, has allowed the latest triazole antifungal posaconazole (NOXAFIL, Schering-Plough Corporation) to be given a favourable provisional rating for prophylactic antifungal treatment in leukemic patients.

ECIL organisation committee member, Professor Catherine Cordonnier, Paris, France, who was acknowledged as the driving force behind the development of the new guidelines, anticipates that they will be published in full in an appropriate journal before the end of 2006.

Risk factors for invasive fungal infections

As mortality rates from fungal infections continue to rise, the need for the new ECIL guidelines has become more pressing.

Dr Patricia Munoz, University of Madrid, Spain, reported that there has been a 3.4 fold increase in deaths from IFIs in the period 1980-1997, with the death rate/100,000 population rising from 0.7 in 1980 to 2.4 in 1997.

Speaking at a Schering-Plough sponsored symposium, 'Invasive Fungal Infections in the Immunocompromised Patient,' Dr Munoz said that because

of this dramatic increase, fungal infections are now the seventh most common cause of fatal infection. Immunocompromised patients most at risk of IFIs include:

- HSCT and solid organ transplant recipients
- Patients with leukemia and other haematological malignancies

‘The primary risk factor for an IFI in these patients is neutropenia, and the risk becomes greater as the severity and duration of neutropenia increases,’ said Dr Munoz. ‘The incidence of IFI in patients receiving chemotherapy for haematological malignancies can reach 24% and rates of IFI during chronic graft-versus-host-disease (GVHD) can be as high as 39%.’ She added that the rates of mortality for Candida and Aspergillus infections are reported to be 40-50%. In HSCT recipients even higher mortality rates of 80-100% are seen in IFIs caused by Aspergillus, Fusarium and Zygomycetes.

A worrying rise in IFIs has also recently been observed in patients with chronic obstructive lung disease (COPD) and in some intensive care units (ICUs), COPD is now the main underlying condition for invasive aspergillosis (IA). According to Professor Emilio Bouza, Madrid, Spain, of the 48 cases of IA classified by underlying condition, the largest group (36%) were the COPD patients, followed by leukemia patients (15%), solid organ cancer patients (10%), HIV (8%), lymphoma (4%) transplantations (6%) and others (21%).

‘Antifungal prophylaxis is recommended for COPD patients as they are a high-risk group and once they become infected with IA, mortality rates reach 80-100%,’ he said. ‘For this group, it is also worth trying to decrease glucocorticosteroid use and ensure that HEPA filtration is available.’

Delegates also heard that other factors, which increase the risk of IFIs, include:

- High-dose corticosteroid use
- Renal failure
- Total parenteral nutrition

- Catheter use
- Cytomegalovirus infection
- ICU stay of >10 days
- Longer transplantation surgery
- Liver transplantation
- Abdominal surgery
- Early post-surgical tissue ischaemia
- Candida colonisation prior to hospital stay

Changing epidemiology of invasive moulds

Professor Johan Maertens, Leuven, Belgium, outlined how the emergence of rare fungi as well as the development of new antifungals has meant that there has been a change in the main fungal pathogens encountered by clinicians. 'Aspergillosis and Candida species still account for around 70% of all IFIs, but there is a changing spectrum of opportunistic fungi such as *Fusarium* species, Zygomycetes and other moulds,' he said.

Managing infections caused by rare and emerging fungi can be challenging, as some organisms are not susceptible to conventional agents and others may develop resistance after exposure to therapy. Professor Maertens explained how the use of fluconazole has led to a decrease in invasive candidiasis, leaving aspergillus as the most important problem. 'The use of voriconazole has improved treatment for aspergillosis, but at the same time it has led to the appearance of other moulds such as Zygomycetes.'

Diagnostic difficulties

The changing spectrum of pathogens has emphasised the need for effective methods of diagnosing serious fungal infections before they become life threatening. Professor Kieren Marr, Seattle, Washington, USA, pointed out that classical methods of detecting invasive organisms such as bronchoscopy give a definitive diagnosis too late on in the course of the infection. Furthermore, radiographic methods are non-specific and do not discriminate between IA and other opportunistic lung infections. 'In a review of 391 patients

who died from an IFI, a diagnosis pre-death was only obtained in 79% of patients,' she said.

Current tests for detecting fungal pathogens include:

- Galactomannan (GM) test for serum fungal antigens
- (1-3)-beta-D-glucan test for serum fungal antigens
- Polymerase chain reaction (PCR) test for fungal nucleic acids

'The GM assay has variable sensitivity (30%-100%) and higher specificity (86%-99%) than PCR and beta-D-glucan tests, but its performance is less effective when used in those receiving antifungal prophylaxis and in solid organ transplant recipients,' Professor Marr added. 'The beta -D-glucan test is promising, but does not diagnose IA as quickly as the GM test. On the other hand, the PCR test is very sensitive and appears to be more effective at early diagnosis of IA. However, as there are many variables associated with its use it is difficult to standardise the tests,' she said.

As all the current tests that rely on surrogate markers have problems associated with their use, Professor Marr considers that a combination of testing methods is probably the most useful way of getting an early definitive diagnosis.

Management strategies for patients with proven invasive fungal infections

Whilst acknowledging the importance of earlier and targeted treatment in improving morbidity and mortality rates, Professor Maertens said that there remained a number of effective treatments that could be given in the empirical and 'proven IFI' setting. He explained that empirical treatment was where therapy is given to at-risk patients with neutropenia not responding to broad-spectrum antibiotics. He recommended caspofungin as an effective empirical treatment, but in the case of proven aspergillosis infection, he said that because voriconazole failed to meet its study endpoints, clinicians should use liposomal amphotericin B as first line therapy. 'In the case of proven

susceptible candida infection, fluconazole may be effective,' he added. 'If there is resistance, however, caspofungin should be used. If there are other moulds present, therapy should be based on the specific organism.'

Prophylactic treatment in the absence of invasive fungal infection

In the absence of sensitive, reliable diagnostic tests for IFIs the decision of when to give antifungal therapy remains critical to improving patient outcomes, said Professor Francesco Menichetti, University Hospital, Pisa, Italy.

'Meta analyses of randomised controlled trials of antifungal prophylaxis with fluconazole and ketoconazole in HSCT recipients have shown that prophylactic treatment can reduce total mortality by as much as 25% and IFIs by 50%', he said .

He added, however, that although fluconazole prophylaxis is particularly beneficial for preventing fungal infections caused by *Candida* species, it is not effective against *Aspergillus* species, a mould whose incidence is rising. 'Itraconazole has superior activity against *Aspergillus* but tolerability is a concern with patients withdrawing from treatment because of gastrointestinal side-effects.'

Professor Menichetti reported that more promising results have been seen from two large double-blinded studies that have used posaconazole prophylactically. 'In the first prospective blinded study of 602 patients, posaconazole was shown to be superior to therapy with the standard azoles fluconazole or itraconazole in preventing proven/probable IFIs in neutropenic patients with acute myelogenous leukaemia and myelodysplastic syndrome. This study also showed that posaconazole gave a survival benefit with significantly fewer deaths (n=5) than occurred in the standard treatment arm (n=16),' said Professor Menichetti.

The second double-blind trial used posaconazole prophylactically in 600 HSCT recipients and showed that posaconazole was more effective than

fluconazole in preventing IA and IFI overall, leading Professor Menichetti to suggest that posaconazole has a major role to play in preventing IFI in patients at high risk.